Academic and Community Cancer Research United (ACCRU)

Phase I/II, Open-Label Study of R-ICE (Rituximab-Ifosfamide-Carboplatin-Etoposide) with Lenalidomide (R2-ICE) in Patients with First-Relapse/Primary Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

For any communications regarding this protocol, please contact the protocol resource person on the following page.

Study Chairs

ACCRU: [redacted]

Study Cochairs: [redacted]

Statistician: [redacted]

Drug Availability
Commercial Agents: Rituximab, Ifosfamide, Carboplatin, Etoposide
Drug Company Supplied: Lenalidomide (IND #060100)

√ Study contributor(s) not responsible for patient care.

Research Coordinating Center

[redacted]

Document History	**Effective Date**
Pre-activation ACCRU	November 20, 2015
Activation ACCRU (Addendum 1)	May 20, 2016
Addendum 2	July 29, 2016

Protocol Resource

Questions:	Contact Name:
Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission	[redacted]
Drug administration, infusion pumps, nursing guidelines	[redacted]
Protocol document, consent form, regulatory issues	[redacted]
Paraffin Embedded Tissue Pathology	[redacted]
Non-paraffin Biospecimens	[redacted]
Adverse Events (MedWatch, Non-AER, AML/MDS)	[redacted]

*No waivers of eligibility per ACCRU

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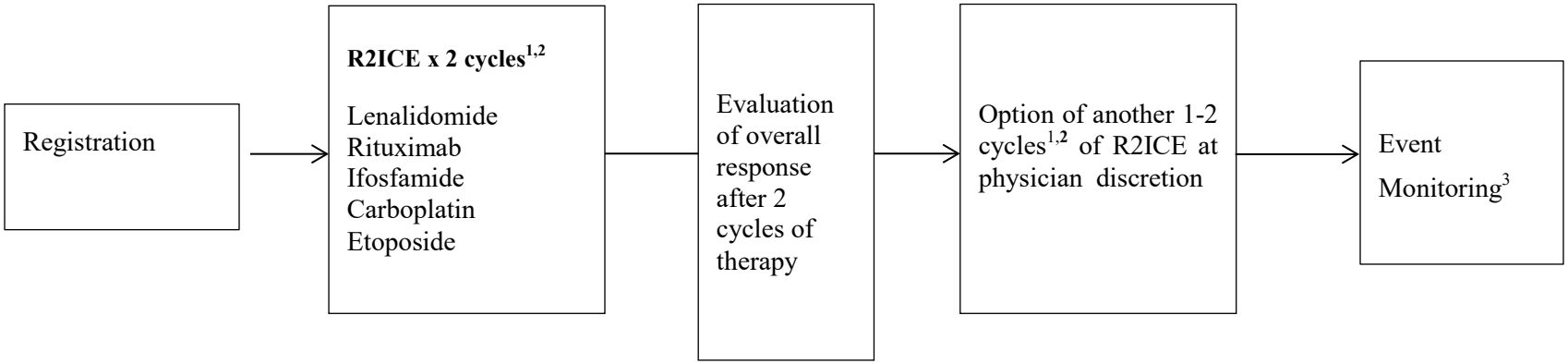
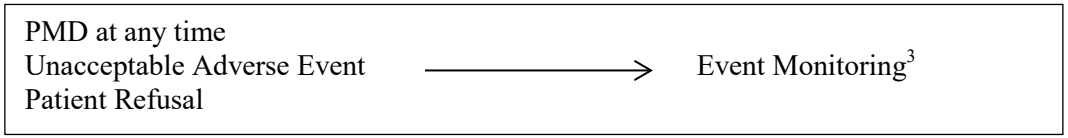
Schema

Prior to discussing protocol entry with the patient, call the ACCRU Registration Office (507-284-4130) for dose level and to insure that a place on the protocol is open to the patient.





[1]See section 7.0 for drug administration and schedule
[2]Cycle length = 21 days
[3] See section 18.0. Patients may receive stem cell transplant (SCT) at physician discretion. If patient goes to SCT, it should be recorded on the event monitoring form.

Generic name: Lenalidomide Brand name(s): REVLIMID® ACCRU Abbreviation: REVLIMID Availability: Investigational	Generic name: Carboplatin Brand name(s): Paraplatin ACCRU Abbreviation: CBDCA Availability: Commercial
Generic name: Rituximab Brand name(s): Rituxan® ACCRU Abbreviation: RITUX Availability: Commercial	Generic name: Etoposide or VP-16 Brand name(s): Toposar® ACCRU Abbreviation: VP16 Availability: Commercial
Generic name: Ifosfamide Brand name(s): Ifex® ACCRU Abbreviation: IFOS Availability: Commercial	

1.0 Background

1.1 Diffuse Large B-Cell Lymphoma: First-Relapse/Primary-Refractory

The first-relapse/primary-refractory diffuse large B-cell lymphomas (DLBCL) constitute at least a quarter of all patients with DLBCL. The majority of these are patients who relapse within the first 1.5 years of treatment. For patients with primary-refractory and first-relapse DLBCL, the response rate achieved prior to proceeding with a stem cell transplant (SCT) is a key variable. Usually this is an autologous stem cell transplant (ASCT). ASCT can be potentially curative for these patients who tend to show chemosensitivity by achieving either a complete response (CR) or partial response (PR) with their salvage chemotherapy prior to the transplant (Kewalramani et al., 2004; Vacirca et al., 2014). Patients with CR tend to do better than patients who achieved PR after salvage chemotherapy.

1.11 Current Treatment Regimens for DLBCL: First-Relapse/Primary Refractory

Treatment for relapsed/refractory disease has lacked a standard of care with a broad range of chemoimmunotherapy options (Witzig et al., 2015). The initial addition of rituximab to the ifosfamide-carboplatin-etoposide (ICE) regimen for patients with diffuse large B-cell lymphoma (DLBCL) lead to a significant improvement in the complete response (CR) and partial response (PR) rates (Kewalramani et al., 2004). The overall response rate (ORR = CR + PR) to ICE alone is estimated to be around 70% (25-30% CR). The CR rate in the earlier study almost doubled to 53% with R-ICE compared to 27% in historic controls who received ICE alone. R-ICE therefore became one of the most commonly used salvage treatment regimens for patients with primary-refractory/first-relapse DLBCL (Table 1). Specifically with patients with first-relapse, the CR rates with R-ICE compared to ICE in historic cohorts are noted to be 65% versus 34%. The ORR was noted to be 96% versus 79% respectively (Kewalramani et al., 2004).

Overall, the R-ICE salvage chemotherapy regimen is very well tolerated. Grade 3 and/or 4 adverse events are infrequent (Kewalramani et al., 2004). Varied numbers of cycles of chemotherapy have been tried and proposed (Table 1). In some studies, 1 cycle of R-ICE was followed by conditioning with high dose chemotherapy and auto stem cell transplant (ASCT) (Stewart et al., 2011). The response rates in those settings, post 1 cycle of R-ICE, have been low (4 (6%) complete responses and 40 (63%) partial responses). Additionally, R-ICE chemotherapy does not lead to problems with stem cell mobilizations for patients needing an ASCT (Stewart et al., 2011).

Furthermore, when designing future studies and looking at response rates of prior studies, it is important to note if the study focused on primary-refractory DLBCL, first-relapse DLBCL or both, since the response rates and biology of the two tend to be different (Kewalramani et al., 2004). First-relapse DLBCL overall tend to do better as compared to patients with primary-refractory DLBCL. In the CORAL (Collaborative Trial in Relapsed Aggressive Lymphoma) study, the overall response rates in patients with relapsed versus refractory disease was 88% versus 46%; $P < 0.001$ (Gisselbrecht et al., 2010).

Table 1: Response rates to different regimens in patients with primary refractory/relapse diffuse large B-cell lymphoma

Regimen	N	CR	PR	ORR	Study
CORAL study R-ICE versus R-DHAP; 3 cycles	396 202 vs. 194	--	--	62.8% vs. 63.5%	(Thieblemont et al., 2011)
R-ICE 3 cycles	75	40%	22%	62%	(Hernandez-Ilizaliturri et al., 2011)
R-ICE 3 cycles	36	53%	25%	78%	(Kewalramani et al., 2004)
R-ICE 3 cycles	32	50%	28.1%	78.1%	(Guo et al., 2014) Chinese Study
R2-ICE Lenalidomide 25 mg-RICE (7 out of 14 days) – 2 cycles	15	60%	13%	73%	(Feldman et al., 2014)
R-NIMP GOELAMS study[1] 3 cycles	50 (20 non-GCB versus 9 GCB)	44% (40% vs. 30%)	22% (10% vs. 56%)	66% (50% vs. 89%)	(Gyan et al., 2013)
R-Benda Every 28 days 2 cycles	61	15.3%	30.5%	45.8%	(Vacirca et al., 2014)
GDP versus DHAP 2 cycles; Rituximab if B-Cell lymphoma	310 vs. 309	13.8 vs. 14.6	32.3 vs. 30.1	46.1% vs. 44.7%	(Crump, 2014)
ICE Nordic study 3 cycles	39	17.9%	41%	59%	(Jerkeman et al., 2004)
Lenalidomide 25 mg (21 out of 28 days) 2 cycles	40 (17 non-GCB versus 23 GCB)	15% (29.4% vs. 4.3%)	12.5% (23.5% vs. 4.3%)	27.5% (53% vs. 9%)	(Hernandez-Ilizaliturri et al., 2011)

[1] Rituximab, vinorelbine, ifosfamide, mitoxantrone and prednisone; every 28 days

The other point of interest in patients with DLBCL is the heterogeneity within this group of tumors (Gyan et al., 2013; Bellas et al., 2014) Based on gene expression profiling (GEP), DLBCL can be broadly divided into germinal center B-cell-like (GCB) and activated B-cell like (ABC) subtypes. The latter often referred to as the non-GCB subtype, tends to have a worse outcome (34% overall survival versus 76%; P < .001).(Hans et al., 2004) This is because some of the known prognostic variables (BCL2, BCL6 and MYC rearrangements) are present in the 2 different subtypes to varying degrees. (Thieblemont et al., 2011)

1.2 Lenalidomide in Hematologic Malignancies and DLBCL

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), antiangiogenic activity (Zhang et al., 2005) and impacts both the microenvironment and the 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 (Richardson et al., 2002; Rajkumar et al., 2005).
Recently there has been increased interest in the response to the lenalidomide in patients with the non-GCB poor prognostic variety. Retrospective analysis of the outcomes of patients with GCB vs non-GCB DLBCL treated with salvage lenalidomide at 4 academic institutions showed a significant difference in clinical response to this immunomodulatory agent. (Hernandez-Ilizaliturri et al., 2011) ORR was 52.9% versus 8.7% (P = .006); CR rate was 23.5% versus 4.3%. Median PFS was 6.2 versus 1.7 months (P = .004), although no difference in overall survival (OS) was observed.

Feldman and colleagues in a phase I/II trial also were able to show that the addition of lenalidomide to the R-ICE regimen did not result in any serious adverse events with nine out of fifteen patients (60%) achieving a complete response with 2 (13%) achieving a partial response. (Feldman et al., 2014) Additionally 1 patient in this study failed stem cell collection for an ASCT.

The addition of lenalidomide to the R-ICE regimen could potentially improve the overall response rates (ORR) as well as the complete response (CR) rates for DLBCL without compromising the aspect of stem cell collection and mobilization; thereby improving the overall survival in these subset of patients. Our hypothesis is that the magnitude of benefit is likely to be more in the non-GCB subtype, however, it would likely have a positive impact on both GCB and non-GCB subtypes of DLBCL.

Dosing of Lenalidomide:

As noted above, patients tolerated the addition of 25 mg dose daily of lenalidomide from days 1-7 of a 14-day cycle of R-ICE chemotherapy without need for any dose modifications. For eight of the fifteen patients, the cycle was every 21 days (Feldman et al., 2014).

Previously, our group was able to show that lenalidomide could be safely added to the R-CHOP regimen (R2CHOP). There were no dose limiting toxicities with the 25 mg daily dose for days 1 through 10 (Nowakowski et al., 2011).

Other examples of dosing and schedules of regimens where lenalidomide is added to other chemotherapy regimens include:

- Bendamustine/Dexamethasone; every 28days; Lenalidomide 15 mg 1 through 21 days
- Bortezomib/Dexamethasone; every 21 days; Lenalidomide 25 mg Days 1 through 14
- BiRD (Biaxin [clarithromycin] / Revlimid [lenalidomide] / dexamethasone) every 28 days; Lenalidomide 25 mg Days 1 through 21

There is also evidence to suggest that it is not only the dose but the duration of exposure to lenalidomide that is important in its role as an immunomodulatory agent.

Based on this and consensus between our experts we plan on dosing lenalidomide days 1 through 14 in a 21 day treatment cycle of R-ICE as noted in Table 7.1. We will start with 15 mg daily and escalate to 20 mg daily as noted by Feldman and colleagues but with a longer duration for 14 days instead of 7 days. There are adjustment to doses based on renal function outlined by the manufacturer and other studies, however, for the purposes of the study, patients would need a creatinine ≤ 2.0 mg/dL or calculated creatinine clearance must be ≥ 30 ml/min using the Cockcroft-Gault formula to be eligible for the study.

A cycle of R2ICE versus RICE chemoimmunotherapy would be 21 days. For the first stage of the study to determine the MTD, building upon the work published on the 'RICER' regimen of Feldman and colleagues, a 3 x 3 dose-escalation design would be used, in which a cohort of three consecutive patients would be assigned initially to the lowest dose of lenalidomide in combination with RICE (Feldman et al., 2014). If no patient developed a dose-limiting toxicity (DLT) during cycle 1 (one cycle being 21 d), the subsequent cohort of three patients would be assigned to the next dose. If any patient in any cohort developed a DLT, that cohort would be expanded by another three patients. In the absence of a DLT being identified, the 20 mg cohort would be expanded to a total of six patients in the current study.

In the original study of the RICER, lenalidomide was dosed for7 days and the following 4 cohorts were used (Feldman, Mato et al. 2014):

- Cohort 1: RICE + Lenalidomide 10mg days 1-7
- Cohort 2: RICE + Lenalidomide 15mg days 1-7
- Cohort 3: RICE + Lenalidomide 20mg days 1-7
- Cohort 4: RICE + Lenalidomide 25mg days 1-7

For the purposes of this study, the same cohorts would be expanded to have lenalidomide given 14 days per 21 days cycle instead of the 7 days as noted above.
For the second phase of the study, patients will be treated with the MTD determined by Lenalidomide plus R-ICE (R2ICE regimen) from stage I (Figure 3).

1.3 Rationale for the Current Study

Despite various effective salvage chemotherapy regimens available in the primary-refractory/first-relapse setting, the overall response rate achieved for patients with DLBCL could still be improved upon to increase the proportion of patients going for a SCT. The goal of our study, therefore, would be to determine if the addition of lenalidomide to the R-ICE chemoimmunotherapy regimen (R2-ICE) would lead to a clinically meaningful improvement in the overall response rates (ORR) for patients with primary-refractory/first-relapse DLBCL. As a secondary end point, we would also look at the complete metabolic response (CMR) rates.

As a secondary objective at the time of analysis, following the algorithm developed by Hans et al, we would analyze patient outcomes based on their subtypes (GCB versus non-GCB subtypes), international prognostic index (IPI) and the timing of their recurrence (≤ 12 months versus > 12 months). (Hans, Weisenburger et al. 2004; Thieblemont, Briere et al. 2011) . In particular our focus would be to see if it leads to improvement in the non-GCB subtype given the overall adverse outcome in this subgroup of patients. We would use nanostring technology here in addition to the traditional Hans algorithm to classify patients into GCB and non-GCB subtypes. Additionally, we would also evaluate and compare the rates the stem cell mobilization achieved in patients receiving R2ICE chemoimmunotherapy compared to historical controls.

1.4 Phases of the Study

1.41 Phase I

Building upon work done by Feldman and colleagues, we would determine the maximum tolerable dose (MTD) of Lenalidomide in combination with R-ICE prior to ASCT. The planned number of cycles would be 2 followed by evaluation with a PET/CT scan. Patients would be allowed to get 1 or 2 more cycles of the treatment regimen based on the arms randomized to prior to proceeding to stem cell collection and transplant as noted in the study schema, after which they would proceed to the event monitoring phase.

In the first phase of the study, since the main objective is to determine the MTD, all kinds of B-cell lymphomas would be allowed. For the second phase, only patients with DLBCL would be eligible to participate. Patients with primary mediastinal lymphoma as well as transformed lymphoma would be allowed to participate in both phases of the study.

1.42 Phase II

Based on the MTD determined by the phase I part of the study, lenalidomide would be combined with R-ICE to form the R2-ICE regimen as outlined by the study schema. This would be a Phase II open-label single arm study.

1.5 Correlative Research

1.51 Impact of DLBCL molecular subtype on efficacy of R2-ICE: DLBCL is a heterogeneous disorder with different subtypes based on Hans algorithm: germinal center B-cell type (GCB) and activated B-cell type (ABC). The latter group is often included in non-GCB type in immunohistochemistry (IHC) based classification algorithms. This classification is based on the so called cell-of-origin (COO) grouping system (Scott, 2014). The ABC (non-GCB subtype) has been associated with worse outcome both in the pre- and post- rituximab era. Retrospective analysis of the outcomes of patients with GCB vs non-GCB DLBCL treated with salvage lenalidomide at 4 academic institutions was recently performed (Hernandez-Ilizaliturri et. al., 2011). Forty patients with relapsed/refractory DLBCL were included (24 men; 16 women; median age, 66 years; median of 4 prior treatments, including rituximab chemotherapy). Patients were classified as GCB (n = 23) or non-GCB (n = 17) DLBCL according to the Hans algorithm. The subgroups were similar in terms of stage, IPI score, prior number of treatments, and rituximab resistance. A significant difference in clinical response to lenalidomide was observed in non-GCB versus GCB patients. ORR was 52.9% versus 8.7% (P = .006); CR rate was 23.5% versus 4.3%. Median PFS was 6.2 versus 1.7 months (P = .004), although no difference in OS was observed between non-GCB and GCB DLBCL patients. There is also evidence to suggest that the DLBCL subtype may have an impact on lenalidomide efficacy in the upfront therapy on work done by our group earlier (Nowakowski et. al, 2011, and Nowakowski, 2014) ; however, its impact in the relapsed and primary-refractory setting still remains to be determined.

In the current study as part of the correlative studies, we will assess impact of DLBCL subtype on the overall response rates achieved for patients with primary-refractory/first-relapse lymphoma. In addition to using immunohistochemistry as proposed by the Hans algorithm, we would further employ gene expression profiling using nanostring technology for classification of these subtypes (Scott, 2014).

2.0 Goals

2.1 Primary

2.11 Phase I: To assess the safety and maximum tolerated dose (MTD) of the addition of lenalidomide to the R-ICE chemoimmunotherapy regimen (R2ICE) for the treatment of primary-refractory/first-relapse B-cell lymphoma

2.12 Phase II: To determine if the addition of lenalidomide (based on dose determination from phase I) to the R-ICE chemoimmunotherapy regimen (R2-ICE) would lead to clinically meaningful improvement in the overall response rates (ORR) for patients with first-relapse/refractory DLBCL.

2.2 Secondary

2.21 To evaluate the effect of the addition of lenalidomide to RICE on the number (percentage) of patients proceeding to SCT.

2.22 To evaluate the effect of the addition of lenalidomide to RICE on other surrogate outcome measures including complete metabolic response (CMR) rate and overall survival

2.23 To describe the toxicities associated with the addition of lenalidomide to the R-ICE chemoimmunotherapy regimen (R2ICE).

2.3 Correlative Research

2.31 To evaluate ORR based on GCB versus non-GCB subtypes. Hans algorithm by immunohistochemistry and gene expression profiling using nanostring technology for classification of these subtypes will be used (Scott, 2014). Outcomes will also be compared based on patients' IPI scores and time of recurrence of lymphoma.

2.32 To evaluate ORR based on percent SUV reduction and percent anatomic size reduction on interim PET/CT scans.

2.33 To evaluate ORR based on Minimal Residual Disease (MRD) detection (positive vs. negative) and quantification after 2 cycles of treatment.

2.34 Future tissue and blood based studies: Additionally, samples collected during this study would be stored for future and ongoing research. (see details below).

3.0 Patient Eligibility

Prior to discussing protocol entry with the patient, call the ACCRU Registration Office (507-284-2753) for dose level and to insure that a place on the protocol is open to the patient.

3.1 Inclusion Criteria

3.11 Age ≥18 years.

3.12 Histological confirmation of expressing CD20 antigen (Cheson et al.,1999) as determined by pathology at the respective institution and central pathology review at Mayo Clinic Rochester.

NOTES:

- For Phase I, all types of B-cell lymphomas are allowed to participate.
- For phase II, only DLBCL patients are allowed to participate.
- For Phase I *only,* patients with primary mediastinal large B-cell (PMLBCL) or transformed lymphoma are allowed to participate.

ADDITIONAL NOTES REGARDING SLIDE SUBMISSION:

- Central pathology review is mandatory, but is retrospective in nature. Slides must be submitted ≤30 days after registration to allow for confirmation of DLBCL diagnosis and to have sufficient material for GCB/ABC assessment by a gene-expression profiling method (see Section 17).
- Patients *can* be enrolled prior to submission of slides.
- For Phase II, if central review of pathology shows that the patient does NOT have DLBCL or the amount of FFPE material is not considered sufficient for COO analysis, the patient may remain on the study but the patient should be replaced.

3.13 Measurable disease (at least 1 lesion ≥ 1.5 cm in diameter) as detected by PET/CT and as defined in Section 11.0.

3.15 Only 1 line of previous anti-lymphoma therapy is allowed and not currently receiving any other agent that would be considered as a treatment for the lymphoma. Patients must be ≥ 2 weeks from prior anti-lymphoma therapy. The use of steroids and/or rituximab up to 1 week prior to registration for management of symptoms is allowed.

3.16 ECOG Performance Status (PS) 0-2. (Form available on the ACCRU web site: [redacted]

3.17 Adequate organ function as defined by the following laboratory values obtained ≤7 days prior to registration.:

- Absolute neutrophil count (ANC) ≥1500/mm^3
- Platelet count ≥75,000/mm^3
- Total bilirubin ≤ 2 × ULN (unless related to lymphoma or Gilbert's disease) OR ≤ 5 × ULN for subjects with documented or suspected Gilbert's disease, or related to involvement of the liver by the lymphoma.
- Aspartate transaminase (AST) and ALT (SGPT) ≤3 x ULN unless evidence of the direct liver and/or bone involvement by lymphoma, then ≤ 5 x ULN
- Renal function assessed by calculated creatinine clearance as follows (see Appendix: Cockcroft-Gault estimation of CrCl):
  - Phase I subjects must have calculated creatinine clearance ≥ 60ml/min by Cockcroft-Gault formula.

- Phase II subjects must have calculated creatinine clearance ≥ 30ml/min by Cockcroft-Gault formula. See section below, "Dosing Regimen", regarding lenalidomide dose adjustment for calculated creatinine clearance ≥ 30ml/min and < 60ml/min.

Cockcroft-Gault Equation:

Creatinine clearance for males = $\frac{\textbf{(140 - age)(weight in kg)}}{\text{(72)(serum creatinine in mg/dL)}}$

Creatinine clearance for females = $\frac{\textbf{(140 - age)(weight in kg)(0.85)}}{\textbf{(72)(serum creatinine in mg/dL)}}$

3.18 For women of childbearing potential only: Negative pregnancy test ≤10-14 days prior to registration. NOTE: the patient must have an additional negative pregnancy test ≤24 hours prior to receiving the initial prescription of lenalidomide, per requirements of the REVLIMID REMS™ program.

3.19a Provide informed written consent.

3.19b Willing to return to enrolling institution for follow-up (during the Active Monitoring Phase of the study (i.e.active treatment and observation)).

3.19c Willing to provide blood samples for correlative research purposes (see Sections 4, 6.22, 14.0).

3.19d Considered transplant-eligible, as determined by the opinion of the investigator at the participating institution. The participating institution does not need to be a transplant center but patients can be referred to a transplant center if needed.

3.19e Willing and able to register into and comply with the mandatory requirements of Celgene's REVLIMID REMS™ program.

3.19f Females of reproductive potential are willing and able to adhere to the scheduled pregnancy testing as required by Celgene's REVLIMID REMS™ program.

3.19g Willing and able to take aspirin (81mg) daily as prophylactic anticoagulation (patients intolerant to ASA may use warfarin or low molecular weight heparin).

3.2 Exclusion Criteria

3.21 Any of the following because this study involves an agent that has known genotoxic, mutagenic and teratogenic effects:

- Pregnant women
- Nursing women
- Men or women of childbearing potential who are unwilling to employ adequate contraception

NOTE: Patients unwilling or unable to do any of the following are also excluded:

- Men must agree to use a latex condom during sexual contact with a female of child-bearing potential even if they have had a successful vasectomy.
- Women of child bearing potential must agree to use 2 methods of reliable contraception simultaneously as indicated in Appendix II.
- All patients must be counseled at a minimum of every 21 days about pregnancy precautions and risks of fetal exposure.

3.22 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 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.

3.23 Immunocompromised patients and patients known to be HIV positive and currently receiving antiretroviral therapy. NOTE: Patients known to be HIV positive, but without clinical evidence of an immunocompromised state, *are eligible* for this trial. Patients with HIV on antiretroviral therapy other than AZT and/or stavudine and without prior AIDS defining conditions and adequate CD4 count (>400) *are eligible*. The safety of lenalidomide-RICE (R2ICE) in patients with HIV infection and advanced immunosuppression and in patients with organ transplants requiring immunosuppression has not been established.

3.24 History of myocardial infarction ≤180 days prior to registration or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

3.26 Receiving any other investigational agent which would be considered as a treatment for the primary neoplasm. As noted in section 3.15, patients must be ≥ 2 weeks from prior anti-lymphoma therapy. The use of steroids and/or rituximab up to 1 week prior to registration for management of symptoms is allowed.

3.27 Other active malignancy ≤3 years prior to registration. EXCEPTIONS: Non-melanotic skin cancer, carcinoma-in-situ of the cervix, or 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. NOTE: If there is a history of prior malignancy, they must not be receiving other specific treatment such as radiation, chemotherapy, or immunotherapy for their cancer.

3.28 Unable or unwilling to take any prophylaxis. NOTE: Lenalidomide therapy is associated with increased risk of thrombosis. Patients with history of or new/active deep vein thrombosis/embolism/thrombophilia **<u>are allowed</u> to participate if they are on appropriate therapeutic anticoagulation during the treatment on the trial**. These patients would not need the aspirin with the lenalidomide unless clinically indicated. Therefore, patients must be able and willing to receive anticoagulation (prophylaxis versus therapeutic as clinically indicated).

3.29 History of radiation therapy to ≥ 25% of the bone marrow for other diseases.

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

3.29b Patients with active or prior CNS lymphoma or cerebrospinal fluid involvement with malignant lymphoma cells. NOTE: These patients are usually treated with CNS directed therapy. Screening for CSF/CNS involvement is NOT required but can be performed per treating MD discretion.

3.29c Active hepatitis B as defined by seropositivity for hepatitis B surface antigen (HBsAg). Subjects with positive hepatitis B core antibody titers and normal liver transaminases are allowed provided that antiviral prophylaxis is administered per institutional guidelines. NOTE: Subjects with hepatitis C antibody will be eligible provided that they do not have elevated liver transaminases or other evidence of active hepatitis.

4.0 Test Schedule

NOTE: Variation of ≤3 days of scheduled visit is permitted.

Tests and procedures	Screening ≤21 days prior to registration	Screening ≤10-14 days prior to registration	Screening ≤7 days prior to registration	Cycle 1 Day 1	Cycle 1 Day 2	Active Monitoring Phase				
						Cycle 1 Day 3	Cycle 2 Day 1	Response Evaluation after 2 cycles (Cycle 2 Day 21)	Optional Cycles: 3 and 4 Day 1	End of Treatment
History and exam, wt, ECOG PS			X	X[1]			X	X	X	X[11]
Height			X							
Adverse event assessment			X				X	X	X	X
Hematology: CBC with differential			X	X[2]			X[2]	X[2]	X[2]	X
Chemistry: SGOT (AST), alk phos, T. bili,[3] creatinine, calcium, phos, glucose, Na, K, glucose			X	X			X	X	X	X
Lactate Dehydrogenase (LDH)			X							
Thyroid stimulating hormone (TSH)[4]			X							
HIV screen	X									
Hepatitis B screen[8]	X									
Pregnancy test[7]		X		X			X	X	X	X
PET CT scans[5] (see Appendix III)	X							X[5]		
Central pathology review (see Section 17.2)[R, 9]			X							
PET/CT scan image submission (See Appendix III)	X							X		
CT Scan[6]	X									
Mandatory blood sample (see Section 14.0)[R, 10]			X	X	X	X		X		

1 If physical examination, vital signs, weight and ECOG performance status were done ≤ 7 days of registration, they do not need to be repeated on Day 1.
2 CBC with differential is required twice weekly until hematologic recovery or as clinically indicated.
3 Only if Total Bilirubin > upper normal limit.
4 TSH levels following baseline may be assessed as clinically indicated.
5 ≤ 21 days prior to registration. PET/CT scans should be performed to assess for response in patients as defined by the revised Cheson's criteria (Cheson, 2014). This response assessment would be performed by the treating institution. However, images would be required to be submitted for future central review

per the guidelines in Appendix III for the purpose of study analysis. Patients who are CMR, PMR, or NMR will continue treatment per protocol for 2 cycles. Per physician discretion patients may receive a 3rd and 4th cycle of treatment.

6 Measurements can be done using the CT part of the PET scan. CT scans of the chest, neck, abdomen & pelvis are mandatory if CT portion of PET scan is not available.

7 For women of childbearing potential only. Must be done ≤10-14 days prior to registration *and* ≤24 hours prior to the start of lenalidomide, per requirements of the REVLIMID REMS™ program. NOTE: The subject may not receive lenalidomide until the study doctor has verified that the results of these pregnancy tests are negative. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). FCBP with regular or no menstruation must have a postmenopausal pregnancy test done weekly during the first cycle, then every 21 days while on therapy (including breaks in therapy); at discontinuation of Lenalidomide and at Day 21 post the last dose of Lenalidomide. Females with irregular menstruation must have a pregnancy test done weekly for the first cycle, then every 14 days while on therapy (including breaks in therapy), at discontinuation of Lenalidomide and at Day 14 and Day 21 post the last dose of Lenalidomide.

8 Persons at high risk of hepatitis B virus infection should be screened before initiation of rituximab. Carriers of hepatitis B should be closely monitored (see Section 9.5).

9 Slides should be submitted ≤30 days of enrollment, as instructed in Section 17. Central pathology review is required, but is retrospective and will not prohibit enrollment into the study.

10 Correlative research blood collected prior to treatment Cycle 1 Day 1, Cycle 1 Day 2, Cycle 1 Day 3 and Cycle 2 Day 21 (see Section 14.0).

11 Follow-up period is every 3 months for years 1 to 3, then yearly in years 4 and 5.

R Research funded (see Section 19.0; patients must be willing to submit mandatory blood samples as outlined in Section 14.0).

5.0 Grouping Factors

5.1 Phase I vs. Phase II

6.0 Registration Procedures

NOTE: There is no randomization involved for this Phase I/II study. The form online is titled Registration/Randomization, but, for this trial, is meant for registration purposes only.

6.1 Phase I

Prior to discussing protocol entry with the patient, call the ACCRU Registration Office ([redacted]) for dose level and to insure that a place on the protocol is open to the patient.

6.11 Registration Procedures

6.111 To register a patient, fax ([redacted]) a completed eligibility checklist to the Academic and Community Cancer Research United (ACCRU) Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.2 Phase II

6.21 Registration Procedures

6.212 To register a patient, access the ACCRU web page at [redacted] on "Training Page" and enter the registration/randomization application. The 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 Academic and Community Cancer Research United (ACCRU) 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 by using the Help button. Prior to initiation of protocol study intervention, this process must be completed in its entirety and a ACCRU subject ID number must be available as noted in the instructions. It is the responsibility of the individual and institution registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the registration/randomization application can be confirmed in any of the following ways:

- Contact the ACCRU Registration Office [redacted]. If the patient was fully registered, the ACCRU 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."

6.3 Phase I and II

6.31 Correlative Research

A mandatory correlative research component is part of this study, the patient will be automatically registered onto this component (see Sections 3.19c, 14.1 and/or 17.11).

As part of ongoing research for ACCRU lymphoma studies, paraffin-embedded tissue blocks/slides and blood products will be banked for future studies

6.32 Prior to accepting the registration, registration/randomization application will verify the following:

- 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

6.33 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [redacted] If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.34 At the time of registration, the following will be recorded:

- Patient has/has not given permission to store and use his/her sample(s) for future research to learn about, prevent, or treat cancer.
- Patient has/has not given permission to store and use his/her sample(s) for future research to learn, prevent, or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).
- *Patient has/has not given permission for ACCRU to give his/her sample(s) to outside researchers.*

6.35 Treatment on this protocol must commence at an ACCRU institution under the supervision of a medical oncologist or hematologist.

6.36 Treatment cannot begin prior to registration and must begin ≤14 days after registration.

6.37 Pretreatment tests/procedures (see Section 4.0) must be completed within the guidelines specified on the test schedule.

6.38 All required baseline symptoms (see Section 10.3) must be documented and graded.

6.39a Blood draw kits must be ordered per instructions in section 14.21.

7.0 Protocol Treatment

7.1 Dosing of lenalidomide:

7.11 Phase I

R2-ICE Treatment Schedule: Cycle length is 21 days.

Agent	Dose[1]	Route	Day
Lenalidomide[2]	As assigned by Randomization Center	PO	As assigned by Randomization Center
Aspirin[2]	81 mg	PO	Days 1-14
Rituximab[3]	375 mg/m^2	IV	Day 1
Ifosfamide	5000 mg/m^2	IV	Day 2
Mesna	5000 mg/m^2	IV	Day 2
Carboplatin	AUC 5	IV	Day 2
Etoposide	100 mg/m^2	IV	Days 1-3
Pegfilgrastim[4]	6 mg	SubQ[4]	Day 4
Dexamethasone[5]	20 mg	IV[5]	Day 1-2
Tumor lysis prophylaxis[6]			

1 Body surface area based on actual body weight
2 For patients on the R2-ICE arm taking Lenalidomide, low dose Aspirin 81 mg daily will continue until the platelet counts fall below 50,000. Patients who cannot take aspirin will be placed on prophylactic warfarin or low molecular weight heparin (Lovenox 40 mg daily) until the platelet counts fall below 50,000.
3 Rituximab may be rounded to nearest 50 mg. Patients will get acetaminophen 1000 mg/dose 30 minutes prior to infusion and every 4 hours as needed for infusion related reactions (not to exceed 4000 mg/24 hours from all sources). In addition, diphenhydramine 50 mg/dose 30 minutes prior and then 25 mg/dose IV every 4 hours as needed for infusion related reactions with rituximab. This may be repeated once if symptoms are not relieved within 15 minutes of initial dose. Meperidine 25 mg/dose IV push prn rigors, may repeat once if first dose ineffective.
4 Pegfilgrastim should be given 18 hours after chemotherapy on Day 4-5. G-CSF (filgrastim) or other growth factors can be used (instead of Pegfilgrastim) based on institutional practice.
5 Dexamethasone 20 mg IV Day 1 and 2; 30 minutes prior to Rituximab and Carboplatin to prevent reactions.
6 Tumor lysis prophylaxis per institutional practice. For patients with AKI, large tumor burden and/or uric acid > 8 mg/dl, consideration should be given to giving rasburicase 6 mg IV once and repeated as needed.

Ifosfamide, carboplatin, and etoposide are commercially available chemotherapies that are approved by the U.S. Food and Drug Administration and other regulatory agencies for use in patients with multiple types of cancer and in various combinations. Use of these drugs to treat patients with DLBCL is considered a standard regimen in the United States.

Etoposide 100 mg/m2 will be administered by IV infusion over approximately 1 hour on Days 1–3 of each cycle.

Carboplatin dose will be calculated using the Calvert formula (below) to achieve an area under the curve (AUC) of 5 mg/mL * min (maximum dose = 800 mg) and will be administered by IV infusion on Day 2 of each cycle, over approximately 1-2 hours:

Carboplatin dose in mg = 5 mg/mL*min x [GFR (mL/min) + 25 (mL/min)]
Glomerular filtration rate (GFR) will be estimated using the modified Cockcroft-Gault formula:

$$GFR = \frac{(140 - \text{age [yrs]}) \times \text{actual weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}}$$

Note: Multiply by another factor of 0.85 if patient is female.

Ifosfamide 5 g/m2 will be administered beginning Day 2 of each cycle by continuous IV infusion over 24 hours +/- 2 hours. Mesna 5 g/m2 should be mixed in the same bag and administered in conjunction with ifosfamide. Patients may be hospitalized during this 24-hour infusion period.

Post-infusion mesna should be given in accordance with institutional guidelines (e.g. oral or IV for 6-12 hours following infusion).

Rituximab at 375 mg/m2 will be administered via IV infusion per institutional guidelines. Subjects will receive 2 cycles of RICE or R2ICE before response assessment after cycle 2, or significant/serious drug related toxicity occurs. Per investigator discretion, patients can receive up to 2 more cycles of therapy before they proceed with a transplant.

ICE will be administered via IV infusion as follows: ifosfamide 5 g/m2 continuously for 24 hours with mesna on Day 2; carboplatin area under the curve (AUC) = 5 mg/mL × min [800 mg maximum) on Day 2; etoposide 100 mg/m2 on Days 1, 2, and 3 in 21-day cycles.

7.12 Phase II

R2ICE Treatment Schedule: Cycle length is 21 days.

Agent	Dose[1]	Route	Day
Lenalidomide[2]	As determined by phase I	PO	As determined by phase I
Aspirin[2]	81 mg	PO	Days 1-14
Rituximab[3]	375 mg/m^2	IV	Day 1
Ifosfamide	5000 mg/m^2	IV	Day 2
Mesna	5000 mg/m^2	IV	Day 2
Carboplatin	AUC 5	IV	Day 2
Etoposide	100 mg/m^2	IV	Days 1-3
Pegfilgrastim[4]	6 mg	SubQ[4]	Day 4
Dexamethasone[5]	20 mg	IV[5]	Day 1-2
Tumor lysis prophylaxis [6]			

1 Body surface area based on actual body weight
2 For patients on the R2-ICE arm taking Lenalidomide, low dose Aspirin 81 mg daily will continued till the platelet counts fall below 50,000. Patients who cannot take aspirin will be placed on prophylactic warfarin or low molecular weight heparin (Lovenox 40 mg daily) until the platelet counts fall below 50,000. Lenalidomide is provided at no charge to patients by Celgene Corporation for patients on the R2ICE arm.
3 Rituximab may be rounded to nearest 50 mg. Patients will get acetaminophen 1000 mg/dose 30 minutes prior to infusion and every 4 hours as needed for infusion related reactions. In addition, diphenhydramine 50 mg/dose 30 minutes prior and then 25 mg/dose IV every 4 hours as needed for infusion related reactions with rituximab. This may be repeated once if symptoms are not relieved within 15 minutes of initial dose. Meperidine 25 mg/dose IV push prn rigors, may repeat once if first dose ineffective.
4 Pegfilgrastim should be given 18 hours after chemotherapy on Day 4-5. G-CSF (filgrastim) or other growth factors can be used (instead of Pegfilgrastim) based on institutional practice.
5 Dexamethasone 20 mg IV Day 1 and 2; 30 minutes prior to Rituximab and Carboplatin to prevent reactions.
6 Tumor lysis prophylaxis per institutional practice. For patients with AKI, large tumor burden and/or uric acid > 8 mg/dl, consideration should be given to giving rasburicase 6 mg IV once and repeated as needed.

7.2 Length of Treatment: Patients will receive treatment per protocol for 2 cycles. At the end of 2 cycles, patients who are CMR, PMR, or NMR may receive a 3rd and 4th cycle of treatment per physician discretion.

7.3 Stem Cell Transplant (SCT): After the completion of 2 cycles of R2ICE treatment, patients who have achieved an objective status of CMR, PMR or NMR may proceed to SCT during the event monitoring phase. The SCT should be recorded on the event

monitoring form. Depending on the timing of the transplant, patients per physician discretion can continue treatment for a 3rd and 4th cycle prior to transplant.

7.4 For this protocol, the patient must return to the consenting ACCRU institution for evaluation at least every 21 days during treatment as specified in the test schedule (see Section 4.0).

7.5 Local Medical Doctor (LMD) treatment:

Patients must receive treatment with R2ICE per protocol at the participating ACCRU institution. However, patients are allowed to receive the *transplant* at a non-ACCRU institution.

7.6 Phase I – Determination of Maximum Tolerated Dose (MTD)

7.61 Dose Escalation

Lenalidomide			
Dose Level	Dose	Day	Route
-2	10 mg	Daily for 10 days	Orally
-1	10 mg	Daily for 14 days	Orally
*1	15 mg	Daily for 14 days	Orally
2	20 mg	Daily for 14 days	Orally

***starting dose level**

7.612 Three patients will be treated at each dose level and observed for a minimum of 21 days (1 cycle), to assess toxicities, before new patients are treated. Doses will not be escalated in any individual patient.

7.613 Investigators are to contact the ACCRU Operations Office (507-266-0800) as soon as any dose-limiting toxicity (DLT) occurs.

7.62 Definitions of DLT

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

- Any grade ≥ 3 non-hematologic adverse event. The following are some of the exceptions noted:
  - Alopecia, anorexia, or fatigue.
  - Grade 3 nausea and/or vomiting if not requiring tube feeding or total parenteral nutrition TPN, or diarrhea if not requiring or prolonging hospitalization that can be managed to Grade ≤ 2 with antiemetic or antidiarrheal medications

- Grade 3 fever with neutropenia, with or without infection.
- Grade 3 infection.
- Grade 3 tumor lysis syndrome that resolves within 72 hours after initiation of treatment.
- Any grade electrolyte alteration that resolves to grade ≤ 1 within 72 hours after it occurs.

- Hematological adverse events include the following:
  - Failure of platelet recovery to 50,000/mm³ by day 29
  - Failure of absolute neutrophil recovery to 1000/mm³ by Day 29

8.0 Dosage Modification Based on Adverse Events

Dose adjustments of ICE chemotherapy are to be performed per institutional standards. All patients will receive prophylactic hematopoietic growth factors (e.g., granulocyte-colony stimulating factor [G-CSF]) to shorten the period of neutropenia and transfusions of blood products should be provided during the course of treatment per institutional guidelines.

Standard practice and local prescribing information will be followed for rituximab and background chemotherapy. Omitting or discontinuing background therapy must lead to omitting or discontinuing of lenalidomide as well.

Dose Modifications at the start of next treatment cycles:
Dose modifications of Lenalidomide will be based on the dose levels as noted in Table 8.1 and on adverse events noted during preceding cycles (see Table 8.2 for guidance regarding dose reductions based on adverse events).

Dose modifications during a treatment cycle:
Please note, while patient is actively on Lenalidomide, modifications are not allowed during the particular treatment cycle and are only allowed Day 1 of any particular cycle. Decreasing by one dose level would be for the next cycle of treatment. During active treatment cycle, treatment can be held for up to 7 days if needed.

If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. Reductions apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose.

ALERT: *ADR reporting may be required for some adverse events (See Section 10)*

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

Lenalidomide*				
	Starting Dose 20 mg days 1-14	Starting Dose 15 mg days 1-14	Starting Dose 10 mg days 1-14	Starting Dose 10 mg days 1-10
1st dose reduction	15 mg days 1-14	10 mg days 1-14	10 mg days 1-10	10 mg Daily for days 1-7
2nd dose reduction	10 mg days 1-14	10 mg days 1-10	10 mg Daily for days 1-7	Discontinue
3rd dose reduction	10 mg days 1-10	10 mg Daily for days 1-7	Discontinue	
4th dose reduction	10 mg Daily for days 1-7	Discontinue		
5th dose reduction	Discontinue			

* Cycle length is 21 days for all treatment cycles

8.2 Dose modifications for Lenalidomide

Use the following definitions to determine actions in the Action columns of the following tables:

- **Omit** = The current dose(s) for the specified drug(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time
- **Hold/Delay** = The current dose(s) of all drugs during a cycle is delayed. The patient does make up the delayed dose(s) when the patient meets the protocol criteria to restart drugs.
- **Discontinue** = The specified drug(s) are totally stopped.

TREATMENT MODIFICATIONS FOR LENALIDOMIDE Use the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0* unless otherwise specified		
CTCAE System/Organ/Class (SOC)	**ADVERSE EVENT**	**ACTION**
BASED ON INTERVAL ADVERSE EVENT DURING TREATMENT (DAYS 2-21)		
Any grade ≥ 3 non-hematologic adverse event	Non-hematologic	No dose reductions allowed while patient is actively getting treatment. Can omit lenalidomide for up to 7 days if needed.
Any grade hematologic adverse event		Does not require dose reduction or omission of Lenalidomide.
AT TIME OF RETREATMENT (DAY 1)		
Investigations/ Neutrophil count decreased	Grade ≥ 3	Hold treatment until ANC ≥ 1000: • Days 22-28: if ANC ≥ 1000 proceed with treatment without dose reductions. • Days 29-35: If ANC recovers to ≥ 1000, reduce Lenalidomide by one dose level (see Table 8.1). • Days ≥36: discontinue treatment and go to event monitoring.
Investigations/ Platelet count decrease	Grade ≥ 3	Hold treatment until platelets ≥ 50,000: • Days 22-28, if platelets ≥ 50,000 proceed with treatment without dose reductions. • Days 29-35: If platelets ≥ 50,000, reduce Lenalidomide by one dose level (see Table 8.1). • Days ≥36, discontinue treatment and go to event monitoring.
Any grade ≥ 3 non-hematologic adverse event	Non-hematologic	Need to recover to grade 2 or lower before proceeding. Dose reductions of lenalidomide for the next cycle would be based on Table 8.1

* Located at [redacted]

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. Dose increments would not be allowed once the reductions are made for subsequent cycles.

9.0 Ancillary Treatment/Supportive Care

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

9.2 Blood products should be utilized as clinically warranted and following institutional policies and recommendations.

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 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 Carriers of hepatitis B virus (HBV) should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis during and for up to several months following Rituxan therapy. In patients who develop viral hepatitis, Rituxan and any concomitant chemotherapy should be discontinued and appropriate treatment, including antiviral therapy, initiated. There are insufficient data regarding the safety of resuming Rituxan therapy in patients who develop hepatitis subsequent to HBV reactivation.

9.6 All patients would receive growth factor support in the form of Pegfilgrastim or filgrastim (G-CSF) as per institutional guidelines and availability and coverage. Pegfilgrastim can be given 24 hours after chemotherapy on Day 4-5 but before 72 hours prior to finishing of chemotherapy. G-CSF (filgrastim) could be used starting the day after chemotherapy based on institutional practice.

9.7 Steroids in the form of Dexamethasone 20 mg IV Day 1 and 2 is to be given 30 minutes prior to Rituximab and Carboplatin to prevent reactions.

9.8 To prevent ifosfamide related bladder toxicity, mesna should be given in accordance with institutional guidelines (e.g. oral or IV for 6-12 hours following infusion).

9.9 Tumor lysis prophylaxis should be done per institutional practice. Typically, 300 mg of Allopurinol can be given daily for tumor lysis prophylaxis before cycle 1 of therapy. For patients with acute kidney injury (AKI), large tumor burden and/or uric acid > 8 mg/dl, consideration should be given to giving rasburicase 6 mg IV once and repeated as needed.

10.0 Adverse Event (AE) Reporting and Monitoring

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: [redacted]

a. Adverse event monitoring and reporting is a routine part of every clinical trial.

b. Identify the grade and severity of the event using the CTCAE version 4.0.

c. Determine whether the event is expected or unexpected (see Section 10.2).

d. Determine if the adverse event is related to the study intervention (agent, treatment or procedure) (see Section 10.3).

e. Determine whether the event must be reported as an expedited report. If yes, determine the timeframe/mechanism (see Section 10.4).

f. Determine if other reporting is required (see Section 10.5).

g. Note: All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.6 and 18.0).

10.1 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

NOTE: A severe AE, as defined by the above grading scale, is NOT the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

Expected events - are those described within the Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), and/or the investigator brochure, (if an investigator brochure is not required, otherwise described in the general investigational plan).

Unexpected adverse events or suspected adverse reactions are those not listed in Section 15.0 of the protocol, the study specific consent form, package insert (if applicable), or in the investigator brochure (or are not listed at the specificity or severity that has been observed); if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan.

Unexpected also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs but have not been observed with the drug under investigation.

Unanticipated Adverse Device Event (UADE)
Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects

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

Events determined to be possibly, probably or definitely attributed to a medical treatment suggest there is evidence to indicate a causal relationship between the drug and the adverse event.

10.31 **AEs Experienced Utilizing Investigational Agent(s) and Commercial Agent(s) on <u>SEPARATE</u> Arms**

- An AE that occurs on an arm using an investigational agent /intervention under an IND/IDE must be assessed in accordance with the guidelines in the appropriate **IND/IDE** Reporting Table in Section 10.4.

- An AE that occurs on an arm using a commercial agent on a separate treatment arm must be assessed as specified in the protocol**. <u>Refer to Commercial Reporting Table in Section 10.4.</u>**

10.32 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the <u>SAME</u> Arm**

When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the **entire combination (arm) is then considered an investigational intervention for reporting**. These AEs should be assessed as specified in the appropriate **IND/IDE** reporting guidelines in Section 10.4

10.33 **Special Situations for Expedited Reporting**
Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

For this protocol only, the following Adverse Events/Grades are expected to occur within this population and do not require Expedited Reporting. These events must still be reported via Routine Reporting (see Section 10.6).*

System Organ Class (SOC)	Adverse event/ Symptoms[1]	CTCAE Grade at which the event will *not* be expeditedly reported
Blood and lymphatic system disorders	Anemia	Grade 3 or 4
Gastrointestinal disorders	Nausea	Grade 3 or 4
	Vomiting	Grade 3 or 4
General disorders and administration site conditions	Fatigue	Grade 3
Investigations	White blood cell decreased	Grade 3 or 4
	Lymphocyte count decreased	Grade 3 or 4
	Neutrophil count decreased	Grade 3 or 4
	Platelet count decreased	Grade 3 or 4

[1]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.

*Report any clinically important increase in the **rate** of a serious suspected adverse reaction (at your study) site over that which is listed in the protocol or investigator brochure as an expedited event.

*Report an expected event that is greater in severity or specificity than expected as an expedited event

*An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity or specificity, expedited reporting is required.

A list of known/expected AEs is reported in the investigator brochure, package insert or the literature, including AEs resulting from a drug overdose.

10.331 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.

- **Reportable categories of Death**

    - Death attributable to a CTCAE term.

    - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.

    - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.

    - Death due to progressive disease should be reported as **Grade 5 "Neoplasms benign, malignant and unspecified (including cysts and polyps) – Other (Progressive Disease)"** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.

10.332 Secondary Malignancy

- A ***secondary malignancy*** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE to be reported. Three options are available to describe the event:

    - Leukemia secondary to oncology chemotherapy (e.g., Acute Myeloctyic Leukemia [AML])

    - Myelodysplastic syndrome (MDS)

    - Treatment-related secondary malignancy

- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.333 Second Malignancy

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting.

10.335 Pregnancy

- 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, or approved equivalent form. The female subject may be referred to an obstetrician-gynecologist, (not necessarily one with reproductive toxicity experience) or other appropriate healthcare professional for further evaluation.

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

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

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.

10.336 Overdose

Overdose, as defined for this protocol, refers to Lenalidomide (Revlimid®) in pill form with R-ICE (Rituximab-Ifosfamide-Carboplatin-Etoposide)IV chemotherapy dosing only.

On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of Lenalidomide (Revlimid®) in pill form with R-ICE (Rituximab-Ifosfamide-Carboplatin-Etoposide assigned to a given patient, regardless of any associated adverse events or sequelae.

PO any amount over the protocol-specified dose
IV 10% over the protocol-specified dose
SC 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

Celgene Drug Safety Contact Information:

10.4 Expedited Adverse Event Reporting Requirements for IND/IDE Agents

10.41 Expedited Reporting via the **ACCRU Adverse Event Expedited Report Form** for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
An adverse event is considered serious if it results in **ANY** of the following outcomes:

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to the sponsor within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	7 Calendar Days	24-Hour 3 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in Section 10.33 of the protocol.

Expedited AE reporting timelines are defined as:

- "24-Hour; 3 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- "7 Calendar Days" - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2] For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Effective Date: May 5, 2011

Additional Instructions:

1. Any event that results in persistent or significant disability/incapacity, congenital anomaly, or birth defect must be reported via expedited mechanisms if the event occurs following treatment on a trial under an IND.

2. Use the ACCRU protocol number and the protocol-specific patient ID provided during trial registration on all reports.

3. **ACCRU Sites*:*** Provide copies by fax [redacted] to the ACCRU SAE Coordinator. The ACCRU SAE Coordinator will then electronically send the report to Celgene:

The above expedited reports (24-hour and 3 or 7 day) must be submitted via the **ACCRU Adverse Event Expedited Report Form**.

Submit reports to the ACCRU SAE Coordinator via fax [redacted]

4. Once the ACCRU SAE Coordinator receives the report via fax, the ACCRU SAE Coordinator will forward a copy of the above expedited reports to:

   - **The ACCRU IND Coordinator,** who will notify the FDA as warranted by the event and stipulated in the U.S. Code of Federal Regulations.

   - **Celgene:**

     Expedited Reporting by Investigator to Celgene:

     For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events of being related to lenalidomide based on the Investigator Brochure. In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

     Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours of being aware of the event. 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 report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-CL-DLBCL-ACCRU-004373) and the institutional protocol number should be included on

SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

10.5 Other Required Reporting

10.51 Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOS) in general, include any incident, experience, or outcome that meets **all** of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;

2. Related or possibly related to participation in the research (in this guidance document, possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and

3. Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

Some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased *risk* of harm, but no harm occurs.

Note: If there is no language in the protocol indicating that pregnancy is not considered an adverse experience for this trial, and if the consent form does not indicate that subjects should not get pregnant/impregnate others, then any pregnancy in a subject/patient or a male patient's partner (spontaneously reported) which occurs during the study or within 120 days of completing the study should be reported as a UPIRTSO.

If the event meets the criteria for an UPIRTSO, submit to your IRB as required by your institutional policies.

10.52 Pre-treatment symptoms/conditions to be graded at baseline and adverse events to be graded at each evaluation per the CTCAE v4.0 grading unless otherwise stated in the table below:

System Organ Class (SOC)	Adverse event/Symptoms	Baseline	Each evaluation
Infections and Infestations	Hepatitis viral*	X	X
Vascular Disorders	Thromboembolic Event	X	X
Blood and lymphatic system disorders	Febrile neutropenia	X	X
Gastrointestinal disorders	Upper gastrointestinal hemorrhage	X	X
Skin and subcutaneous tissue disorders	Rash Maculopapular	X	X

*See Drug Information Section 15.27.

10.53 **Case Report Forms** - Academic and Community Cancer Research United (ACCRU)

Submit the following AEs not specified in Section 10.5 (paper or electronic, as applicable):

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

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

10.533 Grade 5 AEs (Deaths)

10.5331 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.

10.5332 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.

10.54 **Late-Occurring Adverse Events -** Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation Using PET/CT Cheson's response criteria for malignant lymphoma

11.1 Response Considerations (**Lymphoma**)

Schedule of Evaluations: For the purposes of this study, patients should be evaluated for response at cycle 2 day 21.

Definitions for clinical response for patients with lymphoma are from the recently revised Cheson's et al criteria published in 2014, derived from the original criteria published in 2007 (Cheson, 2014 and Cheson, et al 2007). Lymph node measurements should be taken from the CT portion of the PET/CT, or other dedicated CT scans where applicable. Measurement of lymphadenopathy will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SPD). Measurable extra nodal 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 (e.g., 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 and pathologically negative.

Response is based on PET/CT based on the revised 2014 Cheson's criteria (Cheson 2014).

PET/CT scans are required at baseline and after 2 cycles of treatment for all patients and should be submitted per instructions in Appendix III.

Response criteria (Cheson, 2014)

	PET-CT Based Response	CT-Based Response
Complete Response	**Complete metabolic response (CMR)**	**Complete radiologic response (CR) (all of the following)**
Lymph nodes and extralymphatic sites	Score 1, 2, or 3* with or without a residual mass on 5PS† It is recognized that in Waldeyer's ring or extranodal sites with high physiologic uptake or with activation within spleen or marrow (eg, with chemotherapy or myeloid colony-stimulating factors), uptake may be greater than normal mediastinum and/or liver. In this circumstance, complete metabolic response may be inferred if uptake at sites of initial involvement is no greater than surrounding normal tissue even if the tissue has high physiologic uptake	Target nodes/nodal masses must regress to ≤ 1.5 cm in LDi No extralymphatic sites of disease
Nonmeasured lesion	Not applicable	Absent
Organ enlargement	Not applicable	Regress to normal
New lesions	None	None
Bone marrow	No evidence of FDG-avid disease in marrow	Normal by morphology; if indeterminate, IHC negative
Partial Response	**Partial metabolic response (PMR)**	**Partial remission (PR) (all of the following)**
Lymph nodes and extralymphatic sites	Score 4 or 5† with reduced uptake compared with baseline and residual mass(es) of any size At interim, these findings suggest responding disease At end of treatment, these findings indicate residual disease	≥ 50% decrease in SPD of up to 6 target measurable nodes and extranodal sites When a lesion is too small to measure on CT, assign 5 mm X 5 mm as the default value When no longer visible, 0 X 0 mm For a node > 5 mm X 5 mm, but smaller than normal, use actual measurement for calculation
Nonmeasured lesions	Not applicable	Absent/normal, regressed, but no increase
Organ enlargement	Not applicable	Spleen must have regressed by > 50% in length beyond normal
New lesions	None	None
Bone marrow	Residual uptake higher than uptake in normal marrow but reduced compared with baseline (diffuse uptake compatible with reactive changes from chemotherapy allowed). If there are persistent focal changes in the marrow in the context of a nodal response, consideration should be given to further evaluation with MRI or biopsy or an interval scan	Not Applicable

No Response or Stable Disease	**No metabolic response (NMR)**	**Stable disease (SD)**
Target nodes/nodal masses, extranodal lesions	Score 4 or 5 with no significant change in FDG uptake from baseline at interim or end of treatment	< 50% decrease from baseline in SPD of up to 6 dominant, measurable nodes and extranodal sites; no criteria for progressive disease are met
Nonmeasured lesions	Not applicable	No increase consistent with progression
Organ enlargement	Not applicable	No increase consistent with progression
New lesions	None	None
Bone marrow	No change from baseline	Not Applicable
Progressive disease	**Progressive metabolic disease (PMD)**	**Progressive disease (PD) requires at least 1 of the following**
Individual target nodes/nodal masses Extranodal lesions	Score 4 or 5 with an increase in intensity of uptake from baseline and/or New FDG-avid foci consistent with lymphoma at interim or end-of-treatment assessment	PPD progression: An individual node/lesion must be abnormal with: LDi > 1.5 cm and Increase by ≥ 50% from PPD nadir and An increase in LDi or SDi from nadir 0.5 cm for lesions ≤2 cm 1.0 cm for lesions > 2 cm In the setting of splenomegaly, the splenic length must increase by > 50% of the extent of its prior increase beyond baseline (eg, a 15-cm spleen must increase to > 16 cm). If no prior splenomegaly, must increase by at least 2 cm from baseline New or recurrent splenomegaly
Non-measured lesions	None	New or clear progression of preexisting non-measured lesions
New lesions	New FDG-avid foci consistent with lymphoma rather than another etiology (eg, infection, inflammation). If uncertain regarding etiology of new lesions, biopsy or interval scan may be considered	Regrowth of previously resolved lesions A new node > 1.5 cm in any axis A new extranodal site > 1.0 cm in any axis; if < 1.0 cm in any axis, its presence must be unequivocal and must be attributable to lymphoma Assessable disease of any size unequivocally attributable to lymphoma
Bone marrow	New or recurrent FDG-avid foci	New or recurrent involvement
Abbreviations: 5PS, 5-point scale; CT, computed tomography; FDG, fluorodeoxyglucose; IHC, immunohistochemistry; LDi, longest transverse diameter of a lesion; MRI, magnetic resonance imaging; PET, positron emission tomography; PPD, cross product of the LDi and perpendicular diameter; SDi, shortest axis perpendicular to the LDi; SPD, sum of the product of the perpendicular diameters for multiple lesions. *A score of 3 in many patients indicates a good prognosis with standard treatment, especially if at the time of an interim scan. However, in trials involving PET where de-escalation is investigated, it may be preferable to		

consider a score of 3 as inadequate response (to avoid undertreatment). Measured dominant lesions: Up to six of the largest dominant nodes, nodal masses, and extranodal lesions selected to be clearly measurable in two diameters. Nodes should preferably be from disparate regions of the body and should include, where applicable, mediastinal and retroperitoneal areas. Non-nodal lesions include those in solid organs (eg, liver, spleen, kidneys, lungs), GI involvement, cutaneous lesions, or those noted on palpation. Nonmeasured lesions: Any disease not selected as measured, dominant disease and truly assessable disease should be considered not measured. These sites include any nodes, nodal masses, and extranodal sites not selected as dominant or measurable or that do not meet the requirements for measurability but are still considered abnormal, as well as truly assessable disease, which is any site of suspected disease that would be difficult to follow quantitatively with measurement, including pleural effusions, ascites, bone lesions, leptomeningeal disease, abdominal masses, and other lesions that cannot be confirmed and followed by imaging. In Waldeyer's ring or in extranodal sites (eg, GI tract, liver, bone marrow), FDG uptake may be greater than in the mediastinum with complete metabolic response, but should be no higher than surrounding normal physiologic uptake (eg, with marrow activation as a result of chemotherapy or myeloid growth factors).
†PET 5PS: 1, no uptake above background; 2, uptake ≤mediastinum; 3, uptake > mediastinum but ≤ liver; 4, uptake moderately > liver; 5, uptake markedly higher than liver and/or new lesions; X, new areas of uptake unlikely to be related to lymphoma.

12.0 Descriptive Factors

12.1 Phase I only: Dose level (as assigned by registration office): -2 vs. -1 vs. 1 vs. 2

12.2 International Prognostic Index (IPI) [Shipp et al, 1993]: low risk (0 or 1 risk factors) vs. low intermediate (2 risk factors) vs. high intermediate (3 risk factors) vs. high (4 or 5 risk factors)

Risk Factors	0 points	1 point
Age	≤ 60 yrs.	> 60 yrs.
Serum LDH	≤ 1 x normal	> 1 x normal
ECOG PS	0 or 1	≥2
Stage	I or II	III or IV
Extranodal involvement	≤1 site	>1 site

Total number of risk factors = sum of the number of points for each prognostic factor.

13.0 Treatment/Follow–up Decision at Evaluation of Patient

13.1 Patients who are CMR, PMR, or NMR will continue treatment per protocol for 2 cycles. The patient may receive a 3rd and 4th cycle of treatment per MD discretion.

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

13.3 Patients who go off protocol treatment for reasons other than PMD will go to the event-monitoring phase per Section 18.0.

13.4 Phase I Only: If a patient fails to complete the first cycle of treatment for reasons other than toxicity, the patient will be regarded as not evaluable and will be replaced.

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 (or off study, if applicable).

- 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 and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

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

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 (background/ methodology section)**	**Where to find specific details for specimen submission**
Blood/blood products	Mandatory	Serial Draws	Correlative Studies (Section 14.31)	Section 14.2

14.2 Blood/Blood Products Handling

14.21 Kits are required for this study.

14.211 The kit contains supplies and instructions for collecting, processing, and shipping specimens.

14.212 Participating institutions may obtain kits by completing and faxing the Supply Order Form (found in the Forms Packet) to the number listed on the form. Fill out the site address to where the kits will be shipped on the fax supply form. Because we are now being charged for all outgoing kits, a small, but sufficient, supply of the specimen collection kits should be ordered prior to patient entry. Do not send unused kits back to BAP.

14.213 Kits will be sent via FedEx® Ground at no additional cost to the participating institutions. **Allow at least two weeks to receive the kits.**

14.214 Kits will not be sent via rush delivery service unless the participating institution provides their own FedEx® account number or alternate billing number for express service. **ACCRU will <u>not</u> cover the cost for rush delivery of kits.**

14.22 All samples must be collected **Monday-Thursday ONLY.**

14.23 Label specimen tubes with protocol number, ACCRU patient ID number, and time and date blood drawn.

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

Mandatory	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 and submitted by participating site	After registration, but prior to treatment Cycle 1 Day 1	Cycle 1 Day 2	Cycle 1 Day3	At restaging after cycle 2, i.e. at time of PET scan/end of treatment	Additional processing required at site after blood draw?	Storage/ shipping conditions[1]
Mandatory	ACD (yellow)	10 ml (1)	Whole Blood	X			X	No	Refrigerate/c old pack (DO NOT FREEZE)
Mandatory	EDTA* (purple)	10 ml (1)	Whole Blood	X			X	No	Refrigerate/c old pack (DO NOT FREEZE)
Mandatory	EDTA* (purple)	10 ml (1)	Whole Blood	X	X	X	X	No	Refrigerate/c old pack (DO NOT FREEZE)
Mandatory	None (red)	10mL(1)	Whole Blood	X			X	No	Refrigerate/c old pack (DO NOT FREEZE)
Total (100 cc)				40 cc	10 cc	10 cc	40 cc		

[1] After all samples have been collected according to kit instructions, ship all specimens according to shipping instructions (see Section 14.25 for detailed shipping instructions.)

14.25 Shipping

14.251 Verify ALL sections of the Blood Specimen Submission Form (see Forms Packet), Mayo Medical Laboratories (BAP) Requisition Form (provided in kit), and specimen collection labels are completed and filled in correctly. Enter information from the Blood Specimen Submission

14.252 Specimens must be shipped the same day they are drawn.

14.253 Ship ACD, EDTA, and no additive (red top) whole blood tubes with a properly prepared cold pack. See kit instructions for specific details for cold pack preparation (i.e., frozen or refrigerated) and proper packing of blood and cold pack to avoid freezing of specimen.

14.254 Ship specimens via Priority Overnight service, **Monday – Thursday ONLY,** to Mayo Foundation, [redacted] **Do not collect or send samples the day before, the day of, or the observed day of a national holiday. Friday Shipments are allowed as long as the shipment is marked for Saturday delivery.**

14.255 The BAP kits will contain a smart shipper label (white barcoded label) affixed to the white colored shipping boxes. The smart shipper label is a pre-addressed return label, which replaces the need for an airbill. Shipping costs will be covered by ACCRU if this brown colored box is used for shipping specimens to Mayo Foundation [redacted]

14.3 Study Methodology and Storage Information

Collection tube description and/or additive (color of tube top)	Component Available	Minimal Residual Disease assessment (MRD)	Cell Surface Markers (Flow Cytometry)	DNA (SNPs)	RNA	Western blotting	Cytokines
ACD (yellow)	Mononuclear cells (from Ficoll)		X (preferred)	X	X	X	
EDTA (purple)	Plasma	X					X
EDTA (purple)	Buffy coat		X	X (preferred)		X	
None (red)	Serum						X
EDTA	Whole Blood	X					

14.31 Blood/blood product samples will be collected for protocol specific research. The following paragraphs offer descriptions of current assays being run on lymphoma trials. These may vary by protocol.

14.311 **Serum free light chains**: Serum will be processed from the red top tube and will be frozen, batched, and analyzed for serum free light chains in [redacted] research laboratory, [redacted] In a recent publication by Martin at all (Translational Research 149(4): 231 - 235, 2007) 36% of patients with mantle cell lymphoma had positive serology for serum free light chains. In this study we will assay for serum free light chains at on study and after two cycles of treatment. All samples will be evaluated with the Freelite serum free light chain assay (The Binding Site, Birmingham, UK). This is a commercial assay run routinely in [redacted] laboratory.

14.312 **Single nucleotide polymorphisms (SNPs) in host immune genes**: Buffy coat will be isolated in the Laboratory of [redacted] for future genomic DNA. We have previously demonstrated our

ability to analyze SNPs in patients with lymphoma. For example, Cerhan et al. (Blood 109: 5439 - 46) demonstrated that host gene SNP profiles could predict prognosis in follicular lymphoma. This information is not yet available for mantle cell lymphoma; therefore we will study that in this protocol. Genomic DNA samples will be batched and analyzed in the Mayo Clinic Cancer Center Genotyping Shared Resource.

14.313 **Vitamin D metabolites:** Serum from the red top tube will be cryopreserved and batched for 25 hydroxy vitamin D levels. These will be studied in the laboratory of Matthew T. E. Drake, M.D., Ph.D., Mayo Clinic Rochester, by liquid chromatography/tandem mass spectrometry. The rationale to study vitamin D in lymphoma comes from the finding that lymphoma is more common in climates with less sunshine. A recent study in the Journal of Clinical Oncology (26:2984 - 2991, 2008) demonstrated a significant improvement in overall survival in colon cancer patients with a higher level of vitamin D.

14.314 **Serum Cytokines**: Thirty cytokines, including pro-inflammatory, Th1 and Th2 associated cytokines, will be analyzed for each time point. The cytokines to be analyzed are IL-1β, IL-1RA, IL-2, IL-2R, IL-4, IL-5, IL-6, IL-7, IL-8, IL-10, IL-12p40/p70, IL-13, IL-15, IL-17, TNF-α, IFN-α, IFN-γ, GM-CSF, MIP-1α, MIP-1β, IP-10, MIG, Eotaxin, RANTES, MCP-1, VEGF, G-CSF, EGF, FGF-basic, and HGF. Assays will be run in triplicate according to the manufacturers' protocol. Data will be collected using the Luminex-100 system Version 1.7 (Luminex, Austin, TX) available in our lab at the research base. Data analysis will be performed using the MasterPlex QT 1.0 system (MiraiBio, Alameda, CA). A five-parameter regression formula will be used to calculate the sample concentrations from the standard curves and a change of 50% from the baseline value will be considered significant.

14.315 **Flow cytometry**: $1x10^6$ cells will be washed in phosphate-buffered saline (PBS) containing 0.5% bovine serum albumin (BSA), incubated with specific antibodies to the marker in question and analyzed on a FACSCalibur flow cytometry (Becton-Dickinson). Isotype controls will be done for each sample.

14.4 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

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)** – IND number 060100

The most current version of the Investigator Brochure will be maintained in the study folder on the ACCRU website. Updated Investigator's Brochures should be obtained from the study folder as they become available.

Each investigator should obtain a copy of the Investigator's Brochure prior to initiation of the study.

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.

The lenalidomide 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 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, it may cause birth defects or embryo-fetal death. 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, 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, nasopharyngitis, 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, cough, dyspnea, epistaxis, pharyngitis, pulmonary embolism, dry skin, pruritus, rash, and deep vein thrombosis.

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

Uncommon, limited to important or life-threatening (< 1%): hypersensitivity, Graft vs. Host Disease

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’s 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. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

Further information about the Revlimid REMS™ program is available at [redacted]

Outdated or remaining drug is to be destroyed on-site as per procedures in place at each institution.

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.

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

15.2 Rituximab (Rituxan®, C2B8)

Refer to the package insert for complete prescribing information.

15.21 **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.

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

15.23 **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.

15.24 **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).

15.25 **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
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

15.26 **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.

15.27 **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: Rash, pruritus, angioedema
Gastrointestinal: Nausea, diarrhea, abdominal pain, weight gain
Hematologic: Lymphopenia, anemia, leukopenia, neutropenia, neutropenic fever, thrombocytopenia
Hepatic: ALT increased
Neuromuscular & skeletal: Neuropathy, weakness, muscle spasm, arthralgia
Respiratory: Cough, rhinitis, epistaxis
Miscellaneous: Infection, night sweats, mild-to-moderate infusion-related reactions: Chills, fever, rigors, dizziness, hypertension, myalgia, nausea, pruritus, rash, and vomiting.

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Hypotension, peripheral edema, hypertension, flushing, edema
Central nervous system: Dizziness, anxiety, agitation, migraine
Dermatologic: Urticaria
Endocrine & metabolic: Hyperglycemia
Gastrointestinal: Vomiting, dyspepsia,
Neuromuscular & skeletal: Back pain, myalgia, paresthesia
Ocular: Conjunctivitis, lacrimation disorder
Respiratory: Dyspnea, throat irritation, bronchospasm, upper respiratory tract infection, sinusitis
Miscellaneous: LDH increased

Rare known potential toxicities, <1% (Postmarketing and/or case reports):
Acute renal failure (associated with tumor lysis syndrome), anaphylactoid reaction/anaphylaxis, angina, aplastic anemia, ARDS, arrhythmia, bowel obstruction, bronchiolitis obliterans, cardiac failure, cardiogenic shock, disease progression (Kaposi's sarcoma), fatal infusion-related reactions, gastrointestinal perforation, hemolytic anemia, hepatic failure, hepatitis, hepatitis B reactivation, hyperviscosity syndrome (in Waldenstrom's macroglobulinemia), hypoxia, interstitial pneumonitis, lichenoid

dermatitis, lupus-like syndrome, marrow hypoplasia, MI, neutropenia, optic neuritis, pancytopenia, paraneoplastic pemphigus, pleuritis, pneumonia, pneumonitis, polyarticular arthritis, pure red cell aplasia, renal toxicity, serum sickness, Stevens-Johnson syndrome, supraventricular arrhythmia, systemic vasculitis, toxic epidermal necrolysis, urticaria, 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

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

15.29 **Nursing Guidelines:**

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

15.292 Hypotension, bronchospasms, and angioedema have occurred in association with Rituxan infusion. Because of this it is recommended that patients be pre-medicated with acetaminophen and diphenhydramine before 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 are available for immediate use in the event of a hypersensitivity reaction during administration.

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

15.294 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.

15.295 It has been found that patients with bulky disease (lesion >10 cm in diameter) have an increased incidence of adverse events. Monitor for signs and symptoms of tumor lysis syndrome, and acute renal failure.

15.296 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.

15.297 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.

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

15.299 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.

15.299a 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.

15.299b There is the possibility of reactivation of Hepatitis B (HBV). Patients 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.

15.3 Ifosfamide

Refer to the package insert for complete prescribing information.

15.31 **Background**: Ifosfamide is an alkylating agent that prevents cell division by cross-linking DNA strands. It inhibits protein synthesis and DNA synthesis. Ifosfamide is a cell cycle phase nonspecific agent.

15.32 **Formulation**: Commercially available for injection as:
Injection, solution: 1 gram/20 mL (20 mL), 3 gram/60 mL (60 mL)
Injection, solution reconstituted, 1 gram, 3 gram

15.33 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature (either 20 to 25 ºC or 68 to 77 ºF). Injections are prepared by adding *Sterile Water for Injection, USP* or *Bacteriostatic Water for Injection, USP* (benzyl alcohol or parabens preserved), to the vial and shake to dissolve.

Dosage Strength	Quantity of Diluent	Final Concentration
1 gram	20 mL	50 mg/mL
3 grams	60 mL	50 mg/mL

Solutions of ifosfamide may be diluted further to achieve concentrations of 0.6 to 20 mg/mL in the following fluids: 5% Dextrose Injection, USP; 0.9% Sodium Chloride Injection, USP; Lactated Ringer's Injection, USP; Sterile Water for Injection, USP

Reconstituted solutions should be refrigerated and used within 24 hours. Further dilutions are stable for 24 hours refrigerated.

15.34 **Administration:** Refer to the treatment section for specific administration instructions. Administer IV over at least 30 minutes (infusion times vary by protocol; refer to specific protocol for infusion duration).

15.35 **Pharmacokinetic information**:
Distribution: V_d: approximates total body water; penetrates the CNS, but not in therapeutic levels
Protein binding: negligible
Metabolism: Hepatic to active metabolites ifosforamide mustard, 4-hydroxy-ifosfamide, acrolein, and inactive dichlorethylated and carboxy metabolites
Half-life elimination: High dose (5000 mg/m^2) ~ 15 hours; lower dose (1600-2400 mg/m^2) ~ 7 hours
Excretion: High dose (5000 mg/m^2) – urine (70-86%; 61% as unchanged drug); lower dose (1600-2400 mg/m^2) – urine (12-18% as unchanged drug)

15.36 **Potential Drug Interactions**:
Cytochrome P450 Effect: Substrate of CYP2B6 (major), 2C8 (minor), 2C9 (minor), 3A4 (minor); **Inhibits** CYP3A4 (weak); **Induces** CYP2C9 (weak/moderate)
Increased Effect/Toxicity: Ifosfamide may increase the levels/effects of: Aripiprazole, clozapine, dofetilide, lefunomide, lomitapide, natalizumab, pimozide, tofacitinib, vaccines (live), vitamin K antagonists; levels of ifosfamide may be increased by: Busulfan, CYP2B6 inhibitors (strong/moderate), CYP3A4 inhibitors (strong/moderate), dabrafenib, denosumab, dofetilide, trastuzumab
Decreased Effect: Ifosfamide may decrease the levels/effects of: BCG, Coccidiodin skin test, sipuleucel-T, vaccines (inactivated), vaccines (live); levels of ifosfamide may be decreased by CY2B6 inducers, CYP3A4 inducers, echinacea

15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, > 10%:
Central nervous system: CNS toxicity or encephalopathy
Dermatologic: Alopecia
Endocrine & metabolic: Metabolic acidosis
Gastrointestinal: Nausea and vomiting
Hematologic: Leukopenia (nadir 8-14 days), anemia, thrombocytopenia
Renal: Hematuria

Less common known potential toxicities, 1% - 10%:
Central nervous system: Fever
Gastrointestinal: Anorexia
Hematologic: Neutropenic fever
Hepatic: Bilirubin increased, liver dysfunction, transaminases increased
Local: Phlebitis
Renal: Renal impairment
Miscellaneous: Infection

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Acute respiratory distress syndrome, acute tubular necrosis, agranulocytosis, alkaline phosphatase increased, allergic reaction, alveolitis (allergic), amenorrhea, aminoaciduria, amnesia, anaphylactic reaction, angina, angioedema, anuria, arrhythmia, arthralgia, asterixis, atrial ectopy, atrial fibrillation/flutter, azoospermia, bladder irritation, bleeding, blurred vision, bone marrow failure, bradycardia, bradyphrenia, bronchospasm, bundle branch block, BUN increased, capillary leak syndrome, cardiac arrest, cardiogenic shock, cardiomyopathy, cardiotoxicity, catatonia, cecitis, chest pain, cholestasis, coagulopathy, colitis, conjunctivitis, creatinine clearance decreased/increased, creatinine increased, cylindruria, cytolytic hepatitis, delirium, delusion, dermatitis, diarrhea, DIC, DVT, dysesthesia, dyspnea, dysuria, echolalia, edema, ejection fraction decreased, enterocolitis, enuresis, enzymuria, erythema, extrapyramidal disorder, facial swelling, Fanconi syndrome, fatigue, gait disturbance, GGT increased, GI hemorrhage, glycosuria, gonadotropin increased, granulocytopenia, growth retardation (children), hemolytic anemia, hemolytic uremic syndrome, hemorrhagic cystitis, hepatic failure, hepatic sinusoidal obstruction syndrome (SOS; formerly veno-occlusive disease [VOD]), hepatitis fulminant, hepatitis (viral), hepatorenal syndrome, herpes zoster, hyperglycemia, hyper-/hypotension, hypersensitivity reactions, hypocalcemia, hypokalemia, hyponatremia, hypophosphatemia, hypoxia, ileus, immunosuppression, infertility, infusion site reactions (erythema, inflammation, pain, pruritus, swelling, tenderness), interstitial lung disease, jaundice, LDH increased, leukoencephalopathy, lymphopenia, malaise, mania, mental status change, methemoglobinemia, MI, mucosal inflammation/ulceration, multiorgan failure, mutism, myocardial hemorrhage, myocarditis, nephrogenic diabetes insipidus, neuralgia, neutropenia, oligospermia, oliguria, osteomalacia (adults), ovarian failure, ovulation disorder, palmar-plantar erythrodysesthesia syndrome, pancreatitis, pancytopenia, panic attack, paranoia, paresthesia, pericardial effusion, pericarditis, peripheral neuropathy, petechiae, phosphaturia, pleural effusion, *Pneumocystis jiroveci* pneumonia, pneumonia, pneumonitis, pollakiuria, polydipsia, polyneuropathy, polyuria, portal vein thrombosis, premature atrial contractions, premature menopause, progressive multifocal leukoencephalopathy, proteinuria, pruritus, pulmonary edema, pulmonary embolism, pulmonary fibrosis, pulmonary hypertension, QRS complex abnormal, radiation recall dermatitis, rash (including macular and papular), renal failure, renal parenchymal damage, renal tubular acidosis, respiratory failure, reversible posterior leukoencephalopathy syndrome (RPLS), rhabdomyolysis, rickets, salivation, secondary malignancy, seizure, sepsis, septic shock, SIADH, skin necrosis, spermatogenesis impaired, status epilepticus, sterility, Stevens-Johnson syndrome, stomatitis, ST segment abnormal, supraventricular extrasystoles, tachycardia, tinnitus, toxic epidermal necrolysis, tubulointerstitial nephritis, tumor lysis syndrome, T-wave inversion, uremia, urticaria, vasculitis, ventricular extrasystoles/fibrillation/tachycardia, ventricular failure, vertigo, visual impairment, wound healing impairment

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 Monitor CBC. Myelosupression is dose limiting. Instruct patient to report any signs/symptoms of infection, unusual bruising or bleeding to the health care team.

15.392 Nausea and vomiting are common. Premedicate with antiemetics as ordered and monitor for their effectivness. Provide for post administration antiemetics as ordered. Antiemetics with sedationg side effects should be avoided as these may mask potential CNS toxicities.

15.393 Inform patient about alopecia.

15.394 CNS toxicities are common. Document patients baseline neurological status. Re-assess neurological status throughout treatment. Instruct patient or family member to report any of the following, somnolence, lethagy, ataxia, disorientation, confusion, dizziness, depressive symptoms, or coma to the health care team immediately.

15.395 Ifosfamide can induce hemorrhagic cystitis, which is dose-limiting. Instruct patient to report any hematuria, dysuria or urinary frequency to the health care team immediately. It is important that Mesna always be used in conjunction with IFOS administration. Doses of Mesna should always be given on time. Oral mesna can be very nauseating. Provide for antiemetics when oral mesna is sent home with patient. Instruct patient that all doses must be taken in their entirety, and on time. If this is not possible due to nausea, patient must return to the clinic or the ER to have the missed dose and all subsequent doses administered IV.

15.396 Monitor renal function tests.

15.4 **Carboplatin (Paraplatin®, CBDCA)**

Refer to the package insert for complete prescribing information.

15.41 **Background**: Carboplatin is an alkylating agent which covalently binds to DNA; interferes with the function of DNA by producing intrerstrand DNA cross-links.

15.42 **Formulation**: Commercially available for injection as:
Solution Reconstituted: 150 mg.
Solution: 10 mg/mL (5 mL, 15 mL, 45 mL, 60 mL)

15.43 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature at 25ºC (77F); excursions permitted to 15ºC to 30ºC (59ºF to 86ºF). Protect from light. Further dilution to a concentration as low as 0.5 mg/mL is stable at room temperature (25ºC) for 8 hours in 0.9% NaCl or D5W.Stability has also been demonstrated for dilutions in D5W in PVC bags at room temperature for 8 days; , however, the manufacturer states to use within 8 hours due to lack of preservative.

15.44 **Administration:** Refer to the treatment section for specific administration instructions. When administered as a part of a combination chemotherapy regimen, sequence of administration may vary by regimen; refer to specific protocol for sequence recommendation. Needles or IV administration sets that contain aluminum should not be used in the preparation or administration of carboplatin; aluminum can react with carboplatin resulting in precipitate formation and loss of potency.

15.45 **Pharmacokinetic information**:
Distribution: $V_{d:}$ 16 L/kg; into liver, kidney, skin, and tumor tissue.
Protein binding: 0%; however the platinum from carboplatin becomes irreversibly bound to plasma proteins.
Metabolism: Minimally hepatic to aquated and hydroxylated compounds.
Half-life elimination:
CrCl > 60 mL/min: Carboplatin: 2.6-5.9 hours (based on dose of 300-500 mg/m^2); Platinum (from carboplatin): $\geq$ 5 days.
Excretion: Urine (~70% as carboplatin within 24 hours; 3% to 5% as platinum within 1-4 days).

15.46 **Potential Drug Interactions**:
Increased Effect/Toxicity: Aminoglycosides increase risk of ototoxicity and/or nephrotoxicity. When administered as sequential infusions, observational studies indicate a potential for increased toxicity when platinum derivatives (carboplatin, cisplatin) are administered before taxane derivatives (docetaxel, paclitaxel).
Herb/Nutraceutical Interactions: Avoid black cohosh, dong quai in estrogen-dependent tumors.

15.47 **Known potential adverse events:** Consult the package insert for the most current and complete information. Percentages reported with single-agent therapy. **Note**: Myelosuppression is dose related, schedule related, and infusion-rate dependent (increased incidences with higher doses, more frequent doses, and longer infusion times) and, in general, rapidly reversible upon discontinuation.

Common known potential toxicities, > 10%:
Central nervous system: Pain
Endocrine & metabolic: Hyponatremia, hypomagnesemia, hypocalcemia, hypokalemia
Gastrointestinal:Vomiting, abdominal pain, nausea
Hematologic: Myelosuppression (dose related and dose limiting; nadir at ~21 days; recovery by ~28 days), leukopenia, anemia, neutropenia, thrombocytopenia
Hepatic: Alkaline phosphatase increased, AST increasedHypersensitivity: Hypersensitivity
Neuromuscular & skeletal: Weakness
Renal: Creatinine clearance decreased, BUN increased

Less common known potential toxicities, 1% - 10%:
Central nervous system: Peripheral neuropathy, neurotoxicity

Dermatologic: Alopecia
Gastrointestinal: Constipation, diarrhea, stomatitis/mucositis, taste dysgeusia
Hematologic: Hemorrhagic/bleeding complications
Hepatic: Bilirubin increased
Infection: Infection
Local: Pain at the injection site
Neuromuscular & skeletal: Peripheral neuropathy
Ocular: Visual disturbance
Otic: Ototoxicity
Renal: Creatinine increased

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Anaphylaxis, anorexia, bronchospasm, cardiac failure, cerebrovascular accident, dehydration, embolism, erythema, febrile neutropenia, hemolytic anemia (acute), hemolytic uremic syndrome, hyper-/hypotension, injection site reaction (pain, redness, swelling), limb ischemia (acute), malaise, metastases, pruritus, skin rash, tissue necrosis (associated with extravasation), urticaria, vision loss

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

15.49 **Nursing guidelines:**

15.491 Monitor CBC and PLTs. Watch for profound neutropenia and give low count precautions and instructions as necessary. Nadir occurs at approximately day 21 with recovery at day 28-30. Thrombo-neutro-leukopenia may be cumulative. Thrombocytopenia can be dose-limiting and is more pronounced than with cisplatin. It can be more severe in patients with previous chemotherapy, concurrent radiation therapy, or patients with impaired renal function. Instruct patient to immediately report any unusual bruising or bleeding. Anemia (70-90% of patients) may be symptomatic with asthenia being the most common complaint. Instruct patient in energy saving lifestyle.

15.492 Assess baseline renal function (creatinine clearance). Reduced renal function can contribute to an increased risk of thrombocytopenia.

15.493 Monitor fluid status - encourage hydration.

15.494 Advise patient of probable taste alterations. Frequent oral hygiene is helpful. Instruct patient in appropriate interventions to achieve and maintain optimal nutritional status.

15.495 Older patients (>65) may experience some peripheral neuropathy with paresthesias. Instruct patients to report any tingling, burning, loss of sensation.

15.496 Mild nausea and vomiting occur in up to 94% of patients, 6-12 hours after treatment and may persist for 24 hours or longer. Diarrhea/cramping/constipation has been experienced by approximately 17%. Premedicate with antiemetics/antidiarrheals—evaluate effectiveness.

15.497 Administer following Taxol (in regimens that contain both drugs) to maximize cell kill.

15.498 Patients have experienced allergic reactions while receiving carboplatin. Watch for signs and symptoms of hypersensitivity reactions. If these occur, stop drug immediately, notify MD, and treat appropriately.

15.5 **Etoposide (VePesid®, Toposar®, VP16)**

Refer to the package insert for complete prescribing information.

15.51 **Background**: Etoposide has been shown to delay transit of cells through the S phase and arrest cells in late S or early G2 phase. The drug may inhibit mitochondrial transport at the NADH dehydrogenase level or inhibit uptake of nucleosides into HeLa cells. It is a topoisomerase II inhibitor and appears to cause DNA strand breaks. Etoposide does not inhibit microtubular assembly.

15.52 **Formulation**: Commercially available for injection as:
Injection, solution: 20 mg/mL (5 mL, 25 mL, 50 mL)

15.53 **Preparation, storage, and stability**: Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature of 25ºC (77ºF); do not freeze. Protect from light. Etoposide should be diluted to a concentration of 0.2-0.4 mg/mL in D5W or NS for administration. Diluted solutions have concentration-dependent stability; more concentrated solutions have shorter stability times. Precipitation may occur with concentrations > 0.4 mg/mL. Following dilution 0.9% Sodium Chloride or D5W to concentrations of 0.2-0.4 mg/mL, then drug is chemically stable for 96 and 24 hours at room temperature respectively.

15.54 **Administration:** Refer to the treatment section for specific administration instructions. Administer standard doses over at least 30-60 minutes to minimize the risk of hypotension.

15.55 **Pharmacokinetic information**:
Distribution: V_d: 7-171 L/m^2; poor penetration across the blood-brain barrier; CSF concentrations <5% of plasma concentrations
Protein binding: 94% to 98%
Metabolism: Hepatic via CYP3A4 and 3A5, to various metabolites.
Half-life elimination: Terminal 4-11 hours
Excretion: Urine (56%; 45% as unchanged drug) within 120 hours; feces (44%) within 120 hours

15.56 **Potential Drug Interactions**:
Metabolism/Transport Effects: Substrate of CYP1A2 (minor),

CYP2E1 (minor), CYP3A4 (major), P-glycoprotein; **Inhibits** CYP2C9 (weak), 3A4 (weak)
Ethanol/Herb/Nutraceutical Interactions: Avoid ethanol (may increase GI irritation). Avoid concurrent St John's wort; may decrease etoposide levels.

15.57 **Known potential adverse events:** Consult the package insert for the most current and complete information. **U.S. boxed warning: Severe dose-limiting and dose-related myelosuppression with resulting infection or bleeding may occur.**

Common known potential toxicities, > 10%:
Dermatologic: Alopecia
Gastrointestinal: Nausea/vomiting, anorexia, diarrhea
Hematologic: Leukopenia, thrombocytopenia, anemia

Less common known potential toxicities, 1% - 10%:
Cardiovascular: Hypotension
Gastrointestinal: Stomatitis, abdominal pain
Hepatic: Hepatic toxicity
Neuromuscular & skeletal: Peripheral neuropathy
Miscellaneous: Anaphylactic-like reaction

Rare known potential toxicities, <1% (Limited to important or life-threatening):
Amenorrhea, blindness (transient/cortical), cyanosis, extravasation, facial swelling, hypersensitivity, hypersensitivity-associated apnea, interstitial pneumonitis, laryngospasm, maculopapular rash, metabolic acidosis, MI, mucositis, myocardial ischemia, optic neuritis, perivasculitis, pruritus, pulmonary fibrosis, radiation-recall dermatitis, rash, reversible posterior leukoencephalopathy syndrome (RPLS), seizure, Stevens-Johnson syndrome, tongue swelling, toxic epidermal necrolysis, toxic megacolon, vasospasm

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

15.59 **Nursing Guidelines:**

15.591 Monitor CBC. Neutropenia may be severe. Instruct patients to report any sign/symptoms of infection to the health care team.

15.592 Rare myocardial infarctions have been reported in patients who have received prior mediastinal XRT. Instruct patient to report any chest pain, or racing of the pulse to the health care team immediately.

15.593 Advise patient of possible mild, reversible alopecia.

15.594 A rapid infusion may cause hypotension and/or allergic reaction; administer medication over 30-60 minutes and monitor VS during administration.

15.595 Drug is a radiosensitizer and irritant. Assess IV patency before and throughout infusion. Patients who have receive prior radiation may experience radiation recall. Assess skin in these areas and monitor closely. Instruct patient to report any rash or skin changes to the health care team immediately.

15.596 Anaphylaxis is rare but has been observed. Symptoms may include hypotension, bronchospasm, fever, or chills. Have the anaphylaxis tray available.

15.597 Nausea and vomiting are usually mild. However the incidence is increased with oral administration. Premedicate with antiemetics as ordered and monitor for their effectiveness.

15.598 Instruct patient in importance of maintaining adequate hydration to avoid hyperuricemia.

15.599a Monitor liver function tests.

15.599b VP16 solution is oil based and settles to bottom of bag or drip chamber. Be sure to agitate bag to avoid reaction to concentrated solution. Reaction would include flushing, shortness of breath, back pain, and anxiety.

15.599c Advise patient that facial flushing is common and may occur even after administration.

15.599d Monitor INR closely in patients on warfarin therapy, as VP-16 may increase PT time.

15.599e May increase the toxicity of methotrexate or cyclosporine (cytotoxicity) when given concurrently.

16.0 Statistical Considerations and Methodology

16.1 Overview: This is a phase I/II study designed to evaluate the safety and efficacy of the addition of lenalidomide to R-ICE (R2-ICE) for patients with first relapse or primary refractory diffuse large B-cell lymphoma. The phase I portion is designed to determine the maximally tolerated dose (MTD) and toxicity profile of lenalidomide in combination with R-ICE using the standard cohort 3+3 design. The phase II portion will utilize a one-stage design with an interim analysis to evaluate the overall response rate of R2-ICE.

16.11 Primary Endpoint:
The primary endpoint of the phase I portion of this trial is to assess the maximum tolerated dose (MTD) of the addition of lenalidomide to R-ICE. The primary endpoint in the phase II portion of this trial is the overall response rate after two cycles of treatment. A response will be defined as a CMR or PMR noted as the

objective status after two cycles of treatment. Throughout Section 16.0, response will be considered synonymous with "success", unless specified otherwise. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for overall response, with the exception of patients who are determined to be a major treatment violation.

16.12 Sample Size:
The phase I portion of this study is expected to require a minimum of 9 and a maximum of 12 evaluable patients. DLBCL patients treated at the MTD in the phase I portion will also be included in the phase II portion. Additional evaluable patients will be accrued at the MTD dose level for a total of 45 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 an additional 6 patients (2 phase I, 4 phase II) to account for ineligibility, cancellation, major treatment violation, or other reasons. Maximum projected accrual is 63 patients.

16.13 Accrual Rate and Study Duration:
The anticipated accrual rate is 4-5 evaluable patients per month. It is anticipated that 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 8 months. Once the phase II portion of the trial begins, we can expect to accrue the required patients in about 10-12 months. We can expect to begin final analysis approximately 1.25 years after beginning the phase II portion, i.e. as soon as the last patient accrued has completed the response evaluation after two cycles of treatment and data entry has been completed. The overall study duration is expected to be a maximum of 2 years.

Phase I Portion

16.2 Study Design: The phase I study is designed to determine the maximally tolerated dose (MTD) and toxicity profile of the addition of lenalidomide to R-ICE in patients with first-relapse or primary refractory diffuse large B-cell lymphoma using the standard cohort 3+3 design. Three patients will be treated at each dose level and observed for a minimum of three weeks (i.e. one full cycle) before new patients are treated. Doses will not be escalated in any individual patient.

16.21 MTD Definition: MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity (DLT) in at least one-third of patients (at least 2 of a maximum of 6 new patients). A total of 6 patients treated at the MTD will be sufficient to identify common toxicities at the MTD. For instance, those toxicities with an incidence of at least 25% will be observed with a probability of at least 82% ($1-(1-0.25)^6$).

Refer to Section 7.62 for definition of dose-limiting toxicity (DLT).

16.22 MTD Determination:

Dose Escalation: The phase I portion of this study will utilize a standard cohort of three design. The dose levels to which patients will be assigned in sequential

cohorts are described in Section 7.61. The first cohort of three patients will be treated at dose level 1. Decisions on when and how to dose escalate are described below.

16.221 Three patients will be treated at a given dose level combination and observed for one cycle (3 weeks) to assess toxicity.

16.222 If DLT is not seen in any of the 3 patients, 3 new patients will be accrued and treated at the next higher dose level. 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.

16.223 If 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 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.

16.224 After enrolling 6 patients on a specific dose level, if DLT is observed in at least 2 of 6 patients, 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.

16.225 Dose de-escalation: If dose-limiting toxicity meets the stopping boundaries set by the above dose escalation algorithm at dose level 1 (for example, more than 1 out of 3 patients or more than 1 out of 6 patients), the next cohort of three patients will be entered at a dose level of -1. If dose level -1 meets the stopping boundaries, the next cohort of three patients will be entered at dose level -2. Further dose re-escalation will depend on the toxicity profile observed at these dose levels, and re-evaluation of the regimen by the study team may be done.

16.226 If a patient fails to complete the first cycle of treatment for reasons other than toxicity, the patient will be regarded as inevaluable and will be replaced.

16.227 Operating Characteristics for standard cohort of 3 design: The following table gives the probability of dose escalation at a single dose level as a function of the true probability of DLT at that level using the cohorts of 3 design described above.

True Rate of DLT (%)	Probability of Dose Escalation
10	0.91
20	0.71
30	0.49
40	0.31
50	0.17

16.23 Analysis Plans: All the relevant results pertaining to toxicity, MTD, response, timed endpoints and laboratory correlates will be examined in an exploratory and hypothesis-generating fashion. The small sample size and the heterogeneous patient population associated with phase I studies restricts the generalizability of the results. Any notable statistical result should only be viewed as preliminary evidence for further study in Phase II trials rather than a definitive finding in and of itself.

16.231 Adverse Events Profile

The number and severity of all adverse events (overall and by dose-level) 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.

16.232 Toxicity Profile

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.

16.233 Response Profile

A response is defined to be a CMR or PMR noted as the objective status after 2 cycles of treatment. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response.

Responses will be summarized by simple descriptive summary statistics delineating complete and partial responses as well as no response and progressive disease in this patient population.

Phase II Portion

16.3 Statistical Design:

16.31 Decision Rule:

Based on recent data and prior randomized controlled trials in the salvage setting for this patient population, the estimated overall response rate for two cycles of R-ICE based on similar salvage chemotherapy is around 45% (Gisselbrecht, Glass et al. 2010; Kewalramani, Zelenetz et al. 2004; Gyan, Damotte et al. 2013; Stewart, Duan et al. 2011; Thieblemont, Briere et al. 2011; Vacirca, Acs et al. 2014; Crump et al., 2014). For the addition of lenalidomide to be clinically meaningful, our hypothesis is that the addition of lenalidomide in the relapse setting would increase the overall response rate by approximately 20%.

The largest success proportion where the proposed treatment strategy would be considered ineffective in this population is 45%. The smallest success proportion that would warrant subsequent studies with the proposed treatment strategy in this patient population is 65%. The following one-stage design with an interim analysis based on a Simon optimum design(Simon 1989) uses 20 or 45 patients to test the null hypothesis that the true success proportion in a given patient population is at most 45%.

16.311 Interim Analysis Decision Rule: Enter 20 patients into the study. If 9 or fewer successes are observed in the first 20 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. Otherwise, if the number of successes is at least 10, we will proceed with accrual.

16.312 Final Decision Rule: Enter an additional 25 patients into the study. If 24 or fewer successes are observed in the first 45 evaluable patients, we will consider this regimen ineffective in this patient population. If 25 or more successes are observed in the first 45 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this population.

16.313 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 are discussed in Section 16.44.

16.314 NOTE: The trial will not be halted while the first 20 patients are evaluated for the interim analysis. However, if the accrual is especially rapid, we may temporarily suspend accrual to prevent missing important acute toxicity patterns.

16.32 Power and Significance Level: Assuming that the number of responses is binomially distributed, with a significance level of 9%, the probability of declaring that the regimen warrants further studies (i.e., statistical power) and the probability of stopping after the interim analysis under various response proportions can be tabulated as a function of the true response proportion as shown in the table below.

If the true success proportion is…	0.45	0.50	0.55	0.60	0.65
Then the probability of declaring that the regimen is promising and warrants further study is…	0.090	0.249	0.491	0.735	0.900
And the probability of stopping after the interim analysis is…	0.591	0.412	0.249	0.128	0.053

16.33 Other Considerations: Toxicity, 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: The analysis for this trial will commence at planned time points (see 16.3) and at the time the patients have become evaluable for the primary endpoint. Such a decision will be made by the Statistician and Study Chair, in accord with CCS Standard Operating Procedures, availability of data for secondary endpoints (eg, laboratory correlates), and the level of data maturity. It is anticipated that the earliest date in which the results will be made available via manuscript, abstract, or presentation format is when the last patient has been followed for at least 2 months.

16.41 Primary Endpoint:

16.411 Definition: The primary endpoint of this trial is the overall response rate after two cycles of treatment. A response will be defined as a CMR or PMR noted as the objective status after two cycles of treatment. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for overall response, with the exception of patients who are determined to be a major treatment violation.

16.412 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients.

Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner (Duffy and Santner 1987).

16.42 Secondary Endpoints:

16.421 **Overall proportion of patients (%) proceeding to stem cell transplant.** Definition: The percentage of patients proceeding to stem cell transplant will be estimated by the number of patients who proceed to transplant divided by the total number of evaluable patients. Exact

binomial 95% confidence intervals for the true success proportion will be calculated.

16.422 **Complete metabolic response (CMR) rate:** The CMR rate will be estimated by the number of patients with an objective status of CMR 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 CMR rate will be calculated.

16.423 **Overall survival (OS)**: 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.

16.424 **Percentage of Adverse Events (%) categorized based on severity using CTCAE system/organ/class criteria 4.0**. Definition: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rate(s). 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 event(s) to the study treatment will be taken into consideration. The frequency and percentage of patients experiencing a particular grade/severity of adverse event would be aggregated and combined data reported.

16.43 Correlative Analyses:

16.431 **Association of histologic subtype as assessed by pathology and its association with the primary endpoint of the study.** Definition: Histologic subtype (GCB vs.ABC vs. unclassified) from tumor tissue at the start of the study will be evaluated by 2 methods: Hans algorithm by IHC and gene expression profiling using nanostring technology. For each method, the relationship between overall response (responder vs. non-responder) CR rate and subtype will be evaluated using Chi-square tests (or Fisher's exact test if the data in the contingency table is sparse).

16.432 **Association of SUV reduction (%) noted on interim PET/CT scan with the primary endpoint of the study.** Definition: This will be evaluated by calculating the percentage (%) SUV reduction noted on interim PET/CT scan and correlated with the overall response (responder vs. non-responder) by using a two sample t-test .

16.433 **Association of anatomic size reduction (%) noted on interim PET/CT scan with the primary endpoint of the study.** Definition: This would be evaluated by calculating the percentage (%) anatomic size reduction noted on interim PET/CT scan and correlated with the overall response (responder vs. non-responder) by using a two sample t-test.

16.434 **Association of Minimum Residual Disease (MRD) detection in blood with the primary endpoint of the study.** Definition: Minimum residual disease (MRD) detection (positive versus negative as per Sequenta, Inc ® technology) in blood will be evaluated in all patients at baseline and after 2 cycles of treatment. The correlation of MRD detection (positive

vs. negative) with overall response will be evaluated using Chi-square tests (or Fisher's exact test if the data in the contingency table is sparse).

16.435 **Association of Minimum Residual Disease (MRD) blood level with the primary endpoint of the study.** Definition: Minimum residual disease (MRD) blood level (measured as per million leucocytes as per Sequenta, Inc.® technology) will be evaluated in all patients at baseline and after 2 cycles of treatment. The correlation of MRD quantification (per million leucocytes as per Sequenta, Inc.®) with overall response (responder vs. non-responder) will be evaluated using two sample t-tests.

16.436 **Storage of serum samples for future research.** Description: Serum samples will be collected and stored for future and ongoing research. Some of the initial work for which this would be utilized would include but not limited to studying the serum free light chains (FLC), serum free DNA and the minimal residual disease (MRD). These measures will be summarized descriptively using medians and ranges (continuous measures) or frequencies (categorical measures).

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 every quarter 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 Rule: The stopping rules specified below are based on the knowledge available at study development. We note that the 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 treatments 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 if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as "possible," "probable," or "definite") that satisfy any of the following:

Phase I (Includes all dose levels in phase I): By the nature of the "cohorts of three" phase I study design, toxicity (i.e., adverse events that are possibly, probably or definitely related to study treatment) stopping

rules are in place for each dose level. Specifically, if 2 or more dose-limiting toxicities (DLTs) are observed during cycle 1 at any given dose level, accrual to that dose level will be stopped, and patients will be accrued to the next lower dose level until a maximum of 6 patients are treated at the lower level. Note that a DLT that affects dose escalation is only that which is observed in the first cycle of treatment. However, all cycles will be reviewed and the study team will determine whether the dose level needs to be adjusted for future patients if ≥1 in the first 3 patients OR ≥ 2 in the first 6 patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment over all cycles at any given dose level

Phase II (includes all phase II patients, including Phase I patients treated at the MTD):

- if 5 or more patients in the first 15 treated patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment, excluding febrile neutropenia and dehydration.

- if after the first 15 patients have been treated, 30% of all patients experience a grade 4 or higher non-hematologic adverse event at least possibly related to treatment, excluding febrile neutropenia and dehydration.

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 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the "ClincialTrails.gov" website. The Primary and Secondary Endpoints along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 2 years after the study opens to accrual. The definition of "Primary Endpoint Completion Date" (PECD) for this study is at the time the last patient registered has completed the response evaluation after two cycles of treatment.

16.6 Inclusion of Women and Minorities

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

16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race or gender, 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.

16.63 The geographical region served by ACCRU, has a population which includes approximately 5-7% minorities. Based on prior ACCRU studies involving similar disease sites, we expect about 5-7% 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:

Accrual Targets			
Ethnic Category	**Sex/Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	1	1
Not Hispanic or Latino	25	37	62
Ethnic Category: Total of all subjects	25	38	63
Racial Category			
American Indian or Alaskan Native	0	0	0
Asian	0	1	1
Black or African American	1	1	2
Native Hawaiian or other Pacific Islander	0	0	0
White	24	36	60
Racial Category: Total of all subjects	25	38	63

Ethnic Categories:

Hispanic or Latino – a person of Cuban, Mexican, Puerto Rican, 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

17.11 Summary Table of Tissue Biospecimens for This Protocol

Type of tissue biospecimen to submit	**Mandatory or optional**	**When to submit**	**Reason for submission (background/methodology section)**	**Where to find specific details for biospecimen submission**
All H&E diagnostic slides	Mandatory	Within 30 days after registration	Pathology Central review	See Section 17.2
CD20 stained slide	Mandatory		Pathology Central review	See Section 17.2
Formalin-fixed paraffin-embedded (FFPE) tissue block or (15) 4µm unstained slides with (1) corresponding H&E stained slide	Mandatory	Within 30 days after registration	Correlative Studies (Section 17.5)	Section See section 17.3

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

17.2 All Diagnostic Slides for Confirmation of Diagnosis (**Mandatory**)

17.21 The following materials below are mandatory (unless indicated otherwise) and required for shipment:

- Diagnostic H&E Stained Slides from Most Recent Tumor Tissue Biopsy
- CD20 stained slide
- Lymphoma Pathology Reporting Form
- Surgical Pathology Report
- Tumor Tissue Immunochemistry or Immunophenotyping by Flow Cytometry Report (if available)
- Pre-study Bone Marrow Biopsy Report (if available)
- Pre-study Peripheral Blood Immunophenotyping by Flow Cytometry Report (if available)

Note: Include the ACCRU patient ID number on all materials listed above.

17.22 The diagnostic slide(s) must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials.

17.23 Verify that Section 1 of the Lymphoma Pathology Reporting Form is completed and filled in correctly.

17.24 Review is being performed at the ACCRU Research Base at Mayo Clinic Rochester. Ship all diagnostic slides and accompanying materials as follows:

17.251 Mayo Clinic Rochester (MCR) patients only: please forward pathology material to [redacted] or review.

17.252 For all memberships, including MCJ and MCA, ship all specimens and accompanying materials to the ACCRU Research Base:

[redacted]

17.253 The ACCRU Operations Office will forward the diagnostic slides to Dr. [redacted] for central review to confirm diagnosis of MCL.

17.3 Paraffin Embedded Tissue Blocks/Slides (Mandatory research tissue)

17.31 Submit one formalin fixed paraffin-embedded (FFPE) tumor tissue block from the most recent tumor tissue biopsy. **A corresponding H&E slide from the submitted block must be provided** to permit quality assessment (QA) of the tissue block. Once the QA is completed, the H&E slide will be returned, unless specified otherwise in section 17.29.

17.32 The FFPE tissue block is preferred; however, **if an institution is unable to provide a tissue block**, cut (15) 4-micron sections and mount sections on charged glass slides. **Label the slides with ACCRU patient ID number, accession number, and order of sections (i.e., 1-11)**. **(1) four micron slide for the H&E stain the first cut slide (i.e., slide labeled 1).** This slide will be reviewed centrally under the research base's protocol for assessing tissue quality. **Do not bake or place covers slips on the slides.**

17.33 The following materials below are required (unless indicated otherwise) for shipment:

- Paraffin Embedded Tissue Blocks with Corresponding H&E Slide (or 15 Unstained Slides with Corresponding H&E Slide)
- Research Tissue Submission Form
- Surgical Pathology Report
- Operative Report *(optional)*

Note: Please include the ACCRU patient ID number on all materials listed above.

17.34 The block/slides/cores must be appropriately packed to prevent damage (e.g., slides should be placed in appropriate slide container) and placed in an individual plastic bag. Label the bag with the protocol number, ACCRU patient ID number, and patient initials.

17.35 Tissue specimens must be shipped ≤30 days after registration.

17.36 Verify that the appropriate sections of the Tissue Specimen Submission Form are completed and filled in correctly. Enter information from the Tissue Specimen Submission Form into the remote data entry system on the same day the specimen is submitted (see Forms Packet).

17.37 Ship all block/slide tissue specimens and accompanying materials to the ACCRU Research Base:

[redacted]

17.38 If corresponding H&E slide was not submitted with the tissue specimen, the ACCRU Operations Office will request a slide to be processed (i.e., cut and H&E stained) from the tumor tissue block. Processing will be performed in the Pathology Research Core (PRC), Mayo Clinic Rochester.

17.39a The ACCRU Operations Office will forward the blocks and/or H&E slide(s) to [redacted] and colleagues to be reviewed under the research base's protocol for assessing tissue quality for the proposed correlative studies.

17.39b After the pathologist assesses the tissue quality, the block and appropriate paperwork will be returned to the ACCRU Operations Office.

17.4 Frozen Tumor Tissue (None)

17.5 Study Methodology and Storage Information

Submitted tissue samples will be handled as follows in the appropriate laboratories in the Department of Laboratory Medicine and Pathology, Mayo Clinic Rochester, at the direction of [redacted]

17.51 **Fluorescence in situ hybridization (FISH):** Probes for protocol-specific markers will be analyzed on the tissue block or tissue microarray.

17.52 **Immunohistochemical stains**: Samples will be stained for protocol-specific markers.

17.53 **Proliferation rate:** The primary tumor tissue will be stained with Ki-67 or Mib-1 to assess the proliferative rate where applicable.

17.54 Remaining tumor tissue will be banked for future research according to the patient consent permission. Tissue blocks and/or slides will be stored in the ACCRU Central Operations Office (Attn: Pathology Coordinator). 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. As protocols are developed, they will be presented for ACCRU and IRB review and approval. (This collection is part of a general strategy of investigation for ACCRU hematology studies.)

17.55 The institutional pathologist will be notified by the ACCRU Operations Office (Pathology Coordinator) if the block may be depleted.

17.56 Blocks requested to accommodate individual patient management will be returned promptly upon request after slides or cores are cut.

17.6 Return of Genetic Testing Research Results

Because the results generated by the genetic testing included in this section are not currently anticipated to have clinical relevance to the patient or their family members, the genetic results will not be disclosed to the patients or their physicians.

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 Timetables

Initial Material(s)

CRF	**Active-Monitoring Phase** (Compliance with Test Schedule Section 4.0)
On-Study	≤2 weeks after registration
Adverse Event – Baseline	
Measurement - Baseline	
CT/PET/MRI Scan Report[1]	
Pathology Reporting Lymphoma (see Section 17.2)	
Research Blood Submission- Baseline (see Section 14.0)	
Research Tissue Submission (see Section 17.3)	
PET/CT Scan CD Submission (see Appendix III)	≤ 30 days after registration
End of Active Treatment/Cancel Notification Form	Submit ≤2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy

1. Submit copy to the ACCRU Ops Office, Attn. QAS for RU051417I.

Central Pathology Review Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)
Pathology Materials (this is for central review, eligibility, etc.)[1]	Submit ≤30 days after registration (see Section 17.2*)*

1. After the central review has been completed, forward a copy of the completed Pathology Reporting Form to the QAS for documentation. Send to: ACCRU Ops Office, Attn. QAS for RU051417I.

Test Schedule Material(s)

CRF	Active-Monitoring Phase (Compliance with Test Schedule Section 4.0)	
	At each evaluation during treatment	At end of treatment
Evaluation/Treatment	X	X
Nadir/Adverse Event	X	X
Measurement	X[1]	X[1]
Research Blood Submission	X (see Section 14.0)	
CT/PET/ Scan Report[1]	X (see Appendix III)	
PET/CT Scan CD Submission[3]	X (see Appendix III)	
End of Active Treatment/Cancel Notification		X
ADR/AER	At each occurrence (see Section 10.0)	
Deviation Form[2]	X	X

1. Submit copy of documentation of response or progression to the [redacted]
2. Submit only if applicable.
3. Cycle 2, Day 21

Follow-up Material(s)

CRF	Event Monitoring Phase[1]				
	q. 3 months until PMD[2]	At PMD[2]	After PMD q. 6 mos.	Death	New Primary
Event Monitoring	X	X	X	X	At each occurrence
Transplant and Engraftment Data Form[3]	Collect when applicable				

1. If a patient is still alive 5 years after registration, no further follow-up is required.
2. **Submit copy of documentation of response or progression to the** [redacted]
3. Complete this form one time after the treating physician has decided whether or not the patient will receive transplant.

19.0 Budget

19.1 Each site should review the test schedule (Section 4.0), taking into account local and regional coverage policies, to determine which items are standard of care and which are research at their site. Refer to the payment synopsis for funding provided per accrual for covering study costs, as well as any additional invoiceables that may be allowed.

19.2 Tests to be research funded:

19.21 Mandatory blood samples for research.

19.3 Celgene will provide Lenalidomide (Revlimid®) 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 REMSprogram.

20.0 References

Bellas, C., D. Garcia, et al. (2014). "Immunohistochemical and molecular characteristics with prognostic significance in diffuse large B-cell lymphoma." PloS one 9(6): e98169.

Cheson BD, Horning SJ, Coiffier B, et al. Report of an International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas. J Clin Oncol 1999;17:1244-53.

Cheson BD, Fisher RI, Barrington SF, et al. Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. J Clin Oncol 2014;32:3059-68.

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD, Specht L, Horning SJ, Coiffier B, Fisher RI, Hagenbeek A, Zucca E, Rosen ST, Stroobants S, Lister TA, Hoppe RT, Dreyling M, Tobinai K, Vose JM, Connors JM, Federico M, Diehl V; International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol. 2007 Feb 10;25(5):579-86.

Crump M, Kuruvilla J, Couban S, et al. Randomized comparison of gemcitabine, dexamethasone, and cisplatin versus dexamethasone, cytarabine, and cisplatin chemotherapy before autologous stem-cell transplantation for relapsed and refractory aggressive lymphomas: NCIC-CTG LY.12. J Clin Oncol. 2014 Nov 1;32(31):3490-6. Epub 2014 Sep 29. PubMed PMID: 25267740.

Duffy D, Santner T. Confidence intervals for a binomial parameter based on multistage tests. Biometrics 1987;43: 81-93.

Feldman, T., A. R. Mato, et al. (2014). "Addition of lenalidomide to rituximab, ifosfamide, carboplatin, etoposide (RICER) in first-relapse/primary refractory diffuse large B-cell lymphoma." British journal of haematology 166(1): 77-83.

Gisselbrecht, C., B. Glass, et al. (2010). "Salvage regimens with autologous transplantation for relapsed large B-cell lymphoma in the rituximab era." Journal of clinical oncology : official journal of the American Society of Clinical Oncology 28(27): 4184-4190.

Gyan, E., D. Damotte, et al. (2013). "High response rate and acceptable toxicity of a combination of rituximab, vinorelbine, ifosfamide, mitoxantrone and prednisone for the treatment of diffuse large B-cell lymphoma in first relapse: results of the R-NIMP GOELAMS study." British journal of haematology 162(2): 240-249.

Hans, C. P., D. D. Weisenburger, et al. (2004). "Confirmation of the molecular classification of diffuse large B-cell lymphoma by immunohistochemistry using a tissue microarray." Blood 103(1): 275-282.

Haslett, P. A., W. A. Hanekom, et al. (2003). "Thalidomide and a thalidomide analogue drug costimulate virus-specific CD8+ T cells in vitro." The Journal of infectious diseases 187(6): 946-955.

Hernandez-Ilizaliturri, F. J., G. Deeb, et al. (2011). "Higher response to lenalidomide in relapsed/refractory diffuse large B-cell lymphoma in nongerminal center B-cell-like than in germinal center B-cell-like phenotype." Cancer 117(22): 5058-5066.

Kewalramani, T., A. D. Zelenetz, et al. (2004). "Rituximab and ICE as second-line therapy before autologous stem cell transplantation for relapsed or primary refractory diffuse large B-cell lymphoma." Blood 103(10): 3684-3688.

List, A., S. Kurtin, et al. (2005). "Efficacy of lenalidomide in myelodysplastic syndromes." The New England journal of medicine 352(6): 549-557.

Lund JL, Ostgard LS, Prandoni P*, et al.* Incidence, determinants and the transient impact of cancer treatments on venous thromboembolism risk among lymphoma patients in Denmark. Thrombosis research 2015;136(5):917-23.

Nowakowski, G. S., B. LaPlant, et al. (2011). "Lenalidomide can be safely combined with R-CHOP (R2CHOP) in the initial chemotherapy for aggressive B-cell lymphomas: phase I study." Leukemia 25(12): 1877-1881.

Nowakowski GS, LaPlant B, Macon WR*, et al.* Lenalidomide combined with R-CHOP overcomes negative prognostic impact of non-germinal center B-cell phenotype in newly diagnosed diffuse large B-Cell lymphoma: a phase II study. J Clin Oncol 2015;33(3):251-7.

Pellagatti, A., M. Jadersten, et al. (2007). "Lenalidomide inhibits the malignant clone and up-regulates the SPARC gene mapping to the commonly deleted region in 5q- syndrome patients." Proceedings of the National Academy of Sciences of the United States of America 104(27): 11406-11411.

Petterson TM, Marks RS, Ashrani AA, et al. Risk of site-specific cancer in incident venous thromboembolism: a population-based study. Thrombosis research 2015;135(3):472-8.

Pocock S, Simon J. Sequential treatment assignment with balancing for prognostic factors in the controlled clinical trial. . Biometrics 1975;31:103-115.

Rajkumar, S. V., S. R. Hayman, et al. (2005). "Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma." Blood 106(13): 4050-4053.

Richardson, P. G., R. L. Schlossman, et al. (2002). "Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma." Blood 100(9): 3063-3067.

Rubinstein LV, Korn EL, Freidlin B, Hunsberger S, Ivy SP, Smith MA. Design issues of randomized phase II trials and a proposal for phase II screening trials. Journal of clinical oncology : official journal of the American Society of Clinical Oncology. 2005;23(28):7199-7206. Prepublished on 2005/09/30 as DOI 10.1200/JCO.2005.01.149.

Simon, R. Optimal two-stage designs for phase II clinical trials. Controlled clinical trials 1989;10(1): 1-10.

Stewart, D. A., Q. Duan, et al. (2011). "A prospective phase II study of RICE re-induction, then high-dose fludarabine and busulfan, followed by autologous or allogeneic blood stem cell transplantation for indolent b-cell lymphoma." Clinical lymphoma, myeloma & leukemia 11(6): 475-482.

Thieblemont, C., J. Briere, et al. (2011). "The germinal center/activated B-cell subclassification has a prognostic impact for response to salvage therapy in relapsed/refractory diffuse large B-cell lymphoma: a bio-CORAL study." Journal of clinical oncology : official journal of the American Society of Clinical Oncology 29(31): 4079-4087.

Vacirca, J. L., P. I. Acs, et al. (2014). "Bendamustine combined with rituximab for patients with relapsed or refractory diffuse large B cell lymphoma." Annals of hematology 93(3): 403-409.

Zhang, H., V. Vakil, et al. (2005). "Circulating endothelial progenitor cells in multiple myeloma: implications and significance." Blood 105(8): 3286-3294.

ACCRU Informed Consent Template for Cancer Treatment Trials (English Language)

***NOTES FOR LOCAL INVESTIGATORS:** **[NOTE: Retain this section and asterisk item below for ACCRU model consents]**

- The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is [redacted]
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
- Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer…What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at [redacted] to request a free copy.
- Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

Phase I/II, Open-Label Study of R-ICE (Rituximab-Ifosfamide-Carboplatin-Etoposide) with Lenalidomide (R2-ICE) in Patients with First-Relapse/Primary Refractory Diffuse Large B-Cell Lymphoma (DLBCL)

This is an important form. Please read it carefully. It tells you what you need to know about this research study. If you agree to take part in this study, you need to sign this form. Your signature means that you have been told about the study and what the risks are. Your signature on this form also means that you want to take part in this study.

This is a clinical trial, a type of research study. Your study doctor will explain the clinical trial to you. Clinical trials include only people who choose to take part. Please take your time to make your decision about taking part. You may discuss your decision with your friends and family. You can also discuss it with your health care team. If you have any questions, you can ask your study doctor for more explanation.

You are being asked to take part in this research study because you have diffuse large B-cell lymphoma that has come back even though you have already received treatment.

Why is this research study being done?

The purpose of this study is to find out what effects, good and/or bad, the addition of lenalidomide to standard chemotherapy (R-ICE) has on you and your cancer. The combination of Lenalidomide with standard chemotherapy is also referred to as R2-ICE.

How many people will take part in the research study?

At the beginning of the study, up to 12 patients will be treated with standard chemotherapy (R-ICE) plus increasing doses of Lenalidomide, to find the highest dose that does not cause unacceptable side effects. This is referred to as the Maximum Tolerated Dose (or MTD). Once that dose is found, up to 51 additional patients will be enrolled in the study. A total of 63 patients are the most that would be able to enter the study.

What will happen if I take part in this research study?

Before you begin the study …

In order to participate in this study you must register into and follow the requirements of the REVLIMID REMS™ program of Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. You will be required to receive counseling every 28 days during treatment with lenalidomide, follow the pregnancy testing (as required by your risk category) and birth control requirements of the program that are appropriate for you and take telephone surveys regarding your compliance with the program.
[Note to Informed Consent Authors: the above paragraph must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

In addition, you will need to have the following exams, tests or procedures to find out if you can be in the study. These exams, tests or procedures are part of regular cancer care and may be done even if you do not join the study. If you have had some of them recently, they may not need to be repeated. This will be up to your study doctor.

Within 1 to 3 weeks before study registration

- **Physical exam** (including height and weight)
- **Performance status:** Your doctor will ask you a series of questions to measure how well you are able to perform ordinary tasks and carry out activities in your daily life.
- **Routine blood tests**
- **Research blood tests –** when you have the routine blood test done, we will also take between 2 teaspoons and 4 tablespoons of additional blood for research and banking for future research. Giving this extra blood is required if you participate in this study.
- **PET-CT scan** to see where the cancer is located and measure any palpable lymph nodes.
- **Pregnancy test** (only for women able to have children)

During the study…

If the exams, tests and procedures show that you can be in the study, and you choose to take part, then you will need the following tests and procedures. They are part of regular cancer care.

- Routine blood tests and physical exam
- PET-CT scan to see where the cancer is located.

You will need these tests and procedures that are part of regular cancer care. They are being done more often because you are in this study.

- Routine blood tests and physical exams (including height and weight)
- Pregnancy test (only for women able to have children)

You will need these tests and procedures that are either being tested in this study or being done to see how the study is affecting your body.

- Research blood sample (between 2 teaspoons and 4 tablespoons). This is required if you decide to participate in this study.
- Review of your previously done tumor biopsy to confirm tumor type and perform research tests on the tumor tissue

Some of the research blood sample will be used for genetic testing. Because the genetic tests in this study are not used for regular medical care, you will not be told the results of the test(s). The test results will not be put in your medical record either.

If it is not known if you have Human Immunodeficiency Virus (HIV) or hepatitis B, you will need to have a blood test done. If your HIV or hepatitis B test result is positive, you will need to have a second test done to make sure the findings are the same. The researcher will tell you how to find medical help and counseling as needed, and you may not be able to take part in the study. Your health insurer or you will have to pay for the cost of the repeat test, any follow-up medical care, or counseling.

If the HIV or hepatitis B test result is positive, it is the state law that they be reported to the State Department of Health. The tests results will also be put in your medical record.

Female patients should not donate blood during treatment and for at least 28 days after taking lenalidomide.

Male patients should not donate blood, semen or sperm during treatment or for at least 28 days after taking

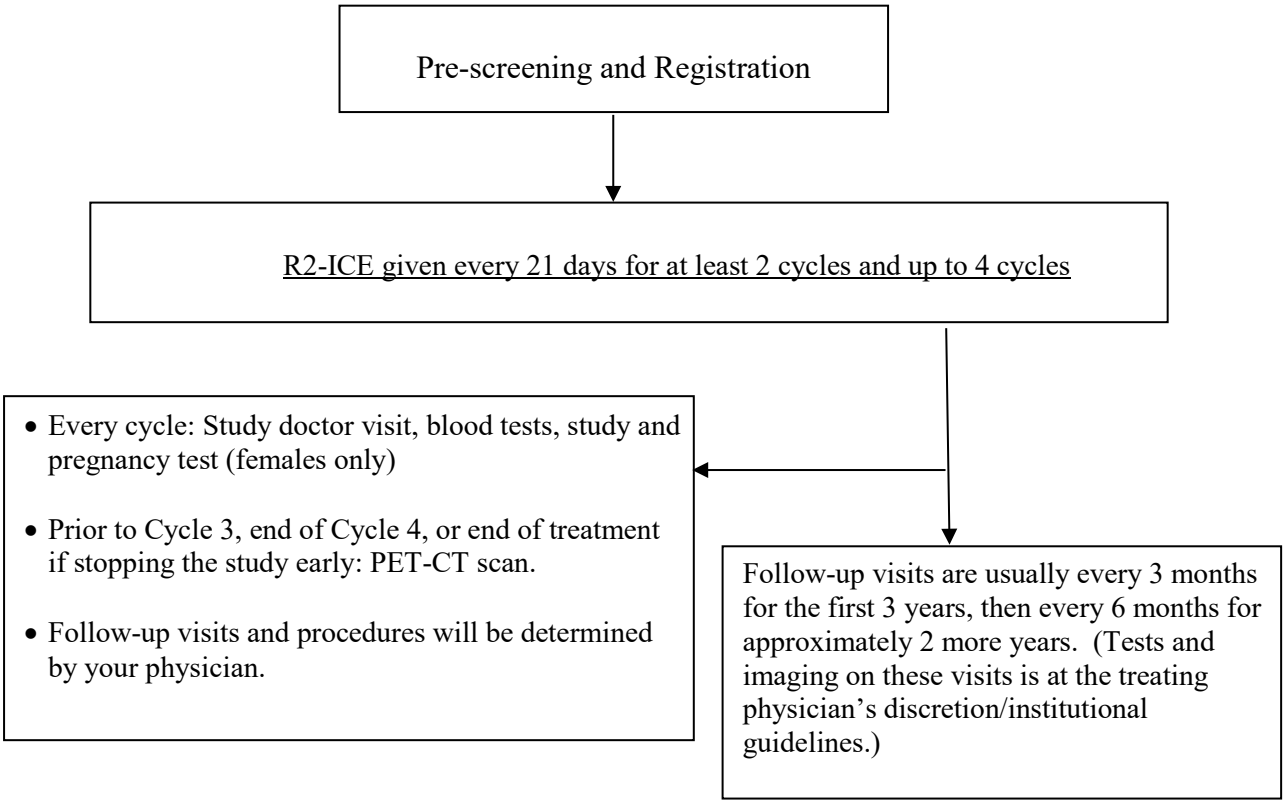
lenalidomide.

When you are finished taking R2-ICE, the following tests are required:

- **Physical exam** (including height and weight)
- **Performance status:** Your doctor will ask you a series of questions to measure how well you are able to perform ordinary tasks and carry out activities in your daily life.
- **Routine blood tests**
- **Research blood tests –** when you have the routine blood test done, we will also take between 2 teaspoons and 4 tablespoons of additional blood for research and banking for future research. Giving this extra blood is required if you participate in this study.
- **PET-CT scan** to see where the cancer is located and measure any palpable lymph nodes.
- **Pregnancy test** (only for women able to have children)

Study Plan

You will receive R2-ICE every 21 days in this study. This 21-day period of time is called a cycle. This cycle will be repeated once, for a total of 2 cycles. Four of the medications (R-ICE) are given in the vein (IV) usually in the hospital (inpatient). The second "R" (Revlimid ® or Lenalidomide) is a pill that is taken along with the other chemotherapy for 1-2 weeks. Scans will be obtained before considering the possibility of a transplant. If your doctor determines that you are benefitting from the treatment (that your disease is not getting worse and you are not having bad side effects), you may receive an additional 1 or 2 cycles of treatment. The chart below gives a simple picture of how the study will proceed. Start reading at the top and read down the list, following the lines and arrows.



How long will I be in the research study?

You will be asked to take R2-ICE for 2 cycles, and possibly 1-2 additional cycles. After you are finished taking R2-ICE, the study doctor will ask you to visit the office for follow-up exams every 3 months for about 3 years or until your disease gets worse, then every 6 months until your disease gets worse. The total length of time for the study, including follow-up visits, is approximately 5 years from the day you are enrolled.

Can I stop being in the research study?

Yes. You can decide to stop at any time. Tell the study doctor if you are thinking about stopping or decide to stop. He or she will tell you how to stop safely.

It is important to tell the study doctor if you are thinking about stopping so any risks from the R2-ICE can be evaluated by your doctor. Another reason to tell your doctor that you are thinking about stopping is to discuss what follow-up care and testing could be most helpful for you.
The study doctor may stop you from taking part in this study at any time if he/she believes it is in your best interest; if you do not follow the study rules; or if the study is stopped.

What side effects or risks can I expect from being in the research study?

You may have side effects while on the study. Everyone taking part in the study will be watched carefully for any side effects. However, doctors don't know all the side effects that may happen. Side effects may be mild or very serious. Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking the study treatment. In some cases, side effects can be serious, long lasting, or may never go away. **There also is a risk of death.**

You should talk to your study doctor about any side effects that you have while taking part in the study.

Risks and side effects related to <u>Lenalidomide</u> include those which are:

<u>Likely</u> <u>(greater than 20% chance that any of these may happen)</u>:

Side effects considered serious are in **bold.*

- **Fatigue or feeling tired**
- **Neutropenia** or a decrease in white blood cells that can make you more prone to infections
- **Thrombocytopenia** or a decrease in platelets which can cause you to bruise or bleed easily and/or may require platelet transfusion
- Constipation or difficulty moving your bowels
- Diarrhea or loose/frequent bowel movements
- Abnormalities of liver tests

<u>Less likely</u> <u>(less than 20% chance that any of these may happen)</u>:

- **Anemia** or a decrease in red blood cells that can cause tiredness which may require red blood cell transfusion
- Nausea
- Loss of appetite
- **Back pain**
- Joint pain

- Muscle cramps
- Swelling of the arms and legs
- Problems falling asleep or staying asleep
- **Fever**
- Cough
- **Shortness of breath** or difficulty catching your breath
- Upper respiratory infection
- Rash
- Itching and dry skin
- Lack or loss of strength
- Dizziness
- Headache
- Abnormal thyroid function or inflammation of thyroid gland
- Abdominal pain and or distension
- Gastrointestinal bleeding
- Bowel obstruction
- Infections involving various organs
- Allergic reaction to drug
- Abnormalities of mineral levels in blood
- Heartburn
- Muscle pain

Serious (occurring in 1% or more of patients and not listed in bold above):

- Neutropenia associated with a fever
- Pulmonary embolism or blood clot in or around the lungs
- Deep vein thrombosis or blood clots in a larger blood vessel
- Atrial fibrillation or irregular heartbeat
- Progression of the disease being studied
- Pneumonia or an infection of the lungs
- Sepsis or an infection of the blood
- Dehydration
- Kidney failure which can cause increases or decreases in the amounts of chemicals in your blood which can cause irregular heartbeats, muscle twitching, seizures, and/or death.
- Myocardial infarction (heart attack)
- Stroke (bleeding in the brain or clotting)

Rare cases of the following events have been reported:

- Angioedema- an allergic skin disease characterized by patches of swelling involving the skin and/or the lining of your nose, mouth, and gastrointestinal tract.
- Anaphylaxis- serious potentially life-threatening type of allergic reaction that may cause breathing difficulty, dizziness, low blood pressure, and loss of consciousness.
- Stevens-Johnson syndrome and toxic epidermal necrolysis- serious allergic skin reactions that begin as a rash in one area and later cover more of the body leading to detachment of the top layer of skin (could be body-wide). Medical journals have reported patients with allergic skin reaction with thalidomide who also developed the same type of reaction with lenalidomide
- Tumor lysis syndrome- metabolic complication that can occur during or without treatment of cancer. These complications are caused by the break-down products of dying cancer cells and include

hyperkalemia (high potassium), hyperphosphatemia (high phosphorus), hyperuricemia and hyperuricosuria (high uric acid in blood and urine), hypocalcemia (low calcium), and consequent acute uric acid nephropathy and acute renal failure (kidney damage).

- Tumor Flare reaction- a condition that involves any of the following increase in the size of the cancerous lymph nodes, rash and slight fever.
- Rhabdomyolysis- a serious condition involving the destruction of skeletal muscle that can lead to kidney failure. Signs and symptoms include dark, red, or cola colored urine and muscle tenderness, stiffness, aching (myalgia) or weakness.
- Increase in blood levels of lipase due to inflammation of pancreas gland.
- Abnormalities of blood clotting
- Bone marrow failure
- Decrease in lymphocytes (type of white blood cells)
- Enlarged spleen
- Abnormal heart rhythms
- congestive heart failure (condition where the heart becomes weak and cannot pump enough blood to the rest of the body
- Decreased function of adrenal gland
- Decreased hearing
- Vision abnormalities
- Clotting in blood vessels of intestines
- Seizures
- Graft-versus-host disease (when transplanted donor tissue attacks the tissues of the recipient's body

Also Reported on Lenalidomide Trials But with the Relationship to Lenalidomide Still Undetermined:

- Tissue swelling (angioedema)
- Rhabdomyolysis (breakdown of muscle fibers). This occurs when muscle cells die and release cell contents into the blood stream. It can cause muscle pain and a number of health problems, including damage to the kidneys. If severe, this could be life threatening.

These events have the potential to be fatal.

Your health care team may give you medicines to help lessen side effects. Many side effects go away soon after you stop taking study drug. In some cases, side effects can be serious, long lasting or may never go away.

You should talk to your study doctor about any side effects that you have while taking part in the study.

Hematologic Toxicity

Lenalidomide is associated with significant neutropenia (decrease in white blood cells that help fight infection) and thrombocytopenia (decrease in platelets that help with blood clotting). You will have your blood counts checked frequently when starting treatment with lenalidomide.

Deep Vein Thrombosis and Pulmonary Embolism

Lenalidomide has demonstrated an increased risk of deep vein thrombosis (DVT, blood clot in a larger blood vessel) and pulmonary embolism (PE, a blood clot in or around the lungs) in some people with certain medical conditions. The study staff will ask you about any risk factors you may have. [If you have a history of blood clots your doctor will prescribe either an injectable blood thinner (low molecular weight heparin)or Coumadin (blood

thinner pill) for the first four months of the study treatment. The doctor may continue to prescribe the medication or aspirin for the remainder of your course of study treatment. All other patients will receive (at the discretion of the treating physician) either oral low–dose aspirin or another treatment to prevent blood clotting during study participation.] Patients unable or unwilling to undergo treatment for prevention of blood clots will not be eligible to

participate in this study. You will be instructed on the signs and symptoms of DVT and PE and if symptoms occur you should contact your study doctor promptly.

Second new cancers

According to researchers, patients with cancer have a higher risk of developing a second new cancer when compared to people without cancer. In clinical studies of newly diagnosed multiple myeloma, a higher number of second cancers were reported in patients treated with induction therapy (treatment as first step to reducing number of cancer cells) and/or bone marrow transplant then lenalidomide for a long period of time compared to patients treated with induction therapy and/or bone marrow transplant then placebo (a capsule containing no lenalidomide). Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers.

Other Risks

If any physician other than the study doctor prescribes medication for you for another condition or you are taking any over-the-counter medications or vitamins, you must inform the study staff. <u>This is important because the interaction of some medications may cause serious side effects.</u>

Lenalidomide has been shown to increase the level of digoxin in the blood in some patients; please tell your doctor if you are taking digoxin.

Your condition may not get better or may become worse while you are in this study.

Risks Associated with Pregnancy

Lenalidomide is related to thalidomide. Thalidomide is a known to cause severe life-threatening human birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the offspring of female monkeys who received the drug during pregnancy. If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females must not become pregnant while taking lenalidomide. You have been informed that the risk of birth defects is unknown. If you are female, you agree not to become pregnant while taking lenalidomide.

Lenalidomide is detected in very small quantities in human semen according to a study for up to three days after stopping the drug. For patients who may not be able to get rid of the drug, such as people with kidney problems, lenalidomide may be present for more than three days. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time. For these reasons male patients receiving lenalidomide must use a latex condom while taking lenalidomide, when temporarily stopping lenalidomide, and for 28 days after permanently stopping lenalidomide treatment during any sexual contact with a pregnant female or a female of child bearing potential even if you have undergone a successful vasectomy.

You have been informed of the risk of birth defects. If you are female, you agree not to become pregnant while taking lenalidomide. For this reason, lenalidomide is provided to patients under a special distribution program called REVLIMID REMS™.

[Note to Informed Consent Authors: the above paragraph must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

You should not donate blood during treatment or for 28 days after the treatment is completed.

You must **NEVER** share lenalidomide with anyone else.

Risks and Side-Effects Associated with Rituximab, Ifosfamide, Carboplatin, and Etoposide (R-ICE):

The components of R-ICE are approved for various types of cancer. R-ICE is commonly used to treat your disease. Your study doctor will explain the risks associated with R-ICE therapy, each of its components and any pre-medication and post-medication given to decrease the risk of side effects.

In addition to the individual side effects of each R-ICE components (included below), your risk of certain side effects may be further increased because of the combination.

Particularly with ICE treatment, many people have a temporary drop in the number of blood cells made by the bone marrow:

- ICE will reduce the number of white blood cells, which can lead to increased risk of getting an infection or feeling ill;
- ICE can decrease the production of red blood cells, which may make you feel tired or breathless;
- ICE can reduce the production of platelets, which helps the blood to clot and stops bleeding. Bruising may occur more easily.

Other common side effects of ICE are:

- Nausea, vomiting, stomatitis or irritation of the stomach lining, loss of appetite, altered taste, diarrhea, fatigue, weakness, fever, alopecia or hair loss, decreased kidney function, blood in the urine, liver dysfunction, phlebitis or inflammation of the vein, back pain, abdominal pain, blue or purple discoloration of the skin, increased sweating, voice changes, neuropathy or numbness/tingling in fingers and toes, tinnitus (ringing in the ears), and hearing loss.
- A drop in blood pressure can happen if etoposide is given quickly.
- Anaphylactic-like reactions characterized by chills fever, irregular heart rate, difficulty breathing, and shortness of breath may be experienced.

- This drug may have a harmful effect on a developing baby, it is important that you use adequate birth control while participating in this study.
- Short term confusion and somnolence (sleepiness) is an uncommon side effect of ifosfamide.

The potential to increase the severity of side effects or cause new side effects by adding lenalidomide is unknown.

As with any medication, allergic reaction is a possibility.

Risks and Side Effects of Ifosfamide (Ifex®) include those which are:

Likely *(events occurring greater than 20% of the time)*:

- Decrease in blood counts leading to an increased risk of infection
- Hair loss
- Vomiting, nausea
- Anemia which may cause tiredness, or may require blood transfusions
- Bruising, bleeding

Less likely *(events occurring less than or equal to 20% of the time)*:

- Loss of energy, confusion and drowsiness
- Drowsiness (sleepiness)
- Weakness, fatigue
- Dizziness, loss of balance
- Bladder irritation resulting in painful urination and blood in urine (hemorrhagic cystitis)
- Decreased kidney function
- Fever
- Diarrhea, constipation
- Mouth sores
- Loss of taste
- Numbness and tingling in fingers and toes
- Electrolyte abnormality, dehydration (low potassium, low sodium, low magnesium, low calcium)
- Skin redness/rash

Rare but serious *(events occurring less than 2-3% of the time)*:

- Life threatening infections, especially when white blood cell count is low
- Damage to the liver (Bilirubin increased, liver dysfunction, transaminases increased)
- Severe damage to lungs (Acute respiratory distress syndrome)
- Allergic reaction
- Heart rhythm abnormalities (atrial ectopy, atrial fibrillation/flutter, bundle branch block)
- Tendency to form blood clots
- Low or high blood pressure
- Heart failure/heart damage (cardiac arrest, cardiogenic shock, cardiomyopathy, cardiotoxicity)
- Vision abnormalities
- Decreased wound healing

Risks and Side Effects of Carboplatin (Paraplatin®, CBDCA) include those which are:

Likely *(events occurring greater than 20% of the time)*:

- Hair loss
- Vomiting, nausea
- Decrease in blood counts leading to an increased risk of infection
- Anemia which may cause tiredness, or may require blood transfusions
- Low platelet count – this may make you bruise more easily and bleed longer if injured
- Belly pain
- Weakness, fatigue
- Loss of appetite and weight loss

Less likely *(events occurring less than or equal to 20% of the time)*:

- Diarrhea, constipation, abdominal pain
- Numbness and tingling in fingers and toes
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Pain at the injection site
- Skin redness/rash
- Change in kidney function (decreased creatinine clearance)
- Changes in taste

- Damage to organs which may cause hearing and balance problems
- Dizziness

Rare but serious *(events occurring less than 2-3% of the time)*:
- Allergic reactions (Red flushed skin and itching on palms and feet, immediate nausea and/or swelling or tingling in the mouth or throat)
- Irritation and damage to skin and tissue at injection site if drug leaked from the vein
- Changes in vision
- Mouth sores
- Life threatening infections, especially when white blood cell count is low
- Tendency to form blood clots
- Low or high blood pressure
- Heart failure

Risks and Side Effects of Etoposide (VePesid®, Toposar®, VP16) include those which are:

Likely *(events occurring greater than 20% of the time)*:
- Hair loss
- Decrease in blood counts leading to an increased risk of infection
- Anemia which may cause tiredness, or may require blood transfusions
- Bruising, bleeding
- Flushed face

Less likely *(events occurring less than or equal to 20% of the time)*:
- Low blood pressure
- Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat
- Vomiting, nausea
- Loss of appetite
- Mouth sores
- Belly pain
- Numbness and tingling in fingers and toes (neuropathy)

Rare but serious *(events occurring less than 2-3% of the time)*:
- Life threatening infections, especially when white blood cell count is low
- Severe allergic reactions associated with a skin rash (may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat and skin desquamation – Stevens Johnson Syndrome)
- Damage to the heart (Myocardial infarction/ischemia)
- Damage to the lungs (interstitial pneumonitis)
- Blue or purple discoloration of the skin (vasospasm)
- A drop in blood pressure can happen if etoposide is given quickly

For more information about risks and side effects, ask your study doctor.

Are there benefits to taking part in the research study?

Taking part in this study may or may not make your health better. While doctors hope R2-ICE will be more useful against cancer compared to the usual treatment, there is no proof of this yet. We do know that the information from

this study will help doctors learn more about R2-ICE as a treatment for cancer. This information could help future cancer patients.

What other choices do I have if I do not take part in this research study?

You do not have to be in this study to receive treatment for your cancer. Your other choices may include:

- Getting treatment or care for your cancer without being in a study
- Taking part in another study
- Getting no treatment

Talk to your doctor about your choices before you decide if you will take part in this study.

Will my medical information be kept private?

We will do our best to make sure that the personal information in your medical record will be kept private. However, we cannot guarantee total privacy. Your personal information may be given out if required by law. If information from this study is published or presented at scientific meetings, your name and other personal information will not be used.

Organizations that may look at and/or copy your medical records for research, quality assurance, and data analysis include:

- Academic and Community Cancer Research United (ACCRU)
- Celgene (provider of Lenalidomide)
- The local IRB
- Government agencies, like the Food and Drug Administration (FDA), involved in keeping research safe for people

In order to obtain lenalidomide free of charge from Celgene, your name, address, phone, date of birth and the fact that you are participating in this trial will be disclosed to Celgene and its agents or vendors that supply lenalidomide and administer the REVLIMID REMS™ program. By signing this consent form you agree to this disclosure.

A description of this clinical trial will be available on [redacted] as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of study results. You can search this Web site at any time.

[Note to Informed Consent Authors: the above paragraph complies with the new FDA regulation found at 21 CFR 50.25(c) and must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

What are the costs of taking part in this research study?

You and/or your health plan/ insurance company will need to pay for some or all of the costs of treating your cancer in this study. Some health plans will not pay these costs for people taking part in studies. Check with your health

plan or insurance company to find out what they will pay for. Taking part in this study may or may not cost your insurance company more than the cost of getting regular cancer treatment. You may be responsible for co-payments and deductibles that are typical for your insurance coverage.

You will NOT have to pay for the following:

- Lenalidomide.
- Extra blood work being done (research blood tests), to better understand how R2-ICE is working.

You WILL have to pay for:

- All doctor's visits, including physical exams and medical histories
- Routine blood test to check your health
- All standard imaging done while on the study (CT scans, PET scans, ECG, etc.)

You will not be paid for taking part in this study.

For more information on clinical trials and insurance coverage, you can visit the National Cancer Institute's Web site at [redacted]. You can print a copy of the "Clinical Trials and Insurance Coverage" information from this Web site.

Another way to get the information is to call 1-800-4-CANCER (1-800-422-6237) and ask them to send you a free copy.

What happens if I am injured because I took part in this research study?

It is important that you tell your study doctor, _____ *[investigator's name(s)],* if you feel that you have been injured because of taking part in this study. You can tell the doctor in person or call him/her at _____ *[telephone number].*

You will get medical treatment if you are injured as a result of taking part in this study. You and/or your health plan will be charged for this treatment. The study will not pay for medical treatment.

What are my rights if I take part in this research study?

Taking part in this study is your choice. You may choose either to take part or not to take part in the study. If you decide to take part in this study, you may leave the study at any time. No matter what decision you make, there will be no penalty to you and you will not lose any of your regular benefits. Leaving the study will not affect your medical care. You can still get your medical care from our institution.

We will tell you about new information or changes in the study that may affect your health or your willingness to continue in the study.

In the case of injury resulting from this study, you do not lose any of your legal rights to seek payment by signing this form.

Who can answer my questions about the research study?

You can talk to your study doctor about any questions or concerns you have about this study. Contact your study doctor _____ *[name(s)]* at _____ *[telephone number]*.

For questions about your rights while taking part in this study, call the _____ *[name of center]* Institutional Review Board (a group of people who review the research to protect your rights) at _____ *(telephone number).* *[Note to Local Investigator: Contact information for patient representatives or other individuals in a local institution who are not on the IRB or research team but take calls regarding clinical trial questions can be listed here.]*

About Using Biological Samples for Research

For this study, we will be collecting between 2 teaspoons to 4 tablespoons of blood for future research, at each draw. This is a mandatory blood draw. This study also has laboratory tests that will be performed to study small samples of blood and biopsy tissue. The blood will be taken after registration, but just before treatment starts on the first day of the first cycle, Days 2 and 3 of cycle 1, at the end of cycle 2, and/or at the end of treatment if discontinued early, and/or if your disease gets worse. It will be drawn at the same time as your usual blood work, which is needed for treatment.

The biopsy tissue sample will be from your *original* biopsy. *No additional biopsies will be done to get this tissue.*

You are required to provide blood and tissue samples in order to take part in the treatment portion of this study.

The blood and tissue samples will be sent to laboratories at Mayo Clinic in Rochester, MN, associated with ACCRU, where the tests will be done. These tests will be done in order to understand how your cancer responds to treatment. It is hoped that this will help investigators better understand your type of cancer. The results of these tests will not be sent to you or your study doctor and will not be used in planning your care. These tests are for research purposes only and you will not have to pay for them.

We would like to keep some of the leftover blood and tissue for future research. If you agree, this blood and/or tissue will be kept and may be used in research to learn more about cancer and other diseases. Please read the online booklet called "Providing Your Tissue for Research: What You Need To Know," to learn more about tissue research: [redacted]

Your blood and tissue may be helpful for research whether you do or do not have cancer. The research that may be done with your blood and/or tissue is not designed specifically to help you. It might help people who have cancer and other diseases in the future.

Reports about research done with your blood and/or tissue will not be given to you or your doctor. These reports will not be put in your health record. The research will not have an effect on your care.

Things to Think About

The choice to let us keep the leftover blood and/or tissue for *future* research is up to you. No matter what you decide to do, it will not affect your care.

If you decide now that your blood and tissue can be kept for research, you can change your mind at any time. Just contact us and let us know that you do not want us to use your tissue. Then any blood and tissue that remains will no longer be used for research.

In the future, people who do research may need to know more about your health. While ACCRU may give them reports about your health, it will not give them your name, address, phone number, or any other information that will let the researchers know who you are.

Sometimes blood and tissue is used for genetic research (about diseases that are passed on in families). Even if your blood and tissue is used for this kind of research, the results will not be put in your health records.

Your blood and/or tissue will be used only for research and will not be sold. The research done with your blood and/or tissue may help to develop new products in the future.

Benefits

The benefits of research using blood and/or tissue include learning more about what causes cancer and other diseases, how to prevent them, and how to treat them.

Risks

The greatest risk to you is the release of information from your health records. We will do our best to make sure that your personal information will be kept private. The chance that this information will be given to someone else is very small.

Making Your Choice

Please read each sentence below and think about your choice. After reading each sentence, circle "Yes" or "No". If you have any questions, please talk to your doctor or nurse, or call our research review board at the IRB's phone number.

No matter what you decide to do, it will not affect your care.

1. My sample(s) may be kept for use in *future* research to learn about, prevent, or treat cancer.

☐ Yes ☐ No Please initial here: _____ Date: _____

2. My sample(s) may be kept for use in *future* research to learn about, prevent or treat other health problems (for example: diabetes, Alzheimer's disease, or heart disease).

☐ Yes ☐ No Please initial here: _____ Date: _____

If you want your sample(s) destroyed at any time, write to the Secretary of the _____ Institutional Review Board _____.
ACCRU has the right to end storage of the sample(s) without telling you.

Please read the following statements and mark your choice:

I permit ACCRU to give my sample(s) to outside researchers:

☐ Yes ☐ No Please initial here:_____ Date:_____

Where can I get more information?

You may call the National Cancer Institute's Cancer Information Service at:

[redacted]

You will get a copy of this form. If you want more information about this study, ask your study doctor.

Signature

I have been given a copy of all _____ *[insert total of number of pages]* pages of this form. I have read it or it has been read to me. I understand the information and have had my questions answered.

I understand I will be registered into the REVLIMID REMS™ program, and agree to receive counseling and to comply with the pregnancy precaution requirements of the REVLIMID REMS™ program.
[Note to Informed Consent Authors: the above paragraph must be included verbatim in all informed consent documents. The text in this paragraph cannot be revised.]

I agree to take part in this study.

Printed Participant Name: _____

Participant Signature: _____

Date: _____

Printed name of person obtaining informed consent:

_____

Signature of person obtaining informed consent:

_____

Date _____

This model informed consent form has been reviewed by the ACCRU and is the official consent document for this study. Local IRB changes to this document are allowed. Sections "What are the risks of the research study" or "What other choices do I have if I don't take part in this research study?" should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they may be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the Academic and Community Cancer Research United (ACCRU) Operations Office for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

Image Submission Process

PET/CT scans should be performed in accordance with the test schedule in Section 4.0 to assess for response. PET/CT scans done at baseline should be submitted within 30 days of enrollment. Similarly PET/CT scans done at the time of response evaluation after 2 cycles should also be submitted within 30 days of response assessment.

Scans should be submitted on CD, accompanied by a radiographic report and sent to the following:

Submit the reports AND radiographic images free of marks that may obscure the lesions or bias the evaluation of the independent reviewer(s). Radiographic images must be deidentified and labelled with the ACCRU study number of RU051417I and the assigned ACCRU patient identification number. Radiographic images must include the date the image was performed and the corresponding time point in the study (see Section 4.0).

PATIENT MEDICATION DIARY

Instructions

- Please indicate on the calendar below *every* day that you take your study medication by placing the dose taken on the line under the date.
- If you miss a dose, place a "**0**" under the date, but remember to take your prescribed dose at the next regularly scheduled time.
- Bring ***all*** bottles and any unused study medication along with this diary when you return for your next appointment.

Medication(s)	**Dose**
Lenalidomide	TBD
Aspirin	81 mg

Study Drug	**Day 1**	**Day 2**	**Day 3**	**Day 4**	**Day 5**	**Day 6**	**Day 7**
Date							
Lenalidomide							
Aspirin							
Comments							

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

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

Date:_____ Participant's Signature_____

Area Below Only To Be Completed only by Coordinator

Number of pills returned_____ Study Coordinator Initials_____

Date_____ Discrepancy Yes____ No_____