March 25, 2018

Martha Kruhm, MS RAC
Head, Protocol and Information Office
Quality Assurance Section
CTEP, DCT, NCI
6130 Executive Blvd, EPN Room 7000
Bethesda, MD 20892

Dear Ms. Kruhm:

Enclosed is Addendum #9 to E1412 *Randomized Phase II Open Label Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma)*. This addendum is in response to the request for rapid amendment from Dr. Howard Streicher on May 11, 2018.

The following revisions to the E1412 protocol have been made in this addendum:

	Section	Change
1.	Cover Page	Updated Version Date.
2.	5.2.1	Inserted NOTE acknowledging migration to CTCAE v5.0.
3.	5.2.5	Revised chart to reference CTCAE v5.0.
4.	5.2.8	Revised chart to reference CTCAE v5.0.
5.	5.3	Updated the CAEPR for lenalidomide to Version 2.7, March 14, 2018.
6.	Appendix XII	Revised "Reporting a Pregnancy Loss" and "Reporting a Neonatal Death" per revised CTCAE v5.0.

The following revisions to the E1412 Informed Consent Document have been made in this addendum:

	Section	Change
1.	Page 1	Updated Version Date.
2.	"Risks and side effects related to the lenalidomide include those which are"	Updated the risk list for lenalidomide to Version 2.7, March 14, 2018.

If you have any questions regarding this addendum, please contact Colin Burnett at cburnett@ecog-acrin.org or (857) 504-2900.

We request review and approval of this addendum to E1412 so ECOG-ACRIN may activate it promptly.

Thank you.

Sincerely,

Pamela Cogliano

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Protocol Development Manager

Enclosure

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ECOG-ACRIN cancer research group
Reshaping the future of patient care

E1412

Randomized Phase II Open Label Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

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LYMPHOMA COMMITTEE CHAIR: Brad S. Kahl M.D.

Version Date: May 25, 2018
NCI Update Date: August 27, 2013

Rev. 6/14

STUDY PARTICIPANTS

ALLIANCE / Alliance for Clinical Trials in Oncology
NRG / NRG Oncology
SWOG / SWOG

ACTIVATION DATE

August 27, 2013

PRE-ACTIVATION DATE

June 14, 2013
Addendum #1 Prior to Activation
Update #1 – 8/13
Addendum #2 – 1/14
Addendum #3 – 6/14
Addendum #4 – 10/14
Addendum #5 – 1/15
Addendum #6 – 10/15
Addendum #7 – 7/16
Addendum #8 – 1/17
Addendum #9

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Agents	IND#	NSC#	Supply
Lenalidomide		703813	NCI CTEP
Rituximab		687451	Commercial
Cyclophosphamide		26271	Commercial
Doxorubicin		123127	Commercial
Vincristine		67574	Commercial
Prednisone		10023	Commercial

Table of Contents

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Rev. 6/14

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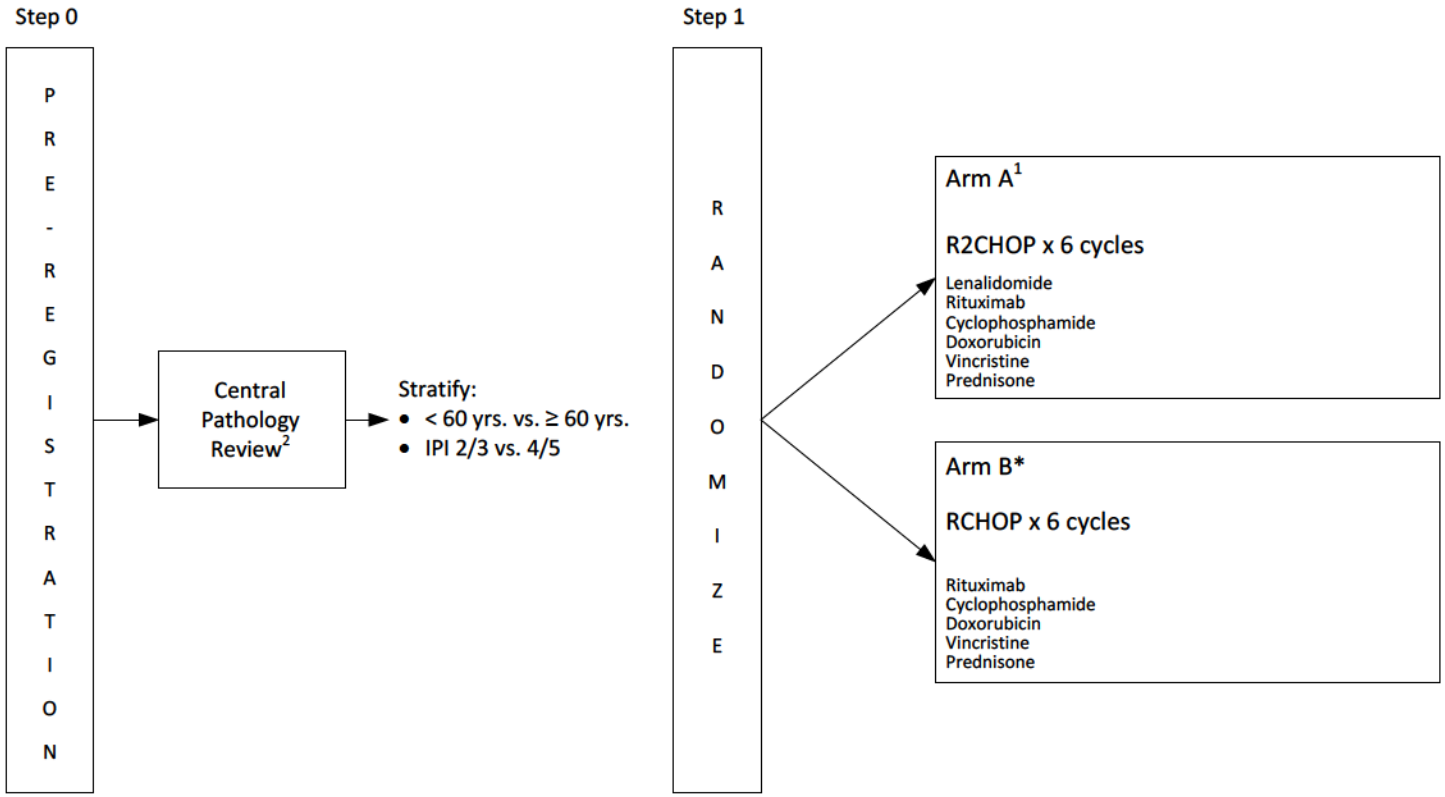
Rev. 1/14, 6/14 CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION

To submit site registration documents:	**For patient enrollments:**	**Submit study data**
CTSU Regulatory Office 1818 Market Street, Suite 1100 Philadelphia, PA 19103 Phone – 1-866-651-CTSU Fax – 215-569-0206 Email: CTSURegulatory@ctsu.coccg.org (for submitting regulatory documents only)	Please refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN) which can be accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org. Contact the CTSU Help Desk with any OPEN-related questions at ctsucontact@westat.com	Data collection for this study will be done exclusively through Medidata Rave. Please see the data submission section of the protocol for further instructions. Do not submit study data or forms to the CTSU Data Operations. Do not copy the CTSU on data submission.
The most current version of the **study protocol and all supporting documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org. Access to the CTSU members' website is managed through the Cancer Therapy and Evaluation Program - Identity and Access Management (CTEP-IAM) registration system and requires user log on with CTEP-IAM username and password.		
For clinical questions (i.e. patient eligibility or treatment-related) contact the Study PI of the Lead Protocol Organization.		
For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.		
For detailed information on the regulatory and monitoring procedures for CTSU sites please review the CTSU Regulatory and Monitoring Procedures policy located on the CTSU members' website https://www.ctsu.org > education and resources tab > CTSU Operations Information >CTSU Regulatory and Monitoring Policy.		
The CTSU Web site is located at https://www.ctsu.org		

Schema



Cycle = 21 days

Accrual = 345

1. See Section 5.1 for drug administration and schedule.
2. Eligibility determination based on central pathology review for confirmation of diagnosis and adequacy of tissue for mandatory assessments. See Section 11 for submission details.

1. Introduction

1.1 Diffuse Large B-cell Lymphoma (DLBCL)

Diffuse large B-cell lymphoma (DLBCL) is the most common lymphoid neoplasm accounting for approximately 30% of NHL.[2] The median age at the diagnosis is 64 years and the majority of patients present with advanced disease. DLBCL is a heterogeneous disorder with 2 major molecular subtypes identified by gene expression profiling (GEP): 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 calcification algorithms. The ABC (non-GCB subtype) has been associated with worse outcome in pre- and post- rituximab era.

1.2 Current treatment of DLBCL

Anthracycline-containing combination chemotherapy remains the standard of care for the initial therapy of patients with advanced DLBCL [3, 4]. Prior to the advent of rituximab, a number of dose intensified cytotoxic therapies were introduced but these regimens failed to provide substantial improvement over the standard anthracycline based combination of cyclophosphamide, vincristine, doxorubicin and prednisone (CHOP) or CHOP-like chemotherapy.[3-7] In contrast, the addition of rituximab, a monoclonal antibody with a different mechanism of action than traditional cytotoxic chemotherapy, significantly improved the results of initial therapies.[8-11]

A number of studies have shown an improvement in response rate (RR), event free survival (EFS) and overall survival (OS) rates with the addition of rituximab to the CHOP regimen (R-CHOP)[8, 9, 12]. The results of these representative studies are summarized in **Table 1**. Based on these and other studies, R-CHOP has become the standard of care therapy for patients with newly diagnosed aggressive B cell lymphoma.

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

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

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

Despite recent improvements in the therapy of DLBCL, approximately 40% of patients with aggressive B cell non-Hodgkin's lymphoma (NHL) relapse following initial immunochemotherapy.[8-11, 23] Although a significant number of patients with relapsed aggressive NHL can be salvaged with intensive high dose chemotherapy, the majority will succumb to the disease. **Thus, the development of a more effective initial therapy in aggressive NHL is essential to improve long-term outcomes.**

1.3 Lenalidomide in hematological malignancies

Lenalidomide (REVLIMID, Celgene Corp., NJ, USA) is a proprietary IMiD™ compound. The mechanism of action of lenalidomide is complex and involves immune modulation [13], antiangiogenic activity [14] and impact on both the microenvironment and the tumor itself [15]. 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 [16]. It is also used in combination with dexamethasone for subjects with previously treated multiple myeloma based on significant antitumor activity [17, 18]. Lenalidomide has also shown activity in refractory/relapsed chronic lymphocytic leukemia/small lymphocytic leukemia (CLL/SLL) [19]. Of forty-five enrolled patients, the majority of which were fludarabine refractory, 47% had evidence of a response, with 9% of the patients attaining CR. Fatigue, thrombocytopenia, and neutropenia were the most common adverse effects noted in 83%, 78%, and 78% of the patients respectively.

Lenalidomide as a single agent in relapsed DLBCL. Lenalidomide has a significant single agent activity in relapsed/refractory DLBCL. In a phase II trial of lenalidomide in patients with relapsed or refractory DLBCL, mantle cell lymphoma (MCL), follicular grade 3 lymphoma (FL-III), or transformed lymphoma (TL) patients received oral lenalidomide 25 mg on days 1-21 every 28 days as tolerated or until progression[20]. Two hundred and seventeen patients were enrolled and received lenalidomide. The ORR was 35% (77/217), with 13% (29/217) complete remission (CR), 22% (48/217) partial remission, and 21% (45/217) with stable disease. The ORR for DLBCL was 28% (30/108). Median progression-free survival for all 217 patients was 3.7 months. For 77 responders, the median response duration lasted 10.6 months. The most common adverse event was myelosuppression with grade 4 neutropenia and thrombocytopenia in 17% and 6%, respectively.

Lenalidomide and DLBCL subtype. Retrospective analysis of the outcomes of patients with GCB vs non-GCB DLBCL treated with salvage lenalidomide at 4 academic institutions was recently performed.[21]. 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. It is unknown if DLBCL type has an impact on lenalidomide efficacy in upfront therapy.

1.4 Lenalidomide in combination with R-CHOP in DLBCL.

A phase I trial was recently conducted and reported that established the MTD of lenalidomide that could be combined with R-CHOP-21 chemotherapy for patients with newly diagnosed aggressive B-cell NHL.[22] Eligible patients were adults with newly diagnosed, untreated CD20 positive DLBCL or follicular grade III NHL that were candidates for R-CHOP-21. Patients received oral lenalidomide days 1-10 with standard dose R-CHOP every 21 days. All patients received pegfilgrastim on day 2 of the cycle and aspirin prophylaxis. The lenalidomide dose levels tested were 15, 20 and 25 mg. Criteria defining MTD were designed to avoid any reduction in dose intensity of R-CHOP-21. Twenty-four patients were enrolled. The median age was 65 (35-82) years and 54% (13/24) were over 60 years. Three patients received 15 mg, 3 received 20 mg and 18 received 25 mg of lenalidomide. No dose limiting toxicity was found. Dose escalation beyond 25 mg days 1-10 was not performed since 25mg daily is an established biologically effective dose. 25 mg days 1-10 was the recommended dose for phase II. The incidence of grade IV neutropenia and thrombocytopenia was 67% and 21%, respectively. Febrile neutropenia requiring hospitalization was rare (4%) and there were no bleeding or toxic deaths. There were no delays in chemotherapy due to cytopenias. The overall response rate was 100% with a complete response (CR) rate of 77%. In a summary, R2CHOP regimen was shown to be safe and associated with high response rates in DLBCL. Importantly, lenalidomide does not affect dose intensity and schedule of RCHOP, it is now necessary to test it against the standard RCHOP21 in a randomized trial setting.

1.5 Rationale for Current Study

Despite recent improvements in the therapy of DLBCL, approximately 40% of patients with DLBCL treated with RCHOP relapse following initial immunochemotherapy.[8-11, 23] Although a significant number of patients with relapsed aggressive NHL can be salvaged with intensive high dose chemotherapy, the majority will succumb to the disease. Thus, the development of a more effective initial therapy in aggressive NHL is essential to improve long-term outcomes

Lenalidomide, an immunomodulatory agent (IMDs), was shown to have significant activity in relapsed aggressive B cell NHL.[24-26] However, the role of lenalidomide in the initial therapeutic intervention in aggressive lymphomas remains unknown. The mechanism of action of lenalidomide is complex and involves immune modulation [13], antiangiogenesis [14], modulation of the microenvironment and direct anti-tumor activity [15]. The single-agent activity of lenalidomide and the fact that its mechanisms of action are different than the other members of the R-CHOP regimen provide strong rationales for the introduction of lenalidomide to upfront therapy in aggressive B cell NHL.

The phase I trial establishing the maximum tolerated dose (MTD) of lenalidomide that could be combined with R-CHOP-21 chemotherapy for patients with newly diagnosed aggressive B-cell NHL has recently been completed [22]. Lenalidomide 25 mg days 1-10 was shown to be safe and is the recommended dose for phase II study.

This study is a multicenter randomized phase 2 study of lenalidomide and RCHOP (R2CHOP) vs. RCHOP in patients with newly diagnosed DLBCL to evaluate the efficacy of this combination. R2CHOP dose and schedule will follow the design established by Nowakowski and colleagues [22]. Patients will be stratified according to clinical risk (IPI score) and age of diagnosis.

The data generated in this study in regards to efficacy of lenalidomide combined with RCHOP (R2CHOP) in patients with newly diagnosed DLBCL will be critical for determination if R2CHOP warrants further evaluation in phase 3 trials.

1.6 Correlative Studies

1.6.1 Impact of DLBCL subtype on efficacy of RCHOP and R2CHOP. DLBCL is a heterogeneous disorder with 2 major molecular subtypes identified by gene expression profiling (GEP): 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 calcification algorithms. The ABC (non-GCB subtype) has been associated with worse outcome in 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.[21]. 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. It is unknown if DLBCL subtype has an impact on lenalidomide efficacy in the upfront therapy.

In the current study, we will assess impact of DLBCL subtype as defined by i) GEP and ii) IHC on efficacy of RCHOP and R2CHOP. Our working hypothesis is that the difference in efficacy of R2CHOP versus RCHOP will be more pronounced in ABC type.

1.6.2 Interim PET scan in predicting treatment outcome: Exploratory studies of the role of interim PET scan in predicting treatment outcome (correlation of SUV reduction and metabolic and anatomic volume reductions with outcome).

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1.7 Justification for Trial Expansion

After registration of 219 patients, the trial was suspended for interim pathology review and GEP assessments. We have now conducted a pathology review of 107 patients (49% of the 219 patients accrued so far). Performing central pathology review before the study's initial accrual goal of 220 has been met has allowed us to estimate the rate of pathology ineligibility and the rate of tissue availability for GEP. Based on this review, we project that E1412 will fall short of

analysis goals, primarily due to pathology ineligibility and inadequacy of the submitted tissue for GEP.

Of 107 pathology cases reviewed, 30 cases (28%) were rejected by the study pathologist due to: alternative diagnosis (not DLBCL or de novo DLBCL) in 20 patients (19%) and poor quality of pathology material submitted not allowing confirmation of diagnosis in 10 patients (9%). While some IHC is still pending, it is assumed that the great majority of the remaining patient tissue samples will be confirmed DLBCL cases based on the initial review. Of these 53 patients had IHC classification performed already and the first group of 36 patients was selected for GEP using Lymph2CX on the Nanostring platform. Of 36 patients, 31 gave a GEP Cell Of Origin (COO) results. There were 18 GCB, 1 unclassifiable, and 12 ABC. For the five samples that did not give CCO, results are being re-analyzed. 80% (8/10) core needle biopsies in the batch gave acceptable GEP COO results.

If the study continued as originally written, we assume that the pathology ineligibility rate will continue at the same level (28%) for the remaining 113 patients of the original accrual goal (220) predicting 158 (72%) eligible patients. Thus, we predict that we will fall short of our initial goal of 200 eligible patients. In addition, based on the results in the Appendix 2, we estimate that of the confirmed DLBCL cases, only 80% will have enough tissue after pathology review for GEP processing. We do note that in cases where the diagnosis of DLBCL was confirmed and adequate tissue was submitted, the Lymph2CX Nanostring assay provided valid results, including those patients where the tissue was from a core needle biopsy.

In summary, based on results so far, we project that of the first 220 we have enrolled, 158 DLBCL eligible patients and 63 ABC-DLBCL will be accrued based on the i) diagnostic criteria, and ii) adequate material to verify diagnosis, iii) GEP results.

Therefore, to increase the proportion of eligible cases going forward, the protocol has been amended to allow a “real time” central pathology eligibility screening process. In brief, after patients consent for the study, the tissue from local site will be sent to the Mayo Clinic, Division of Hematopathology, attn: Dr. William Macon (back up will be Dr. Rebecca King) for pathology review confirming correct histology AND assessment of tissue adequacy for COO determination (Figure 1). The eligibility result will be communicated to the site with 2 working days of tissue receipt at the Mayo clinic. Patients deemed INELIGIBLE for either reason will not be permitted to enroll in E1412. Patients deemed eligible will be permitted to enroll in E1412. Biologic material for the Lymph2CX Nanostring assay will be forwarded from Mayo to Vancouver. All other biologic material will be forwarded to the ECOG-ACRIN Central Biorepository and Pathology Facility (CBPF) for standard cataloging and storage for future research.

This new study design is straightforward and consists of the additional of a pre-registration step during which central pathology eligibility screening occurs. We expect that pathology eligibility rate will be reduced to near 0%, and expect GEP by Nanostring to render GEP results in 90% of tumor samples after screening for adequacy. We expect ABC DLBCL in 40% of cases. We are requesting the study re-open with those changes and accrue an additional 125 patients. To accrue 125 patients, it is expected that we would need to screen 180 patients. The

rationale for an additional 125 is as follows: The statistical plan requires 100 ABC DLBCL patients to be randomized between 2 arms. We estimate needing 43 more ABC DLBCL patients. Given our expectation of a 100% eligibility rate based on pathology, a 90% success of Nanostring, and a 40% ABC DLBCL frequency, 125 additional patients will generate 45 proven ABC DLBCL cases. It is expected that 180 patients will need to be screened to obtained the needed additional 125 patients (final trial accrual of 345).

2. Objectives

2.1 Primary Endpoints

2.1.1 Progression-free survival (PFS).

2.2 Secondary Endpoints

2.2.1 Response rate (RR)

2.2.2 CR rate as defined by PET-CT criteria

2.2.3 Overall survival (OS)

2.3 Correlative Endpoints

2.3.1 Impact of DLBCL molecular subtype on outcome.

2.3.2 Interim PET scan results in relation to treatment outcome.

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3. Selection of Patients

This study requires submission of tissue for pathological eligibility review prior to randomization. Pathology material requirement for pre-review are described in section 11. Tissue is submitted for patients meeting preregistration criteria and is reviewed in 2 business days, however, in case of clinical urgency, the tissue may be submitted at anytime during the preregistration phase to facilitate workup. Each of the criteria in the checklist that follows must be met in order for a patient to be considered eligible for this study. Use the checklist to confirm a patient's eligibility. For each patient, this checklist must be photocopied, completed and maintained in the patient's chart.

In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

ECOG-ACRIN Patient No. _____

Patient's Initials (L, F, M) _____

Physician Signature and Date _____

NOTE: All questions regarding eligibility should be directed to the study chair or study chair liaison.

NOTE: Institutions may use the eligibility checklist as source documentation if it has been reviewed, signed, and dated prior to registration/randomization by the treating physician.

3.1 Pre-registration (Step 0)

_____ 3.1.1 Age ≥ 18 years. DLBCL is rare in children and the R2CHOP regimen has not been tested in that group.

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_____ 3.1.2 Histologically confirmed DLBCL expressing CD20 antigen (J Clin Oncol 17(4):1244-53, 1999). Patients with **transformed lymphoma are excluded.** In this regard, patients with composite lymphoma in the diagnostic tissue (concomitant DLBCL and follicular or other low-grade lymphoma component) **are excluded**. However, patients with DLBCL in primary diagnostic tissue but a bone marrow that shows low grade or indeterminate lymphoma **are eligible**. Patients with known **primary mediastinal large B-cell lymphoma** (PMLBCL) **are excluded** because contemporary data suggest patients with this entity may be best served with the dose adjusted EPOCH-R regimen or with R-CHOP followed by consolidative XRT. Similarly, patients with known c-myc translocation (by fluorescence in situ hybridization) positive DLBCL are encouraged to participate in trials specifically designed for these patients, since contemporary data suggest patients with this entity may be best served with more intensive chemotherapy. However patients with known c-myc DLBCL positive are **NOT** excluded from this study. C-myc testing prior to study enrollment is **NOT** required.

_____ 3.1.3 Stages II bulky disease (defined as mass size of more than 10 cm), stage III, or IV (Ann Arbor Staging). Patients with **stage I and stage II non-bulky disease** frequently are treated with abbreviated

chemoimmunotherapy followed by involved field radiation and may be eligible for other protocols and **are thus excluded** from this study.

_____ 3.1.4 A paraffin-embedded tumor tissue specimen from the initial diagnostic biopsy has been located and ready to ship to the Mayo Clinic Lymphoma Laboratory following pre-registration as indicated in Section 11.

NOTE: Excisional tumor biopsy is preferred. Core needle biopsies will be considered adequate if there is enough tissue for the mandatory central pathology review, immunohistochemistry and GEP. Submission of a tumor block is preferred, but if unavailable submit alternative materials as outlined in Section 11.

_____ 3.1.5 ECOG performance status 0-2

_____ 3.1.6 Previously untreated and not receiving any other agent that would be considered as a treatment for the lymphoma. For subjects with severe systemic symptoms, compressive disease, or rapidly progressing symptomatic adenopathy, are allowed for lymphoma associated symptom treatment with up to 1 mg/kg/day prednisone, or equivalent, for a maximum of 7 days is permitted prior to beginning the treatment, at the discretion of the investigator. A washout period does not apply.

_____ 3.1.7 No known CNS lymphoma or cerebrospinal fluid involvement with malignant lymphoma cells. 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. IT methotrexate or IT cytarabine prophylaxis in patients with negative CSF who are felt to be at high risk of CNS relapse is allowed per local MD discretion. This should be noted on the treatment form.

_____ 3.1.8 Absence of history of myocardial infarction ≤ 6 months, or congestive heart failure requiring use of ongoing maintenance therapy for life-threatening ventricular arrhythmias.

_____ 3.1.9 Absence of history of deep venous thrombosis/embolism, threatening thromboembolism or known thrombophilia. Patients with a history of DVT/PE or thrombophilia may still participate if they are willing to be **on full anticoagulation during the treatment** if randomized to R2CHOP arm A. Full anticoagulation is defined as Warfarin, factor X inhibitors, or low molecular weight heparin at therapeutic doses. The rationale for this requirement is that Lenalidomide therapy is associated with an increased risk of thrombosis.

_____ 3.1.10 Patient must be able and willing to receive anticoagulation therapy with aspirin 70-325 mg daily prophylaxis, low molecular weight heparin, factor X inhibitors or Warfarin. This is due to an increased risk of thrombosis in patients treated with lenalidomide without prophylaxis. Patients unable or unwilling to take any prophylaxis are **NOT** eligible.

_____ 3.1.11 Absence of history of AIDS-related conditions (other than the presenting DLBCL) or posttransplant lymphoproliferative disorder

(PTLD) in immunocompromised patients. 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-RCHOP (R2CHOP) in patients with HIV infection and advanced immunosuppression and in patients with organ transplants requiring immunosuppression has not been established.

_____ 3.1.12 No other active malignancy requiring therapy such as radiation, chemotherapy, or immunotherapy. Exceptions to this are as follows: localized nonmelanotic skin cancer and any cancer that in the judgment of the investigator has been treated with curative intent and will not interfere with the study treatment plan and response assessment.

_____ 3.1.13 No history of radiation therapy to ≥ 25% of the bone marrow for other diseases or history of anthracycline therapy.

_____ 3.1.14 Patients must not be receiving erythroid stimulating agents (EPO: Procrit, Aranesp).

3.2 Randomization (Step 1)

_____ 3.2.1 Patient meets the eligibility criteria outlined in Section 3.1

_____ 3.2.2 Site has received notification from Mayo Clinic – Rochester Division of Hematopathology of the central confirmation of diagnosis and tissue adequacy for mandatory research studies.

_____ 3.2.3 Patients must have measurable disease (at least 1 lesion of ≥ 1.5 cm in one diameter) as detected by CT or the CT images of the PET/CT.

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_____ 3.2.4 IPI of 2 or greater.

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_____ 3.2.5 Ejection fraction of ≥45% by either MUGA or ECHO.

_____ 3.2.6 Absence of 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.

_____ 3.2.7 Adequate organ function:

_____ ANC ≥ 1500;

_____ PLT ≥ 100,000;

_____ Total bilirubin ≤ 1.5 x upper limit of normal (ULN) or if total bilirubin is >1.5 x ULN, the direct bilirubin must be normal;

_____ Alk. phosphatase ≤ 3 x ULN unless evidence of the direct liver involvement by lymphoma – then ≤ 5xULN;

_____ AST ≤ 3 x ULN unless evidence of the direct liver involvement by lymphoma – then ≤ 5xULN

Creatinine ≤ 2 x ULN or CrCl > 30 ml/min.

_____ 3.2.8 Women must not be pregnant or breast-feeding **because this study involves an investigational agent whose genotoxic, mutagenic and teratogenic effects on the developing fetus and newborn are unknown**.

_____ 3.2.9 Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting lenalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. A female of childbearing potential is any woman, regardless of sexual orientation or whether they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

Female? _____ (Yes or No)

Date of blood test or urine study: _____

_____ 3.2.10 Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure.

_____ _____

Physician Signature Date

OPTIONAL: This signature line is provided for use by institutions wishing to use the eligibility checklist as source documentation.

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4. Registration Procedures

CTEP Investigator Registration Procedures

Food and Drug Administration (FDA) regulations and National Cancer Institute (NCI) policy require all investigators participating in any NCI-sponsored clinical trial to register and to renew their registration annually.

Registration requires the submission of:

- a completed ***Statement of Investigator Form*** (FDA Form 1572) with an original signature
- a current Curriculum Vitae (CV)
- a completed and signed ***Supplemental Investigator Data Form*** (IDF)
- a completed ***Financial Disclosure Form*** (FDF) with an original signature

Fillable PDF forms and additional information can be found on the CTEP website at <http://ctep.cancer.gov/investigatorResources/investigator_registration.htm>. For questions, please contact the ***CTEP Investigator Registration Help Desk*** by email at <pmbregpend@ctep.nci.nih.gov>.

CTEP Associate Registration Procedures / CTEP-IAM Account

The Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) application is a web-based application intended for use by both Investigators (i.e., all physicians involved in the conduct of NCI-sponsored clinical trials) and Associates (i.e., all staff involved in the conduct of NCI-sponsored clinical trials).

Associates will use the CTEP-IAM application to register (both initial registration and annual re-registration) with CTEP and to obtain a user account.

Investigators will use the CTEP-IAM application to obtain a user account only. (See CTEP Investigator Registration Procedures above for information on registering with CTEP as an Investigator, which must be completed before a CTEP-IAM account can be requested.)

An active CTEP-IAM user account will be needed to access all CTEP and CTSU (Cancer Trials Support Unit) websites and applications, including the CTSU members' website.

Additional information can be found on the CTEP website at <http://ctep.cancer.gov/branches/pmb/associate_registration.htm>. For questions, please contact the ***CTEP Associate Registration Help Desk*** by email at <ctepreghelp@ctep.nci.nih.gov>.

CTSU Registration Procedures

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This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

Each investigator or group of investigators at a clinical site must obtain IRB approval for this protocol and submit IRB approval and supporting documentation to the CTSU Regulatory Office before they can be approved to enroll patients. Study centers can check the status of their registration packets by querying the Regulatory Support System (RSS) site registration status page of the CTSU member web site by entering credentials

at https://www.ctsu.org. For sites under the CIRB initiative, IRB data will automatically load to RSS.

Downloading Site Registration Documents

Site registration forms may be downloaded from the **E1412** protocol page located on the CTSU members' website.

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Protocols tab in the upper left of your screen
- Click on the **ECOG-ACRIN** link to expand, then select trial protocol **E1412**
- Click on the Site Registration Documents link

Requirements for E1412 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet

Submitting Regulatory Documents

Submit completed forms along with a copy of your IRB Approval and Model Informed Consent to the CTSU Regulatory Office, where they will be entered and tracked in the CTSU RSS.

CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
PHONE: 1-866-651-2878
FAX: (215) 569-0206
E-MAIL: CTSURegulatory@ctsu.coccg.org (for regulatory document submission only)

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.
2. Copy of IRB Informed Consent Document.

   NOTE: Any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample informed consent document must be justified in writing by the investigator and approved by the IRB.

3. A. CTSU IRB Certification Form.
   Or
   B. Signed HHS OMB No. 0990-0263 (replaces Form 310).
   Or
   C. IRB Approval Letter

NOTE: The above submissions must include the following details:

- Indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB
- Full protocol title and number
- Version Date
- Type of review (full board vs. expedited)

- Date of review.
- Signature of IRB official

Checking Your Site's Registration Status

Check the status of your site's registration packets by querying the RSS site registration status page of the members' section of the CTSU website.
(**NOTE:** Sites will not receive formal notification of regulatory approval from the CTSU Regulatory Office.)

- Go to https://www.ctsu.org and log in to the members' area using your CTEP-IAM username and password
- Click on the Regulatory tab at the top of your screen
- Click on the Site Registration tab
- Enter your 5-character CTEP Institution Code and click on Go

Patient Enrollment

Rev. 10/15 **Patients must not start protocol treatment prior to randomization (Step 1).**

Patient registration can occur only after pre-treatment evaluation is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Patient enrollment will be facilitated using the Oncology Patient Enrollment Network (OPEN). OPEN is a web-based registration system available on a 24/7 basis. To access OPEN, the site user must have an active CTEP-IAM account (check at < https://eapps-ctep.nci.nih.gov/iam/index.jsp >) and a 'Registrar' role on either the LPO or participating organization roster.

All site staff will use OPEN to enroll patients to this study. It is integrated with the CTSU Enterprise System for regulatory and roster data and, upon enrollment, initializes the patient in the Rave database. OPEN can be accessed at (https://open.ctsu.org.) or from the CTSU members' web site OPEN tab.

Prior to accessing OPEN site staff should verify the following:

- All eligibility criteria have been met within the protocol stated timeframes.
- All patients have signed an appropriate consent form and HIPAA authorization form (if applicable).

NOTE: The OPEN system will provide the site with a printable confirmation of registration and treatment information. Please print this confirmation for your records.

Further instructional information is provided on the CTSU members' web site OPEN tab or within the OPEN URL. For any additional questions contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

Rev. 10/15 4.1 Pre-Registration (Step 0)

This study requires submission of tissue for pathological eligibility review prior to randomization. Pathology material requirements for pre-review are described in Section 11. Tissue is to be submitted from patients meeting preregistration criteria and is reviewed in two (2) business days, however,

in case of clinical urgency, the tissue may be submitted at anytime during the preregistration phase to facilitate workup.

The following information will be requested

4.1.1 Protocol Number

4.1.2 Investigator Identification

4.1.2.1 Institution and affiliate name (Institution CTEP ID)

4.1.2.2 Investigator's name (NCI number)

4.1.2.3 Cooperative Group Credit

4.1.2.4 Credit Investigator

4.1.2.5 Protocol specific contact information

4.1.3 Patient Identification

4.1.3.1 Patient's initials (first and last)

4.1.3.2 Patient's Hospital ID and/or Social Security number

4.1.3.3 Patient demographics

4.1.3.3.1 Gender

4.1.3.3.2 Birth date

4.1.3.3.3 Race

4.1.3.3.4 Ethnicity

4.1.3.3.5 Nine-digit ZIP code

4.1.3.3.6 Method of payment

4.1.3.3.7 Country of residence

4.1.4 Eligibility Verification

Patients must meet all of the eligibility requirements in Section 3.1

4.1.5 Additional Requirements

4.1.5.1 Patients must provide a signed and dated, written informed consent form.

NOTE: Copies of the consent are not collected by the ECOG-ACRIN Operations Office – Boston.

4.1.5.2 The IRB-approved consent must allow patients the option to provide specimens for use in the optional laboratory research studies and for undefined future research.

4.1.5.3 Pathological samples are required to be submitted for central diagnostic review and defined laboratory research studies as indicated in Section 11.

4.2 Randomization (Step 1)

Mayo Clinic - Rochester Division of Hematopathology will notify (by fax) the submitting institution's CRA of the results of the "real time" central

pathology review confirming correct histology AND assessment of tissue adequacy for GEP assessments.

Patients must not start protocol treatment prior to randomization to step 1.

Treatment should start within three working days after randomization.

The following information will be requested

4.2.1 Protocol Number

4.2.2 Investigator Identification

4.2.2.1 Institution and affiliate name (Institution CTEP ID)

4.2.2.2 Investigator's name (NCI number)

4.2.2.3 Cooperative Group Credit

4.2.2.4 Credit Investigator

4.2.2.5 Protocol specific contact information

4.2.3 Patient Identification

4.2.3.1 Patient's initials (first and last)

4.2.3.2 Patient's Hospital ID and/or Social Security number

4.2.3.3 Patient demographics

4.2.3.3.1 Gender

4.2.3.3.2 Birth date

4.2.3.3.3 Race

4.2.3.3.4 Ethnicity

4.2.3.3.5 Nine-digit ZIP code

4.2.3.3.6 Method of payment

4.2.3.3.7 Country of residence

4.2.4 Eligibility Verification

Patients must meet all of the eligibility requirements in Section 3

4.2.5 Stratification Factors

- International prognostic index (IPI) 2/3 vs 4/5
- Age: < 60 yrs. vs. ≥ 60 yrs.

4.2.6 Additional Requirements

4.2.6.1 Biological samples are to be submitted for future undefined laboratory research studies per patient consent as outlined in Section 11.

4.2.6.2 Data collection for this study will be done exclusively through the Medidata Rave clinical data management system. Access to the trial in Rave is granted through the iMedidata application to all persons with the appropriate roles assigned in Regulatory Support System (RSS. To

access iRave via iMedidata, the site user must have an active CTEP-IAM account (check at <https://eapps-ctep.nci.nih.gov/iam>) and the appropriate Rave role (Rave CRA, Read-Only, Site Investigator) on either the LPO or participating organization roster at the enrolling site.

Upon initial site registration approval for the study in RSS, all persons with Rave roles assigned on the appropriate roster will be sent study invitation e-mail from iMedidata. To accept the invitation, site users must log into the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM user name and password, and click on the "accept" link in the upper right-corner of the iMedidata page. Please note, site users will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (elearnings), and can be accessed by clicking in the upper right pane of the iMedidata screen.

Users that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in RSS will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at http://www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

4.2.6.3 Celgene Pregnancy Prevention Counselor Program (CPPCP)

FDA requires that each clinical trials site have two counselors (investigators are not eligible) trained by Celgene through the CPPCP. The CPPCP is available on the internet for each person who has completed the site counselor identification form (Appendix XI) and registered with Celgene prior to completing the CPPCP. Each patient must be counseled prior to dispensing lenalidomide and documentation is kept in the patient's records. Both the training certificates and the completed Lenalidomide Education and Counseling Guidance Documents are auditable documents and must be produced upon request. Counselors who wish to counsel patients for different protocols at the same site or for the same protocol at different sites should indicate this on the site counselor identification form..

Trained counselors must have a CTEP person ID from their IAM accounts in order to be tracked by the CTSU. Sites must send copies of the training certificates and completed site counselor identification forms to CTSU Operations Office (fax # 1-888-691-8039; for questions, please contact the CTSU Help Desk at 1-888-823-5923). Documentation of two trained counselors at each site is required for both trial activation and drug ordering.

4.2.7 Instructions for Patients who Do Not Start Assigned Protocol Treatment

If a patient who is randomized (Step 1) does not receive any assigned protocol treatment, baseline and follow-up data will still be collected and must be submitted through Medidata Rave according to the schedule in the ***E1412*** Forms Completion Guidelines.

5. Treatment Plan

5.1 Administration Schedule

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5.1.1 Arm A: R2CHOP Treatment Schedule (Experimental Arm).

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R2CHOP repeated every 3 weeks (+/- 3days) for total of 6 cycles.

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Agent	Dose[1]	Route	Day	Cycle Length
Rituximab[2, 11]	375 mg/m2	IV	Day 1	Every 21 days
Cyclophosphamide[3]	750 mg/m2	IV	Day 1	Every 21 days
Doxorubicin[4]	50 mg/m2	IV	Day 1	Every 21 days
Vincristine	1.4 mg/m2 (max 2 mg)	IV	Day 1	Every 21 days
Prednisone[8, 9]	100 mg/m2	po	Day 1-5	Every 21 days
Lenalidomide	25 mg	po	Day 1-10	Every 21 days
Pegfilgrastim[5, 10]	6 mg	SC	Between Days 2-4[7]	Every 21 days
ASA[6]	325 mg	po	Day 1-21	Every 21 days

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1. *Body surface area based on actual body weight*
2. *Rituximab may be rounded to nearest 50 mg.*
3. *Cyclophosphamide dose may be rounded to nearest 50 mg*
4. *Doxorubicin dose may be rounded to nearest 5 mg*
5. *Use of Pegfilgrastim is mandatory in R2CHOP arm.*
6. *Aspirin prophylaxis will be given to all patients unless the patient is on full anticoagulation, see details in eligibility section.*
7. *A single injection of pegfilgrastim can be given between days 2-4 of the cycle.*
8. *Prednisone **dose is 100 mg/m^2** and can be rounded within 15%.*
9. *A bioequivalent dose of corticosteroid may be used as a substitute.*
10. *May substitute other white blood cell growth factor biologic per institutional policy. Please see Section 5.5.5.*
11. *Due to prolonged infusion times on day 1 with chemotherapy and rituximab, providers may split the dose of rituximab over 2 days (day 0 and day 1, where day 1 is CHOP+/-lenalidomide initiation) or deliver rituximab on day 0 and CHOP +/- lenalidomide day 1.*

5.1.2 Arm B: RCHOP Treatment Schedule (Control Arm).

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RCHOP repeat every 3 weeks (+/- 3 days) for total of 6 cycles.

Agent	Dose[1]	Route	Day	Cycle Length
Rituximab[2,10]	375 mg/m2	IV	Day 1	Every 21 days
Cyclophosphamide[3]	750 mg/m2	IV	Day 1	Every 21 days
Doxorubicin[4]	50 mg/m2	IV	Day 1	Every 21 days
Vincristine	1.4 mg/m2 (max 2 mg)	IV	Day 1	Every 21 days
Prednisone[7, 8]	100 mg/m2	po	Day 1-5	Every 21 days
Pegfilgrastim[5,9]	6 mg	SC	Between Days 2-4[6]	Every 21 days

1. *Body surface area based on actual body weight*
2. *Rituximab may be rounded to nearest 50 mg.*
3. *Cyclophosphamide dose may be rounded to nearest 50 mg*

4. *Doxorubicin dose may be rounded to nearest 5 mg*
5. *Pegfilgrastim use per discretion of treating MD in RCHOP arm.*
6. *Pegfilgrastim, if used, can be given between days 2-4 of the cycle.*
7. *Prednisone **dose is 100 mg/m²** and can be rounded within 15%.*
8 *A bioequivalent dose of corticosteroid may be used as a substitute.*
9. *May substitute other white blood cell growth factor biologic per institutional policy. Please see Section 5.5.5.*
10. *Due to prolonged infusion times on day 1 with chemotherapy and rituximab, providers may split the dose of rituximab over 2 days (day 0 and day 1, where day 1 is CHOP+/-lenalidomide initiation) or deliver rituximab on day 0 and CHOP +/- lenalidomide day 1.*

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5.2 Adverse Event Reporting Requirements

5.2.1 Purpose

Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting**: Adverse events are reported in a routine manner at scheduled times during a trial using Medidata Rave.
- **Expedited reporting**: In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

Rev. Add9

NOTE: Effective April 1, 2018 expedited adverse event reporting done via CTEP-AERS will use CTCAE version 5.0 terminology and grading. Routine adverse event reporting and dose modifications guidelines will continue to be based on CTCAE version 4.0 terminology and grading.

5.2.2 Terminology

- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be **ANY** unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.
- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	DESCRIPTION
Unrelated	The AE is ***clearly NOT related*** to treatment
Unlikely	The AE is ***doubtfully related*** to treatment
Possible	The AE ***may be related*** to treatment

Probable	The AE is ***likely related*** to treatment
Definite	The AE is ***clearly related*** to treatment

- **CAEPR (Comprehensive Adverse Events and Potential Risks List):** An NCI generated list of reported and/or potential AEs associated with an agent currently under an NCI IND. Information contained in the CAEPR is compiled from the Investigator's Brochure, the Package Insert, as well as company safety reports.
- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.
- **Hospitalization (or prolongation of hospitalization):** For AE reporting purposes, a hospitalization is defined as an inpatient hospital stay equal to or greater than 24 hours.
- **Life Threatening Adverse Event:** Any AE that places the subject at immediate risk of death from the AE as it occurred.
- **Serious Adverse Event (SAE):** Any adverse event occurring at any dose that results in **ANY** of the following outcomes:
  - Death
  - A life-threatening adverse event
  - Inpatient hospitalization or prolongation of existing hospitalization (for ≥ 24 hours).
  - A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
  - A congenital anomaly/birth defect.
  - Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered a 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.

Rev. 1/15

- **SPEER (Specific Protocol Exceptions to Expedited Reporting):** A subset of AEs within the CAEPR that contains list of events that are protocol specific exceptions to expedited reporting. If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

5.2.3 Reporting procedure

This study requires that expedited adverse event reporting use CTEP's Adverse Event Reporting System (CTEP-AERS). CTEP's guidelines for CTEP-AERS can be found at http://ctep.cancer.gov. A CTEP-AERS report must be submitted electronically to ECOG-ACRIN and the appropriate regulatory agencies via the CTEP-AERS Web-based application located at http://ctep.cancer.gov.

In the rare event when Internet connectivity is disrupted a 24-hour notification is to be made by telephone to

- the AE Team at ECOG-ACRIN (617-632-3610) for Arms A and B
- the NCI (301-897-7497) for Arm A
- the FDA (1-800-FDA-1088) for Arm B

An electronic report MUST be submitted immediately upon re-establishment of internet connection.

Supporting and follow up data: Any supporting or follow up documentation must be uploaded to the Supplemental Data Folder in Medidata Rave within 48-72 hours. In addition, supporting or follow up documentation must be faxed to the NCI (301- 230-0159) for Arm A and the FDA (800-332-0178) for Arm B in the same timeframe.

NCI Technical Help Desk: For any technical questions or system problems regarding the use of the CTEP-AERS application, please contact the NCI Technical Help Desk at ncictephelp@ctep.nci.nih.gov or by phone at 1-888-283-7457.

5.2.4 Determination of reporting requirements

Many factors determine the reporting requirements of each individual protocol, and which events are reportable in an expeditious manner, including:

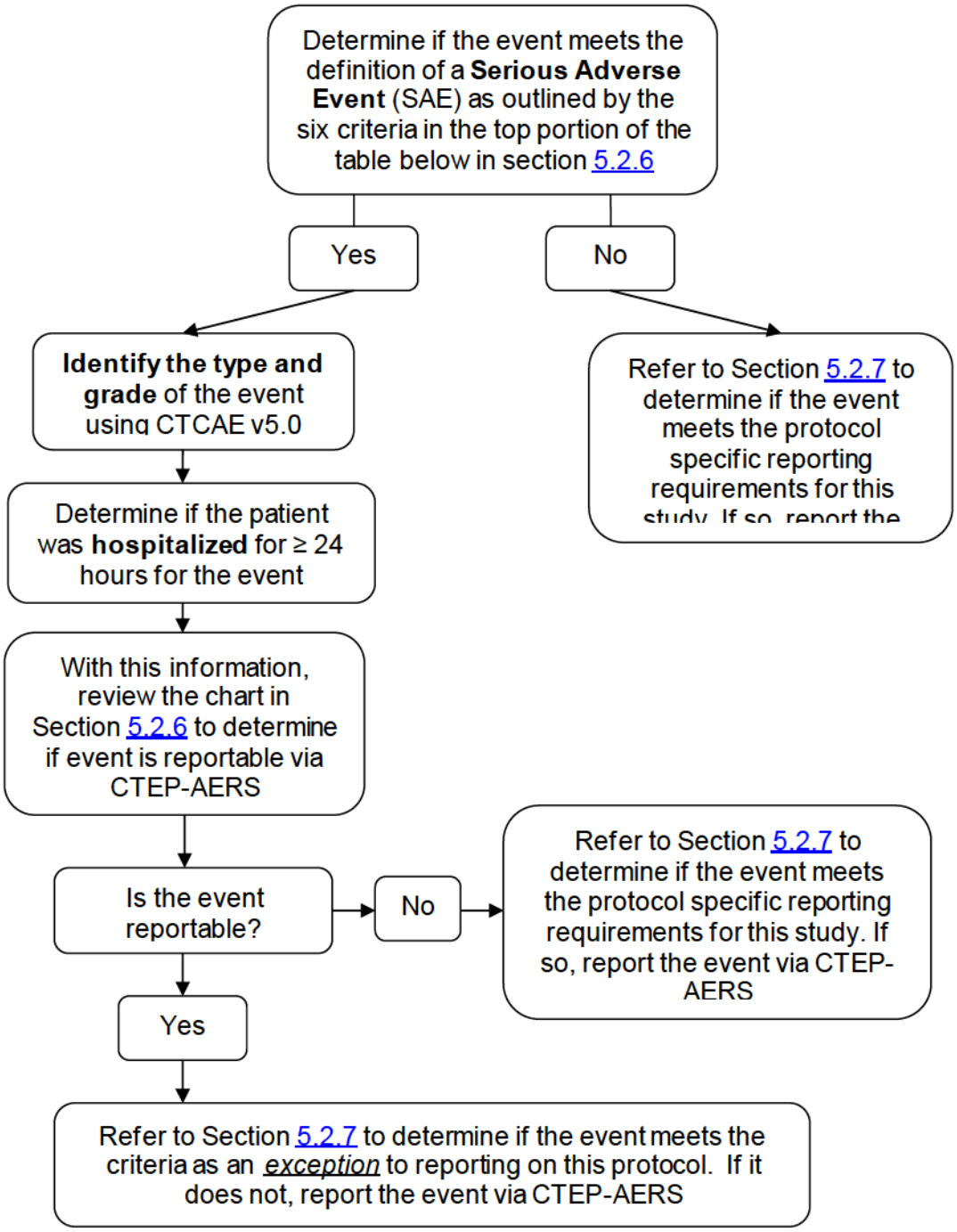
- the phase (0, 1, 2, or 3) of the trial
- whether the patient has received an investigational or commercial agent or both
- the seriousness of the event
- the Common Terminology Criteria for Adverse Events (CTCAE) grade
- whether or not hospitalization or prolongation of hospitalization was associated with the event
- when the adverse event occurred (within 30 days of the last administration of investigational agent vs. ≥ 30 days after the last administration of investigational agent)
- the relationship to the study treatment (attribution)

Using these factors, the instructions and tables in the following sections have been customized for protocol E1412 and outline the specific expedited adverse event reporting requirements for study E1412.

5.2.5 Steps to determine if an adverse event is to be reported in an expedited manner – Arm A

Rev. Add9

5.2.5.1 Guidelines for adverse events **OCCURRING WHILE ON PROTOCOL TREATMENT AND WITHIN 30 DAYS** of the last administration of the investigational agent(s).



5.2.5.2 Guidelines for adverse events **OCCURRING GREATER THAN 30 DAYS** after the last administration of the investigational agent(s).

If the adverse event meets the definition of a **Serious Adverse Event** (SAE) as outlined by the six criteria in the top portion of the table below in Section 5.2.6, AND has an attribution of possible, probably or definite, the following events require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 4 and Grade 5 AEs

NOTE: Any death occurring greater than 30 days after the last dose of investigational agent with an attribution of possible, probable or definite must be reported via CTEP-AERS even if the patient is off study

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.2.6 Expedited Reporting Requirements for Arm A on protocol E1412

Investigational Agents: Lenalidomide

Commercial Agents: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

Late Phase 2 and Phase 3 Studies

Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND *within 30 Days of the Last Administration of the Investigational Agent/Intervention* [1]

NOTE: Footnote 1 instructs how to report serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention.

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **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 NCI via CTEP-AERS within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 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 5 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

5.2.7 Additional instructions, requirements and exceptions for protocol E1412

Additional Instructions:
For instructions on how to specifically report events that result in persistent or significant disability/incapacity, congenital anomaly, or birth defect events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497. This will need to be discussed on a case by case basis

E1412 specific expedited reporting requirements:

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- **Pregnancy**

  Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring while the subject is on Lenalidomide, or within 28 days of the subject's last dose of Lenalidomide, are considered immediately reportable events. **The pregnancy, suspected pregnancy, or positive pregnancy test must be reported via CTEP-AERS within 24 hours of the Investigator's knowledge.** Please refer to Appendix XII for detailed instructions on how to report the occurrence of a pregnancy as well as the outcome of all pregnancies.

E1412 specific expedited reporting exceptions:

For study arm A, the adverse events listed below **do not** require expedited reporting via CTEP-AERS:

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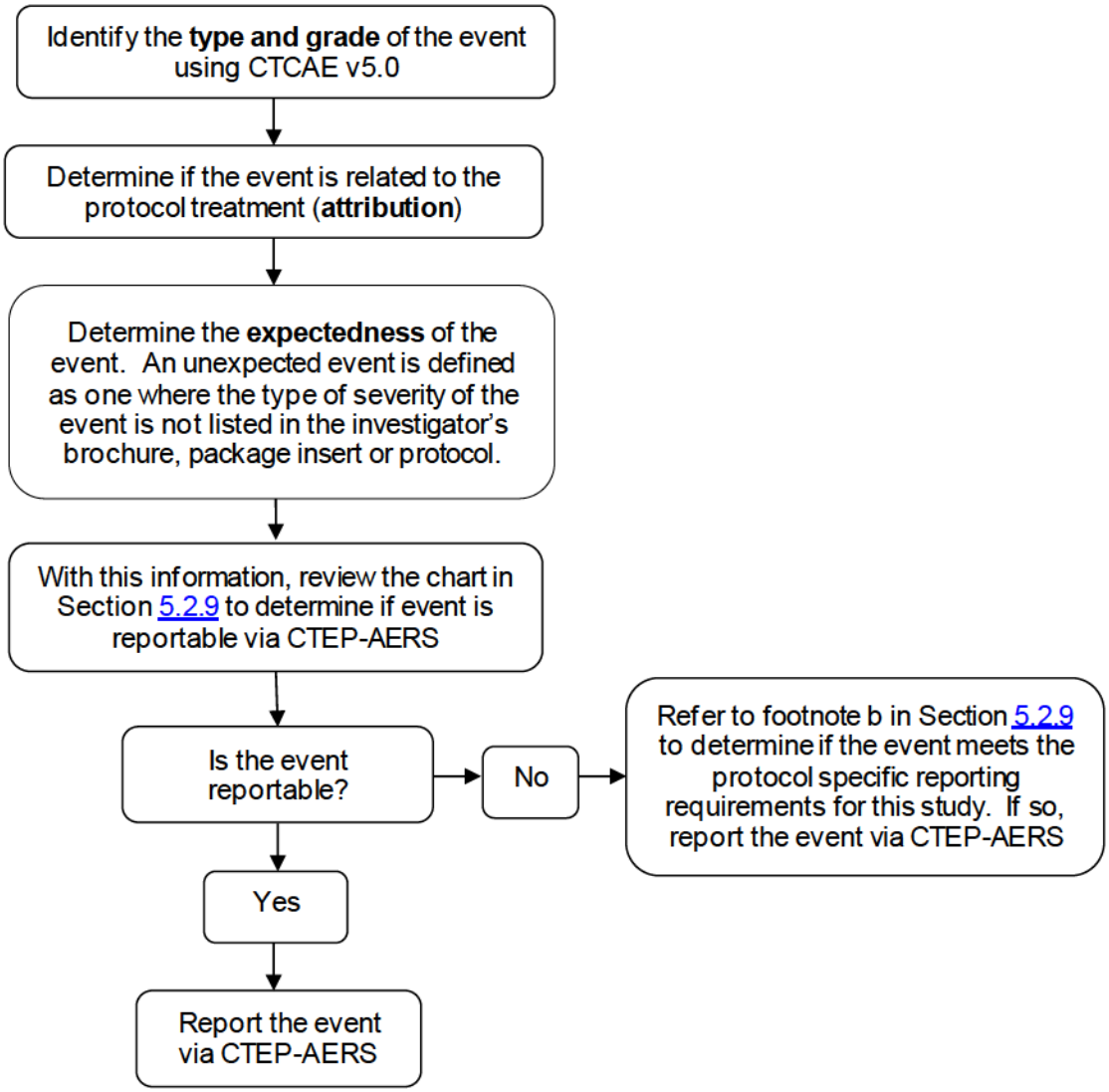
If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ***ONLY*** be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

Rev. Add9

5.2.8 Steps to determine if an event is to be reported in an expedited manner – Arm B



5.2.9 Expedited Reporting Requirements for Arm B on protocol E1412

Commercial Agents: Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone

Expedited reporting requirements for adverse events experienced by patients on arm(s) with commercial agents only –Arm B

Attribution	Grade 4		Grade 5[a]		ECOG-ACRIN and Protocol-Specific Requirements
	Unexpected	Expected	Unexpected	Expected	See footnote (b) for special requirements.
Unrelated or Unlikely			7 calendar days	7 calendar days	
Possible, Probable, Definite	7 calendar days		7 calendar days	7 calendar days	

7 Calendar Days: Indicates a full CTEP-AERS report is to be submitted within 7 calendar days of learning of the event.

a This includes all deaths within 30 days of the last dose of treatment regardless of attribution.

NOTE: Any death that occurs > 30 days after the last dose of treatment and is attributed possibly, probably, or definitely to the treatment must be reported within 7 calendar days of learning of the event.

b Protocol-specific expedited reporting requirements: The adverse events listed below also require expedited reporting for this trial:

Serious Events: Any event following treatment that results in *persistent or significant disabilities/incapacities, congenital anomalies, or birth defects* must be reported via CTEP-AERS within 7 calendar days of learning of the event. For instructions on how to specifically report these events via CTEP-AERS, please contact the AEMD Help Desk at aemd@tech-res.com 301-897-7497.

5.2.10 Other recipients of adverse event reports and supplemental data

DCTD/NCI will notify ECOG-ACRIN/pharmaceutical collaborator(s) of all AEs reported to the FDA. Any additional written AE information requested by ECOG-ACRIN MUST be submitted to BOTH the NCI and ECOG-ACRIN.

Adverse events determined to be reportable via CTEP-AERS must also be reported by the institution, according to the local policy and procedures, to the Institutional Review Board responsible for oversight of the patient.

5.2.11 Reporting second primary cancers

All cases of second and secondary malignancies [including acute myeloid leukemia (AML) and myelodysplastic syndrome (MDS)], regardless of attribution, that occur following treatment on NCI-sponsored trials must be reported as follows:

1. Complete a Second Primary Form within 14 days in Medidata Rave.

2. Report the diagnosis via CTEP-AERS, regardless of attribution, at http://ctep.cancer.gov

   Report under a.) leukemia secondary to oncology chemotherapy, b.) myelodysplastic syndrome, c.) treatment related secondary malignancy, or d.) Neoplasm Other, malignant (grade 3 or 4)

3. Upload a copy of the pathology report to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP confirming the diagnosis.
4. If the patient has been diagnosed with AML/MDS, upload a copy of the cytogenetics report (if available) to ECOG-ACRIN via Medidata Rave and submit a copy to NCI/CTEP.

NOTE: **All new malignant tumors must be reported through CTEP-AERS whether or not they are thought to be related to either previous or current treatment.** All new malignancies should be reported including solid tumors (including non-melanoma skin malignancies), hematologic malignancies, Myelodysplastic Syndrome (MDS)/Acute Myelogenous Leukemia (AML), and *in situ* tumors.

Whenever possible, the CTEP-AERS report should include the following:

- tumor pathology
- history of prior tumors
- prior treatment/current treatment including duration
- any associated risk factors or evidence regarding how long the tumor may have been present
- when and how the tumor was detected
- molecular characterization or cytogenetics or the original tumor (if available) and of any new tumor
- tumor treatment and outcome (if available).

NOTE: The Second Primary Form and the CTEP-AERS report should not be used to report recurrence or development of metastatic disease.

NOTE: If a patient has been enrolled in more than one NCI-sponsored study, the Second Primary Form must be submitted for the most recent trial. ECOG-ACRIN must be provided with a copy of the form and the associated pathology report and cytogenetics report (if available) even if ECOG-ACRIN was not the patient's most recent trial.

NOTE: Once data regarding survival and remission status are no longer required by the protocol, no follow-up data should be submitted via CTEP-AERS or by the Second Primary Form.

Rev. 1/14, 6/14, 10/14, 7/16 Rev. Add9

5.3 Comprehensive Adverse Events and Potential Risks List

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. Frequency is provided based on 4081 patients. Below is the CAEPR for lenalidomide (CC-5013).

NOTE: Arm A- If an AE meets the reporting requirements of the protocol, and it is listed on the SPEER, it should ONLY be reported via CTEP-AERS if the grade being reported exceeds the grade listed in the parentheses next to the event.

Version 2.7, March 14, 2018[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)**
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr 3)***
	Blood and lymphatic system disorders - Other (pancytopenia)		
	Febrile neutropenia		
	Hemolysis		
CARDIAC DISORDERS			
		Atrial fibrillation	
		Heart failure	
		Myocardial infarction[2]	
EAR AND LABYRINTH DISORDERS			
	Vertigo		
ENDOCRINE DISORDERS			
		Hyperthyroidism	
	Hypothyroidism		***Hypothyroidism (Gr 3)***
EYE DISORDERS			
	Blurred vision		
	Cataract		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		
Constipation			***Constipation (Gr 3)***
Diarrhea			***Diarrhea (Gr 3)***
	Dry mouth		
	Dyspepsia		
	Nausea		***Nausea (Gr 3)***
	Vomiting		***Vomiting (Gr 3)***

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr 2)***
	Edema limbs		***Edema limbs (Gr 3)***
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 3)***
	Generalized edema		
	Non-cardiac chest pain		
	Pain		
HEPATOBILIARY DISORDERS			
		Hepatic failure	
		Hepatobiliary disorders - Other (cholestasis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction	
		Anaphylaxis	
		Immune system disorders - Other (angioedema)	
		Immune system disorders - Other (graft vs. host disease)[3]	
INFECTIONS AND INFESTATIONS			
	Infection[4]		***Infection[4] (Gr 3)***
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Bruising		
	Fall		
INVESTIGATIONS			
	Alanine aminotransferase increased		
	Alkaline phosphatase increased		
	Aspartate aminotransferase increased		
	Blood bilirubin increased		
	GGT increased		
	Investigations - Other (C-Reactive protein increased)		
		Lipase increased	
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
Neutrophil count decreased			***Neutrophil count decreased (Gr 4)***
Platelet count decreased			***Platelet count decreased (Gr 4)***
	Weight loss		***Weight loss (Gr 2)***
	White blood cell decreased		***White blood cell decreased (Gr 4)***

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr 3)***
	Dehydration		
	Hyperglycemia		
	Hyperuricemia		
	Hypocalcemia		
	Hypokalemia		
	Hypomagnesemia		
	Hyponatremia		
	Hypophosphatemia		
	Iron overload		
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Bone pain		
	Generalized muscle weakness		
	Muscle cramp		***Muscle cramp (Gr 2)***
	Pain in extremity		
		Rhabdomyolysis[5]	
	Myalgia		***Myalgia (Gr 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy[6]	
		Myelodysplastic syndrome[6]	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (tumor flare)[7]	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (second primary malignancies)	
		Treatment related secondary malignancy[6]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Depressed level of consciousness		
	Dysesthesia		
	Dysgeusia		
	Headache		
	Paresthesia		
	Peripheral motor neuropathy		

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 5.0 Term) [n= 4081]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Peripheral sensory neuropathy		
		Stroke[2]	
	Syncope		
	Tremor		
PSYCHIATRIC DISORDERS			
	Depression		
	Insomnia		***Insomnia (Gr 2)***
	Psychiatric disorders - Other (mood altered)		
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr 2)***
	Dyspnea		***Dyspnea (Gr 3)***
	Epistaxis		
		Pneumonitis	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
	Dry skin		
		Erythema multiforme	
	Hyperhidrosis		***Hyperhidrosis (Gr 2)***
	Pruritus		***Pruritus (Gr 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr 3)***
		Skin and subcutaneous tissue disorders - Other (drug reaction with eosinophilia and systemic symptoms [DRESS])	
	Skin and subcutaneous tissue disorders - Other (pyroderma gangrenosum)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	
SURGICAL AND MEDICAL PROCEDURES			
		Surgical and medical procedures - Other (impaired stem cell mobilization)[8]	
VASCULAR DISORDERS			
	Hematoma		
	Hypertension		
	Hypotension		
	Peripheral ischemia		
	Thromboembolic event[9]		***Thromboembolic event[9] (Gr 3)***
	Vasculitis		

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting

PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2] Myocardial infarction and cerebrovascular accident (stroke) have been observed in multiple myeloma patients treated with lenalidomde and dexamethasone.

[3] Graft vs. host disease has been observed in subjects who have received lenalidomide in the setting of allo-transplantation.

[4] Infection includes all 75 sites of infection under the INFECTIONS AND INFESTATIONS SOC.

[5] The rare adverse event of rhabdomyolysis has been observed with lenalidomide. The reports of rhabdomyolysis were confounded by concurrent use of statins and dexamethasone, concurrent viral and bacterial infections, trauma, and serotonin syndrome. Statins, infections, trauma, and serotonin syndrome are known risk factors for rhabdomyolysis.

[6] There has been an increased frequency of secondary malignancies (including ALL, AML, and MDS) in multiple myeloma patients being treated with melphalan, prednisone, and lenalidomide post bone marrow transplant.

[7] Serious tumor flare reactions have been observed in patients with chronic lymphocytic leukemia (CLL) and lymphoma.

[8] A decrease in the number of stem cells (CD34+ cells) collected from patients treated with >4 cycles of lenalidomide has been reported.

[9] Significantly increased risk of deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis has been observed in patients with multiple myeloma receiving lenalidomide with dexamethasone.

[10] Gastrointestinal hemorrhage includes: Anal hemorrhage, Cecal hemorrhage, Colonic hemorrhage, Duodenal hemorrhage, Esophageal hemorrhage, Esophageal varices hemorrhage, Gastric hemorrhage, Hemorrhoidal hemorrhage, Ileal hemorrhage, Intra-abdominal hemorrhage, Jejunal hemorrhage, Lower gastrointestinal hemorrhage, Oral hemorrhage, Pancreatic hemorrhage, Rectal hemorrhage, Retroperitoneal hemorrhage, and Upper gastrointestinal hemorrhage under the GASTROINTESTINAL DISORDERS SOC.

[11] Gastrointestinal obstruction includes: Colonic obstruction, Duodenal obstruction, Esophageal obstruction, Ileal obstruction, Jejunal obstruction, Obstruction gastric, Rectal obstruction, and Small intestinal obstruction under the GASTROINTESTINAL DISORDERS SOC.

[12] Osteonecrosis of the jaw has been seen with increased frequency when lenalidomide is used in combination with bevacizumab, docetaxel (Taxotere®), prednisone, and zolendronic acid (Zometa®).

NOTE: While not observed in human subjects, 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.

Adverse events reported on lenalidomide (CC-5013) trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that lenalidomide (CC-5013) caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (monocytosis); Disseminated intravascular coagulation; Eosinophilia

CARDIAC DISORDERS - Atrial flutter; Atrioventricular block first degree; Cardiac arrest; Cardiac disorders - Other (cardiovascular edema); Cardiac disorders - Other (ECG abnormalities); Chest pain - cardiac; Left ventricular systolic dysfunction; Palpitations; Pericarditis; Sinus bradycardia; Sinus tachycardia; Supraventricular tachycardia; Ventricular tachycardia

EAR AND LABYRINTH DISORDERS - Tinnitus

ENDOCRINE DISORDERS - Cushingoid

EYE DISORDERS - Dry eye; Flashing lights; Retinopathy

GASTROINTESTINAL DISORDERS - Abdominal distension; Anal mucositis; Ascites; Colonic perforation; Dysphagia; Flatulence; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (pale feces); Gastrointestinal hemorrhage[10]; Gastrointestinal obstruction[11]; Ileus; Mucositis oral; Pancreatitis; Rectal mucositis; Small intestinal mucositis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Malaise; Multi-organ failure

HEPATOBILIARY DISORDERS - Cholecystitis

INFECTIONS AND INFESTATIONS - Conjunctivitis; Infections and infestations - Other (opportunistic infection associated with >=Grade 2 Lymphopenia); Myelitis

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Fracture; Hip fracture; Vascular access complication

INVESTIGATIONS - Activated partial thromboplastin time prolonged; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)

METABOLISM AND NUTRITION DISORDERS - Acidosis; Hypercalcemia; Hyperkalemia; Hypoglycemia

MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Chest wall pain; Joint effusion; Muscle weakness lower limb; Neck pain; Osteonecrosis of jaw[12]

NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain

NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Leukoencephalopathy; Memory impairment; Nervous system disorders - Other (hyporeflexia); Spinal cord compression; Seizure; Somnolence; Transient ischemic attacks

PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Psychosis

RENAL AND URINARY DISORDERS - Urinary frequency; Urinary incontinence; Urinary tract pain

REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (hypogonadism); Vaginal hemorrhage

RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome); Urticaria

VASCULAR DISORDERS - Hot flashes; Phlebitis; Vascular disorders - Other (hemorrhage NOS)

NOTE: Lenalidomide (CC-5013) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

5.4 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

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 website (http://ctep.cancer.gov).

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

Omit = The current dose(s) during a cycle is skipped. The patient does not make up the omitted dose(s) at a later time.

Hold = Refers to decision made at the beginning of the cycle to delay the start of the cycle until the patient meets the protocol criteria to restart drug.

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

Table 5.1 Dose Modification Levels

Dose level		Dose	Day	Route
-4	Lenalidomide	5 mg	Day 1-10	orally
-3	Lenalidomide	10 mg	Day 1-10	orally
-2	Lenalidomide	15 mg	Day 1-10	orally
-1	Lenalidomide	20 mg	Day 1-10	orally
Starting dose level	Lenalidomide	25 mg	Day 1-10	orally

Table 5.2 Adverse Events and Dose Modifications

Use Common Terminology Criteria for Adverse Events (CTCAE) v4.0 unless otherwise specified			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Blood/Bone marrow	Hematologic nadirs: ANC < 500 for ≥ 7 days or PLT < 25,000 for ≥ 7 days or < 10,000 at any time	Lenalidomide/ CTX/ADR	Decrease lenalidomide to the next lowest dose level. If AE reoccurs with subsequent cycles, decrease lenalidomide to the next lowest dose level etc. If the lowest dose level is reached and AE occurs, discontinue lenalidomide. If AE occurs after lenalidomide discontinued, decrease CTX and ADR by 25% and follow standard dosing guidelines.
Cardiac General	Left ventricular systolic dysfunction ≥ grade 3	ADR	Discontinue ADR.
Renal/Genitourinary	Cystitis ≥ grade 2	CTX	Omit CTX until resolution of cystitis. Decrease CTX 50% of preceding dose for next cycle of treatment. If subsequent cycle is well tolerated and there is no grade ≥ 2 renal/GU adverse events, increase CTX to 100% of the original dose.
Neurology	Neuropathy – motor Grade 2	VCR	Omit VCR until neuropathy < grade 2 and resume at 50% dose reduction.
	Neuropathy – motor Grade ≥ 3		Discontinue VCR.
	Neuropathy – sensory Grade 3		Omit VCR until neuropathy < grade 2 and resume at 50% dose reduction.
	Neuropathy – sensory Grade 4		Discontinue VCR
Allergy/Immunology	Allergic reaction or hypersensitivity: Grade 2	Lenalidomide	Omit treatment until ≤ grade 1 and restart with prophylaxis with histamine blockers +/- steroids. If questions, call study chair.
	Allergic reaction or hypersensitivity: Grade 3		Omit therapy; treat the reaction and restart at MD discretion.
	Allergic reaction or hypersensitivity: Grade 4		If attributable to lenalidomide, discontinue treatment with lenalidomide.
Vascular	Venous thrombosis/embolism Grade 3 or 4		Discontinue lenalidomide. Lenalidomide can be restarted when patient is on full anticoagulation.

Use Common Terminology Criteria for Adverse Events (CTCAE) v4.0 unless otherwise specified			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Gastrointestinal	Nausea/Vomiting ≥ Grade 3	Lenalidomide/ RCHOP	Maximize antiemetic therapy; if maximized antiemetic treatment ineffective, take off treatment at physician discretion.
	Mucositis/Stomatitis ≥ Grade 2	ADR	Decrease ADR by 25% of preceding dose for next cycle. If no grade ≥3 GI toxicities in subsequent cycle, increase ADR to 100% of original dose.
	Constipation grade 2 Constipation ≥ grade 3	Lenalidomide	Initiate bowel regimen and continue lenalidomide. Omit lenalidomide until grade 2, initiate bowel regimen and restart lenalidomide.
Dermatology/ Skin	Desquamating (blistering rash) grade 3	Lenalidomide	Omit lenalidomide until ≤ grade 2 and restart at next lower dose level. If Lenalidomide held for more that 21 days, call study chair.
	Desquamating (blistering rash) grade 4		Discontinue lenalidomide.
	Non desquamating rash grade 4		Discontinue lenalidomide.
Infection	Infection with ANC ≥ 1,000/µL	Lenalidomide/ RCHOP	Hold drugs in case of an infection requiring IV antibiotics or hospitalization and restart when infection is controlled. If dosing is held ≥ 21 days call study chair. If adverse event reoccurs on subsequent cycles, decrease lenalidomide to next lower dose level and consider prophylactic antibiotics. If AE re-occurs at this dose level call study chair.
	Infection with ANC < 1,000/µL		Hold drugs in case of an infection requiring IV antibiotics or hospitalization and restart when infection is controlled, decrease lenalidomide to the next lowest dose level. If dosing is held ≥ 21 days call study chair. If adverse event reoccurs despite discontinuation of lenalidomide, then on subsequent cycle reduce CTX by 25% and ADR by 25%, consider prophylactic antibiotics. If dosing is held ≥ 21 days, call study chair.

	New or reactivation of viral hepatitis		Discontinue treatment, treat hepatitis.
Use Common Terminology Criteria for Adverse Events (CTCAE) v4.0 unless otherwise specified			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
BASED ON INTERVAL ADVERSE EVENT			
Other non-hematologic	Grade 3 or 4	Lenalidomide/ RCHOP	Hold drugs until toxicity has resolved to grade 2 or baseline grade then restart drugs. If questions, contact the study chair.
Use Common Terminology Criteria for Adverse Events (CTCAE) v4.0 unless otherwise specified			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
AT TIME OF RETREATMENT			
Blood/Bone marrow	ANC < 1500 and/or PLT < 75,000	Lenalidomide/ RCHOP	Hold drugs. Repeat CBC/diff and if counts recover any time before or on d28 to ANC ≥ 1500 and PLT ≥ 75,000 proceed with full dose.
	Between days 29-35: ANC </=1500 and/or PLT </=75,000		Hold drugs. Use GCSF or GM-CSF at discretion of local MD. Repeat CBC/diff and if counts recover any time before or on d35 to ANC ≥ 1500 and PLT ≥ 75,000 decrease lenalidomide to the next lowest dose level, continue 100% RCHOP. If lenalidomide at the lowest dose level, discontinue. If not recovered continue to hold.
	Day 36 and beyond: ANC </=1500 and/or PLT </=75,000		Hold drugs. Use GCSF or GM-CSF at discretion of local MD. Repeat CBC/diff and when counts recover to ANC ≥ 1500 and PLT ≥ 75,000, discontinue lenalidomide, resume RCHOP with 25% ADR and 25% CTX dose reduction. Future dose modifications of RCHOP should follow standard RCHOP guidelines.
Other non-hematologic	Grade ≥ 3		Hold drugs until toxicity has resolved to grade 2 or baseline grade then restart lenalidomide at next lower dose level. If lenalidomide is at lowest level, discontinue. If next cycle is delayed by ≥ 2 weeks, contact study chair.

Rev. 1/15

NOTE: List of agents in Table 5.2: Lenalidomide, cyclophosphamide (CTX), doxorubicin (ADR), vincristine (VCR), rituximab, cyclophosphamide, doxorubicin, vincristine and prednisone (RCHOP).

5.5 Supportive Care

All supportive measures consistent with optimal patient care will be given throughout the study.

Rev. 1/15

5.5.1 Patients who are not already on anticoagulation should receive aspirin (70-325 mg) daily. This should be discontinued if the patient is intolerant of aspirin or develops bleeding complications irrespective of the platelet count. Patients unable to take ASA must discontinue lenalidomide.

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

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

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

5.5.5 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. Pegfilgrastim support will be given with each cycle of R2CHOP. Pegfilgrastim use in RCHOP arm should follow standard guidelines. Use of other than Pegfilgrastin growth factors including (G-CSF) or granulocyte macrophage-colony stimulating factor (GM-CSF) is allowed per local practice preference. The dose and schedule of the selected drug is also determined per local practice as used with standard RCHOP chemotherapy.

5.5.6 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. Diarrhea: This could be managed conservatively with anti-diarrheal agents such as loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day). In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals. If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting should be hospitalized for intravenous hydration and correction of electrolyte imbalances.

5.6 Duration of Therapy

Patients will receive protocol therapy **for total of 6 cycles** unless:

5.6.1 Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued. In this event submit forms according to the instructions in the ***E1412*** Forms Submission Guidelines

5.6.2 Patient withdraws consent.

5.6.3 Patient experiences unacceptable toxicity.

5.6.4 Non-protocol therapies are administered.

5.6.5 Pregnancy

Rev. 10/15

5.6.6 Patient shows evidence of progressive disease after 3 cycles of therapy. Patients demonstrating response or stable disease may continue through 6 cycles of therapy.

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, and for survival for 10 years from the date of registration.

Rev. 1/14

6. Measurement of Effect

NOTE: These criteria are based upon the criteria from the Revised Response Criteria for Malignant Lymphoma, (Cheson et al.), Journal of Clinical Oncology, 2007, Vol. 25:579-586.

The criteria use the following categories of response: Complete Response (CR), Partial Response (PR), Stable Disease (SD), Relapse and Progression (PD). In the case of stable disease, follow-up assessments must have met the SD criteria at least once after study entry at a minimum interval of six weeks.

The following guidelines are to be used for establishing tumor measurements at baseline and for subsequent comparison:

- The six largest measurable nodes or extranodal masses must be identified as Target Lesions at baseline.
- If there are 6 or fewer measurable nodes and extranodal masses, all must be listed as target
- If there are more than 6 involved measurable nodes or extranodal masses, the 6 largest nodes or extranodal masses should be selected according to the following features: a) they should be clearly measurable in at least two perpendicular measurements; b) they should be from as disparate regions of the body as possible; and c) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
- Measurements for all target nodes and extranodal masses will be reported at baseline. Measurements on non-target nodes are not required.
- The lymph nodes or extranodal masses selected for measurement should be measured in two perpendicular diameters, one of which is the longest perpendicular diameter. The lymph nodes should be measured in centimeters to the nearest one tenth of a centimeter (e.g. 2.0 cm, 2.1cm, 2.2 cm, etc.)
- The two measured diameters of each lymph node site or extranodal mass should be multiplied giving a product for each nodal site or extranodal mass. The product of each nodal site should be added, yielding the sum of products of the diameters (SPD). The SPD will be used in determining the definition of response for those who have less than a complete response.
- Interim PET after 3 cycles is recommended but not mandatory. If interim PET is unavailable response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses. PET at the completion of therapy (PET6) is mandatory.

6.1 Complete Response

Complete disappearance of all detectable clinical evidence of disease, and disease-related symptoms if present prior to therapy.

6.1.1 In patients with no pre-treatment PET scan, or for lymphomas for which the PET scan was positive prior to therapy: a post-treatment residual mass of any size is permitted as long as it is PET-negative.

6.1.2 The spleen and/or liver, if considered enlarged prior to therapy on the basis of a physical examination or CT scan, should not be palpable on

physical examination, and nodules related to lymphoma should disappear. However, no normal size can be specified because of the difficulties in accurately evaluating splenic and hepatic size and involvement. For instance, a spleen considered normal size may contain lymphoma, whereas an enlarged spleen may not necessarily reflect the presence of lymphoma, but variations in anatomy, blood volume, the use of hematopoietic growth factors, or other causes.

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

NOTE: Complete Remission/unconfirmed (CRu): Using the above definition for CR and that below for PR eliminates the category of CRu.

6.2 Partial Response (PR)

The designation of PR requires all of the following:

6.2.1 A ≥ 50% decrease in sum of the product of the diameters (SPD) of up to 6 of the largest dominant nodes or extranodal masses. These nodes or masses should be selected according to the following: (a) they should be clearly measurable in at least 2 perpendicular dimensions; if possible, they should be from disparate regions of the body; (b) they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.

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

6.2.3 Bone marrow assessment is irrelevant for determination of a PR if the sample was positive prior to treatment. However, if positive, the cell type should be specified, e.g. large-cell lymphoma or small cleaved cell lymphoma.

6.2.4 No new sites of disease.

6.2.5 The post-treatment PET should be positive at any previously involved sites.

6.2.6 For variably FDG-avid lymphomas/FDG-avidity unknown, without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT scan criteria should be used.

6.2.7 Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

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

6.3 Stable Disease (SD)

6.3.1 Failing to attain the criteria needed for a PR or CR, but not fulfilling those for progressive disease (see below).

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

6.4 Progression (PD) and Relapse

For determination of relapsed and progressive disease, lymph nodes should be considered abnormal if the long axis is more than 1.5 cm, regardless of the short axis. If a lymph node has a long axis of 1.1 to 1.5 cm, it should only be considered abnormal if the short axis is more than 1 cm. Lymph nodes ≤ 1 x ≤ 1 cm will not be considered as abnormal for relapse or progressive disease.

Treatment decisions in patients with presumed refractory, relapsed or progressive disease should not be made solely on the basis of a single PET scan without histologic confirmation.

6.4.1 Appearance of any new lesion more than 1.5 cm in any axis during or at the end of therapy, even if other lesions are decreasing in size.

Increased FDG uptake in a previously unaffected site should only be considered relapsed or progressive disease after confirmation with other modalities. In patients with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.

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

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

6.4.4 Lesions should be PET positive unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT).

6.4.5 Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these response criteria, 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 negative.

6.5 Duration of Response

This is measured from the documented beginning of response (CR or PR) to the time of relapse. This is measured in responders.

6.6 Survival

Survival is defined as the date of study entry to the date of death.

6.7 Progression-Free Survival

Progression-free Survival (PFS) is defined as the time from entry onto study until lymphoma progression or death from any cause. PFS reflects tumor growth and, therefore, occurs prior to the endpoint of overall survival. It is not confounded by the administration of subsequent therapy. Unlike survival, the precise date of progression is generally unknown. It may be defined as the first date of documentation of a new lesion or enlargement of a previous lesion, or the date of the scheduled clinic visit immediately after radiologic assessment has been completed. Where there is missing information, censoring of the data may be defined as the last date at which progression status was adequately assessed.

6.8 Time to Progression

Time to progression (TTP) is defined as the time from study entry until lymphoma progression or death due to lymphoma. In TTP, deaths from other causes are censored either at the time of death or at an earlier time of assessment, representing a random pattern of loss from the study.

6.9 Disease-Free Survival

Disease-free survival is measured from the time of occurrence of disease-free state (e.g., the adjuvant setting following surgery or radiation therapy) or attainment of a complete remission) to disease recurrence or death without relapse, or a new primary of the same type. This definition may be complicated by deaths that occur during the follow-up period that are unrelated to the lymphoma and there is controversy as to whether such deaths should be considered as events or censored at the time of occurrence. Whereas it is often possible to identify those deaths related to the lymphoma, there is the potential for bias in the attribution of deaths.

6.10 Disease-Specific Survival

Disease-specific survival (e.g., lymphoma-specific survival, cause-specific survival) is defined as the time of randomization until death due to disease. Death due to other reason is censored at the time of death. It is potentially subject to bias because the exact cause of death is not always easy to ascertain. To minimize the risk of bias, the event should be recorded as death from lymphoma, or from toxicity from the drug. Death from unknown causes should be attributed to the drug.

7. Study Parameters

7.1 Therapeutic Parameters

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Tests and procedures	Pre-study	During treatment		Follow-Up[18,19]	
	≤ 28 days prior to registration	≤ 2 days (±2 days) prior to subsequent treatment (cycles 2-6)	After completion of therapy (4-10 weeks after day 1 of cycle 6)	Every 3 months for year 1-2	Every 6 months for year 3
History and exam, weight, height	X	X	X	X	X
Adverse event assessment	X	X	X	X	X
ECOG PS	X	X			
International Prognostic Index (IPI)	X				
Serum pregnancy test[1, 13]	X[1]	X[1]	X[1]		
CBC (HgB, WBC, Differential, PLT)	X	X	X	X	X
Chemistry : Total bilirubin, AST, Alk. Phosphatase, LDH, Creatinine, Sodium, Potassium, Calcium	X	X	X	X	X
Left ventricular function assessment	X[7]				
Direct bilirubin[3]	X				
Hepatitis B and C screen[2]	X				
HIV screening test	X				
PET/CT scan[9, 11]	X[5]	Before cycle 4[4]	X[5]	Every 6 months, yrs 1 and 2[12,16]	At 36 months[12,17]
Other scan (MRI), dedicated CT if clinically indicated by discretion of local physician	X	Before cycle 4	X		
Bone marrow aspirate and biopsy (unilateral or bilateral)	X[10]		X[6]		
Cerebrospinal fluid analysis	X[8]				
Medication Diary	X	X			
Biological Sample Submissions	See Sections 7.2 and 11				
Education and Counseling	X[14]				
Dispense lenalidomide	X[15]				

1. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 and must either commit to continued abstinence from heterosexual intercourse or begin

TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy.

2. Hepatitis B surface antigen (HbsAg) and antibody to Hepatitis B core (anti-HBc); Hepatitis C antibody
3. To be done only if the total bilirubin is abnormal.

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4. Interim PET/CT preferred, if PET/CT scan not available, interim CT scan chest, abdomen and pelvis can be used.
5. PET mandatory. If positive after the completion of cycle 6, a biopsy of PET positive area may be done at MD discretion.
6. Repeat BM only required if initial BM was positive.
7. MUGA or Echo.
8. A lumbar puncture and cytologic examination of the cerebrospinal fluid is not required, but should be performed if clinically indicated. Patients with CNS/CSF involvement are NOT eligible.
9. Measurements should preferably be done by dedicated CT or off the CT images of a PET/CT. The image number should be included with the measurements. If patient has had PET/CT that will satisfy the PET and CT requirement. If questions, call the study chair.
10. Bone marrow must be done ≤ 6 weeks prior to study registration.
11. Images will be submitted to ACRIN via the ACR Imaging Core Lab. See image submissions instructions in Section 10.
12. CT preferred for follow up scans rather than PET.

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13. Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to initiation of lenalidomide. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 21 days and then every 21 days while on study treatment (including breaks in treatment); at discontinuation of lenalidomide and at day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 21 days and then every 10 days while on study treatment (including breaks in treatment), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (Appendix IX: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
14. The Lenalidomide Education and Counseling Guidance Document (Appendix VIII) must be completed and signed by a trained counselor at the participating site prior to each dispensing of lenalidomide treatment. A copy of this document must be maintained in the patient records. The Lenalidomide Information Sheet (Appendix X) will be given to each patient receiving lenalidomide treatment. The patient must read this document prior to starting lenalidomide study treatment and each time they receive a new supply of study drug.
15. Only enough lenalidomide for 28 days or one cycle of study treatment (whichever is shorter) may be provided to the patient each cycle.
16. CT scan or PET (CT preferred) every 6 months for the first 2 years, i.e. at 6, 12, 18 and 24 months post-chemotherapy.
17. CT at 36 months only (year 3).

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18. Patients in follow-up will follow this schedule:

    For tests:

    - Every 3 months if the patient is less than 2 years from study entry.
    - Every 6 months for the 3rd year

    For disease progression, second malignancy and survival:

    Every 12 months for years 4-10

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19. After documented progression patient will only be followed for survival and secondary malignancies. Additional scans and evaluations will no longer be required for submission.

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7.2 Biological Sample Submissions

Specimens are to be submitted as outlined in Section 11.

All specimens submitted must be entered and tracked via the online ECOG-ACRIN Sample Tracking System (STS).

	Baseline	Before Cycle Four (4)	After Completion of Therapy	Submit to:
MANDATORY *for Central Diagnostic Review and Laboratory Research Studies* – Submit following pre-registration to Step 0				
Rev. 1/15 Tumor Tissue	X[1]			Mayo Clinic Lymphoma Laboratory
Submit from patients who are randomized to treatment (Step 1) and answer *"Yes"* to *"I agree to provide additional blood for research."*				
Peripheral Blood, ACD (yellow top tubes)[2]	X[3]	X	X	Mayo Clinic Lymphoma Laboratory
Peripheral Blood, EDTA (purple top tube)[2]	X[3]	X	X	
Peripheral Blood, Red Top tube[2]	X[3]	X	X	

1. Representative tumor tissue (block preferred) and related pathology reports must be submitted for central diagnostic review and defined laboratory research studies following pre-registration (Step 0) as outlined in Section 11. Failure to submit the required materials will render the patient ineligible for participation in the trial (randomization to Step 1).
2. Kits are available for collection and shipment of the blood samples. See Section 11.3.1 for instructions.
3. Prior to treatment.

8. Drug Formulation and Procurement

Availability

Drug Ordering: ***Celgene*** is supplying ***lenalidomide*** through the Division of Cancer Treatment and Diagnosis, NCI, for this protocol. Maintenance of NCI drug accountability records is required. ***Lenalidomide (NSC 703813)*** may be requested by the Principal Investigator (or their authorized designees) at each participating institution. Pharmaceutical Management Branch (PMB) policy requires that drug be shipped directly to the institution where the patient is to be treated. PMB does not permit the transfer of agents between institutions (unless prior approval from PMB is obtained – see general information). Active CTEP-registered investigators and investigator-designated shipping designees and ordering designees can submit agent requests through the PMB Online Agent Order Processing (OAOP) application < https://eapps-ctep.nci.nih.gov/OAOP/pages/login.jspx >. Access to OAOP requires the establishment of a CTEP Identity and Access Management (IAM) account < https://eapps-ctep.nci.nih.gov/iam/ > and the maintenance of an "active" account status and a "current" password. For questions about drug orders, transfers, returns, or accountability, call 240-276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET) or email PMBAfterHours@mail.nih.gov anytime.

NCI Supplied Agent(s) – General Information

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling 240-276-6575 Monday through Friday between 8:30 AM and 4:30 PM Eastern Time.

Drug Returns: All unused drug supplies must be returned to the PMB. When it is necessary to return study drug (e.g., sealed vials remaining when a patient permanently discontinues protocol treatment, expired vials recalled by the PMB), investigators must return the study drug to the PMB using the NCI Return Agent Form available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575.

Drug Accountability: The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, disposition, and return of all drugs received from the PMB using the NCI Investigational Agent Accountability Record available on the NCI home page (http://ctep.cancer.gov) or by calling the PMB at 240-276-6575. These forms will be reviewed for accuracy and completeness during NCI cooperative group quality assurance audits.

8.1 Lenalidomide

8.1.1 Other Names

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

CC-5013, Revlimid™, CDC-501

8.1.2 Classification

Immunomodulatory agent.

CAS Registry Number: 191732-72-6

Molecular Formula: $C_{13}H_{13}N_3O_3$

M.W.: 259.25

8.1.3 Mode of Action

Lenalidomide, a thalidomide analog, is an immunomodulatory agent with a spectrum of activity that is still under investigation. Some of its effects include inhibition of inflammation, inhibition of angiogenesis, inhibition of hematopoietic tumor cell proliferation, modulation of stem cell differentiation and upregulating responses of T cells and NK cells.

8.1.4 Storage and Stability

Store capsules at room temperature (25°C). Excursions are permitted (to 15-30°C).

Refer to the package labeling for expiration date. Lenalidomide stability is adequate for at least 28 days after transferring to a pharmacy vial.

8.1.5 Dose Specifics

25 mg, by mouth, on days 1 through 10 of each cycle, for 6 cycles.

8.1.6 Route of Administration

Take lenalidomide by mouth with or without food. Do not crush, chew or open capsules.

NOTE: Before lenalidomide is dispensed, patients must have 1) a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. Pharmacists may be trained counselors (see Lenalidomide Counselor Program Site Counselor Identification Form in the protocol). The counseling requirements for investigational-use lenalidomide are separate from the RevAssist program. Only a 28-day supply may be dispensed to a patient at one time.

8.1.7 Incompatibilities

Periodic monitoring of digoxin levels is recommended during coadministration with lenalidomide.

Monitor patients receiving concomitant warfarin per standard practice guidelines.

Lenalidomide is not a substrate of human CYP enzymes, nor is it an inhibitor or inducer.

8.1.8 Availability

Celgene supplies and CTEP, NCI, DCTD distributes lenalidomide 5 mg (size 2) and 25 mg (size 0) hard gelatin capsules in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with HDPE caps. Bottles contain 100 capsules per container.

The capsules also contain anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

8.1.9 Side Effects

See Section 5.3 for side effects.

8.1.10 Nursing/Patient Implications

Risks Associated with Pregnancy

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

Definition of female of childbearing potential (FCBP)

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

Before starting study drug:

Female Subjects:

- FCBP must have two negative pregnancy tests (minimum sensitivity of 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

Male Subjects:

- Must agree to use a latex condom during sexual contact with females of childbearing potential while participating in the study and for at least 28 days following discontinuation from the study even if he has undergone a successful vasectomy.

All Subjects:

- Only enough lenalidomide for one cycle of therapy may be dispensed with each cycle of therapy.
- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.
- If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.
- Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately

Counseling

- In investigational studies where lenalidomide is supplied by the NCI, patients will be counseled by a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). Two healthcare professionals at each site will be trained by Celgene in requirements specific to counseling of subjects (investigators cannot counsel patients as part of this requirement). Refer to specific protocol sections for more information about training requirements.
  - Once trained, these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Lenalidomide Education and Counseling Guidance Document and no drug will be dispensed until this step occurs. Counseling includes verification with the patient that required pregnancy testing was performed and results were negative. A Lenalidomide Information Sheet will be supplied with each medication dispense.

8.1.11 References

Richardson PG, Schlossman RL, Weller E, et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed Multiple Myeloma. Blood 2002; 100:3063-7.

Richardson P, Jagannath S, Schlossman R, et al. A Multi-center, Randomized, Phase II Study to Evaluate the Efficacy and Safety of 2 CDC-5013 Dose Regimens When Used Alone or in Combination with Dexamethasone (Dex) for the Treatment of Relapsed or Refractory Multiple Myeloma (MM). Blood 2003; 102:235a.

Zangari M, Tricot G, Zeldis J, Eddlemon P, Saghafifar F, Barlogie B. Results of Phase I Study of CC-5013 for the Treatment of Multiple Myeloma (MM) Patients Who Relapse after High Dose Chemotherapy (HDCT). Blood 2001:775a (A3226).

Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in Multiple Myeloma. Blood 2001; 98:210-6.

8.2 Rituximab

8.2.1 Other Names

IDEC-C2B8, Chimeric anti-CD20 monoclonal antibody, Rituxan.

8.2.2 Classification

Antibody.

8.2.3 Mode of Action

Rituximab is a chimeric murine/human gamma 1 kappa monoclonal antibody (Chinese hamster ovary [CHO] transfectoma). It recognizes the CD20 antigen expressed on normal B cells and most malignant B-cell lymphomas. It binds with high affinity to CD20-positive cells, performs human effector functions *in vitro*, and depletes B cells *in vivo*. The Fab domain of rituximab binds to the CD20 antigen on B-lymphocytes and the Fc domain recruits immune effector functions to mediate Bcell lysis *in vitro*. The biological effect is manifested by B-cell depletion in peripheral blood, lymph nodes, and bone marrow.

8.2.4 Storage And Stability

Intact vials of rituximab are stored at refrigerated temperatures of 2 degrees to 8 degrees Celsius (36 degrees to 46 degrees Fahrenheit). Protect vials from direct sunlight. Once diluted to a concentration of 1 to 4 mg/mL in polyvinylchloride or polyolefin IV bags containing normal saline or 5% dextrose, the product is stable for up to 24 hours at 2 degrees to 8 degrees Celsius, and at room temperature for an additional 12 hours after refrigeration (for a maximum period of 36 hours) if protected from light.

8.2.5 Dose Specifics

Rituximab will be administered at 375 mg/m² intravenously throughout each aspect of this trial (induction and continuation).

8.2.6 Preparation

Withdraw the necessary amount of rituximab and dilute to a final concentration of 1 to 4 mg/mL into an infusion bag containing either 0.9% Sodium Chloride or 5% Dextrose in Water. Gently invert the bag to mix the solution. Caution should be taken during the preparation of the drug, as shaking can cause aggregation and precipitation of the antibody.

8.2.7 Administration

NOTE: Patients should be pre-medicated with acetaminophen and an antihistamine as hypersensitivity prophylaxis.

Rituximab is administered intravenously. An in-line filter is not required. The initial rate is 50 mg/hr for the first hour. If no toxicity is seen, the rate may be escalated gradually in 50 mg/hour increments at 30-minute intervals to a maximum of 300mg/hr. If the first dose is well tolerated, the initial rate for subsequent dose is 100mg/hr, increased gradually in 100 mg/hr increments at 30-minute intervals, not to exceed 400 mg/hr. If the patient experiences fever and rigors, the antibody infusion is discontinued. The severity of the side effects should be evaluated. If the symptoms improve, the infusion is continued initially at one-half the previous rate. Following the antibody infusion, the intravenous line should be maintained for medications as needed. If there are no complications after one hour of observation, the intravenous line may be discontinued. Oral pre-medication (2 tablets, 650 to 1000 mg, of acetaminophen and 25 to 50 mg

diphenhydramine) will be administered 30 to 60 minutes prior to starting each infusion of rituximab. The patient should be treated according to the best available local practices and procedures. In patients with detectable circulating lymphoma cells, it is strongly advised that the initial infusion rate be reduced to 25 mg/hr; these patients may experience more frequent and severe transient fever and rigors, shortness of breath, and hypotension.

NOTE: In addition, alternative rituximab infusion rates (i.e., "rapid rituximab infusion") can be used per institutional guidelines as long as the total number of milligrams of rituximab is the same and that "rapid infusion" is not administered with the patients first rituximab cycle. Further, a rituximab infusion time should never be given over less than 90 minutes (common infusion time for "rapid infusion" is 20% of the bag volume over 30 minutes, and then 80% of the remaining bag volume over 60 minutes).

8.2.7.1 Hypersensitivity and Infusion Reactions

Available at the bedside prior to rituximab administration will be epinephrine for subcutaneous injection, diphenhydramine hydrochloride for IV injection, and resuscitation equipment for the emergency management of anaphylactoid reactions.

Rituximab should be administered intravenously through a dedicated line at an initial rate of 50 mg/hr. If hypersensitivity or infusion-related events do not occur, escalate the infusion rate in 50 mg/hr increments every 30 minutes, to a maximum of 300 mg/hr. If hypersensitivity or infusion-related events develop, the infusion should be temporarily slowed or interrupted. The patient should be treated according to the appropriate standard of care. The infusion can be continued at one-half the previous rate when symptoms abate. Subsequent rituximab infusions can be administered at an initial rate of 100 mg/hr, and increased at 30-minute intervals by 100 mg/hr increments to a maximum of 400 mg/hr.

Rituximab Infusion Rate Adjustments

Infusion Rate	Fever		Rigors		Mucosal Congestion/ Edema		Hypotension
	(or)	→	(or)	→		→	
Decrease ½	> 38.0ºC		Mild		Mild		Mild
Interrupt	> 39.0ºC		Moderate		Moderate		Mild to Moderate

During the rituximab infusion, the patient's vital signs (blood pressure, pulse, respiration, temperature) should be monitored at least every 15 minutes x 4 and then hourly

until the infusion is discontinued. Following the antibody infusion, the intravenous line should be maintained for medications as needed. If there are no complications after one hour of observation, the intravenous line may be discontinued.

8.2.7.2 Cardiovascular

Infusions should be discontinued in the event of serious or life threatening cardiac arrhythmias. Patients who develop clinically significant arrhythmias should undergo cardiac monitoring during and after subsequent infusions of rituximab. Patients with preexisting cardiac conditions including arrhythmias and angina have had recurrences of these events during rituximab therapy and should be monitored throughout the infusion and immediate post-infusion period.

8.2.7.3 Tumor Lysis Syndrome

Rituximab rapidly decreases benign and malignant CD20 positive cells. Tumor lysis syndrome has been reported to occur within 12 to 24 hours after the first rituximab infusion in patients with high numbers of circulating malignant lymphocytes. Patients with high tumor burden (bulky lesions) may also be at risk. Patients at risk of developing tumor lysis syndrome should be followed closely and appropriate laboratory monitoring performed. Appropriate medical therapy should be provided for patients who are at risk for, or who develop, tumor lysis syndrome.

8.2.8 Compatibility/Incompatibilities

Do not mix or dilute rituximab with other drugs. No incompatibilities between rituximab and polyvinylchloride or polyethylene bags have been observed.

8.2.9 Availability

Commercially available: Preservative-free injection 10mg/mL, in 10 and 50 mL single-unit vials.

Please see Package Insert for further information.

8.2.10 Side Effects

Please refer to the Package Insert.

8.2.11 Nursing /Patient Implications

1. Monitor blood pressure, pulse, respiration, and temperature every 15 minutes x 4 or until stable and then hourly until the infusion is discontinued.
2. Have epinephrine for subcutaneous injections, diphenhydramine for intravenous injection, and resuscitation equipment for emergency management of anaphylactoid reactions available.
3. Monitor and alter infusion rates in the presence of toxicities.

4. Carriers of hepatitis B virus should be closely monitored for clinical and laboratory signs of active HBV infection and for signs of hepatitis throughout study participation.
5. Due to the risks of bowel obstruction and bowel perforation, patients should be monitored for complaints of abdominal pain, especially early in the course of treatment.
6. Patients with concurrent RA should be monitored throughout the infusion and rituximab should be discontinued in the event of a serious or life-threatening cardiac event.

Rituximab shows no significant effect on bone marrow reserve and no apparent increased rate of infections in heavily pretreated, relapsed lymphoma patients. Prophylaxis for Tumor Lysis Syndrome (TLS) should be used in patients with bulky tumor masses (> 10cm). Patients should be provided IV hydration and administered allopurinol. Precautionary hospitalization should be made available for patients who experience severe infusional symptoms which do not resolve after discontinuation or completion of the infusion. Hospitalization is not mandated for these patients. This will be left to the discretion of the investigator. It is unlikely that TLS will be seen in this study of stages 1 and 2 diffuse large cell disease.

NOTE: Please refer to the commercially-available package labeling for more information.

8.2.12 References

Product Information: rituximab. IDEC Corporation, December, 1998.

Reff ME *et al.* Depletion of B cell *in vivo* by a chimeric mouse human monoclonal antibody to CD20. Blood 1994; 83:435-45.

Demidem A *et al.* Chimeric anti-CD20 antibody (IDEC-C2B8) is apoptic and sensitizes drug resistant human B cell lymphomas and AIDS related lymphomas to the cytotoxic effect of CDDP, VP-16, and toxins. FASEB 1995; J9:A206.

Maloney DG *et al.* Phase I clinical trial using escalating single dose infusion of chimeric anti-CD20 monoclonal antibody (IDEC-C2D8) in patients with recurrent B-cell Lymphoma. Blood 1993; 82(Suppl 1):445a.

Maloney DG *et al.* Initial report in a phase I/II multiple dose clinical trial of IDEC-C2B8 (chimeric anti-CD20) in relapsed B-cell lymphoma. Proc Am Soc Clin Oncol 1994; 13:993.

8.3 Doxorubicin

8.3.1 Other Names

Adriamycin R, Rubex R, Adriamycin RDF R, Adriamycin PFS R, hydroxydaunorubicin, hydroxydaunomycin, ADR.

8.3.2 Classification

Anthracycline antibiotic.

8.3.3 Mode of Action

Intercalation between adjoining nucleotide pairs in the DNA helix causes inhibition of DNA and DNA-dependent RNA synthesis. Free radical generation is responsible for cardiac toxicity. Doxorubicin also inhibits topoisomerase II.

8.3.4 Storage and Stability

Rubex or Adriamycin RDF intact vials are stable protected from light at room temperature. Adriamycin PFS vials must be refrigerated. Reconstituted solutions are stable for 24 hours at room temperature and 48 hours under refrigeration. The Adriamycin RDF 150 mg multidose vial is stable after reconstitution for 7 days at room temperature or 15 days if refrigerated and protected from sunlight.

8.3.5 Dose Specifics

The usual dose is 60-75 mg/m^2 as a bolus injection or continuous infusion over 2-4 days, repeated every 3-4 weeks. Other dosage schedules are 20 mg/m 2 weekly and 30 mg/m^2 daily for three days, repeated every 3-4 weeks.

8.3.6 Preparation

Add 5, 10, 25, 50, or 75 ml of preservative-free normal saline to the 10, 20, 50, 100, or 150 mg vial to produce a solution containing 2 mg/ml.

8.3.7 Administration

Intravenously, either as a bolus injection or as a continuous infusion through a central venous line.

8.3.8 Incompatibilities

Physically incompatible with heparin, fluorouracil, aminophylline, cephalothin, dexamethasone, diazepam, hydrocortisone, and furosemide.

8.3.9 Compatibilities

Stable with vincristine in normal saline for five days at room temperature protected from light. Also compatible in solution with cyclophosphamide.

8.3.10 Availability

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

8.3.11 Side Effects

1. Hematologic: Leukopenia (dose-limiting), also thrombocytopenia and anemia. Nadir 10-14 days, recovery in 21 days.
2. Dermatologic: Alopecia, usually complete; hyperpigmentation of nailbeds and dermal creases; radiation recall.

3. Gastrointestinal: Nausea and vomiting, sometimes severe; anorexia, diarrhea; mucositis, especially with daily x 3 schedule.
4. Cardiovascular: Arrhythmias, ECG changes; rare sudden death. Congestive heart failure due to cardiomyopathy related to total cumulative dose; risk is greater with total doses > 550 mg/m^2, mediastinal irradiation pre-existing cardiac disease, advanced age; risk is reduced with weekly or continuous infusion regimens.
5. Other: Red discoloration of urine; fever; anaphylactoid reaction; may enhance cyclophosphamide cystitis or mercaptopurine hepatotoxicity.
6. Local effects: Vesicant if extravasated; flush along vein, facial

8.3.12 Nursing Implications

1. Monitor CBC, platelet counts.
2. Vesicant - do not extravasate. Refer to extravasation protocol if inadvertent infiltration occurs.
3 Advise patient of alopecia. Instruct on how to obtain wig, hairpiece, etc. Hair loss generally occurs 2-4 weeks after injection and is usually complete.
4. Advise patient of red discoloration of urine for 24 hours after administration of the drug.
5. Administer antiemetics as indicated.
6. Assess for stomatitis and treat symptomatically. Generally occurs 7-10 days after injection.
7. Be aware of "Adria" flare - most common reaction consists of an erythematous streak up the vein. It is associated with urticaria and pruritus. Occasionally the use of corticosteroids and/or antihistamines has been useful.
8. Monitor for signs and symptoms of cardiomyopathy. Calculate total cumulative dose with each administration.

NOTE: Please refer to the commercially-available package labeling for more information.

8.3.13 References

Speth PA. Clinical pharmacokinetics of doxorubicin. Clin Pharmacokinetics 15:51-31, 1988.

Von Hoff DD, et al. Risk factors for doxorubicin-induced congestive heart failure. Ann Intern Med 91:710-17, 1979.

Lum BL et al. Doxorubicin: Alteration of dose scheduling as a means of reducing cardiotoxicity. Drug Intell Clin Pharm 19:259-64, 1985.
ECOG 2/91

8.4 Cyclophosphamide

8.4.1 Other Names

CytoxanÒ, NeosarÒ, CTX, CPM

8.4.2 Classification

Cyclophosphamide is a prodrug biotransformed to active alkylating metabolites by a mixed function microsomal oxidase system.

8.4.3 Mode of Action

Cyclophosphamide metabolites are thought to disrupt cell division primarily by crosslinking DNA strands. Cyclophosphamide is considered cell cycle phase non-specific.

8.4.4 Storage and Stability

Injectable powder is stored at room temperature 25°C (77°F). The temperature is not to exceed 30°C (90 F°). Reconstituted parenteral solutions are stable for 24 hours at room temperature for 6-14 days if refrigerated.[1-4]

8.4.5 Dose Specifics

Doses may vary significantly based on the myelosuppressive effects of other drugs used in combination or the effects of prior radiation or chemotherapy that may compromise bone marrow reserve.

Cyclophosphamide may be given as a single dose or in several divided doses over a period of time. Some common doses are 500 mg-1.5 gm/m^2 IV every 3 weeks; 50-200 mg/m^2 PO daily x 14 days every 28 days; 400 mg/m^2 daily x 4 days every 4-6 weeks; 60 mg/kg IV x 2 days for bone marrow transplant conditioning.

8.4.6 Preparation

Dissolve the 100 mg, 200 mg, 500 mg, 1 gm, and 2 gm vials in 5, 10, 25, 50, and 100 ml of sterile water, respectively, resulting in a solution of 20 mg/ml. Shake vials vigorously and warm slightly in lukewarm water to facilitate dissolution. The lyophilized form is more easily solubilized.

Reconstituted solutions may be further diluted in D5W, D5W/NS, D5W/Ringer's Injection, Lactated Ringer's Injection, and ½ NS.

8.4.7 Administration

May be given IV push, or by IV infusion. Patients are to be well hydrated to prevent cystitis.

8.4.8 Compatibilities

Numerous compatibility studies have been published. For specific details refer to Handbook on Injectable Drugs by Lawrence A. Trissel.[5]

8.4.9 Availability

Cyclophosphamide is commercially available for parenteral injection as 100 mg, 200 mg, 500 mg, 1 g, and 2 g vials.

8.4.10 Side Effects

Side effects vary significantly based on the specific dose and duration of cyclophosphamide.

Incidence more frequent (>5%):

Anemia, leukopenia (usually asymptomatic; less frequently fever and/or chills); Thrombocytopenia (usually asymptomatic; less frequently unusual bleeding or bruising; black tarry stools; blood in urine or stools; pinpoint red spots on skin). Nadir counts usually occur 7 to 12 days after administration and recovery usually compete by day 17 to 21.

Alopecia

Anorexia, nausea and vomiting

Gonadal suppression (azoospermia, missed menstrual periods) resulting in infertility.

Return of normal gonadal function and fertility occurs with time in many younger men and women.[3]

Hemorrhagic cystitis[3,8]

Incidence less frequent (1-5%):

Stomatitis

Incidence rare (1%):

Anaphylaxis (tachycardia, shortness of breath, wheezing, tightness in throat), flushing or redness of face, diarrhea , skin rash, pneumonitis or interstitial pulmonary fibrosis, syndrome of inappropriate antidiuretic hormone (SIADH), chemical phlebitis (redness, swelling or pain at site of injection), secondary malignancies, blurred vision, cardiac toxicity presenting as congestive heart failure, hemorrhagic myocarditis, myocardial necrosis, and pericarditis (seen with high dose regimens used with bone marrow transplantation).

8.4.11 Drug Interactions

Digoxin: Several studies conducted in lymphoma patients receiving combination chemotherapy including cyclophosphamide revealed a 20–50% reduction in digoxin absorption when digoxin tablets were administered. When digoxin capsules were administered no significant decrease in digoxin absorption occurred. To avoid decreased serum digoxin levels the use of digoxin in liquid form (liquid or capsules containing liquid digoxin) instead of tablets is recommended. [3,10-11]

Pentostatin: Two case reports describe fatal cardiac toxicity in patients receiving CTX 6.4 g/m^2 over 4 days and pentostatin 4 mg/m^2 over 4 hours on day 3. Until additional data from clinical trials

demonstrate the safety of concurrent use of these drugs concurrent administration is not recommended. [3,7]

Succinylcholine: Cyclophosphamide may prolong the effects of succinylcholine by irreversibly inhibiting the enzyme pseudocholinesterase. Limited clinical observations and in vitro studies suggest that prolonged apnea might result when succinlycholine is administered to some patients also receiving cyclophosphamide. Management options include avoiding concurrent therapy or if concurrent therapy can not be avoided, to monitor for prolonged succinylcholine effect in patients receiving both drugs. If cyclophosphamide has been administered within 10 days of succinylcholine, extreme caution should be used after succinylcholine administration. The anesthesiologist should be informed of the potential for succinylchoine-induced apnea and appropriate precautions and monitoring should be implemented. [3,10,11]

Trastuzumab: In early clinical trials the concurrent administration of cyclophosphamide and trastuzumab increased the incidence and severity of cardiac dysfunction. Until additional data from clinical trials demonstrate the safety of concurrent use of these drugs concurrent administration is not recommended. [3,12]

8.4.12 Nursing Implications

1. Monitor CBC, platelet count. Advise patients of increased risk of infection with absolute neutrophil count less than 500 cells/mm3 and increased risk of bleeding with platelet counts less than 20,000 cells/ mm3. Advise patients to call the clinic if they develop a fever above 101°F or notice any easy bruising, petechiae (pinpoint red spots on skin), or prolonged bleeding.
2. Advise patient of possible alopecia. Instruct how to obtain wig, hairpiece, etc.
3. Assess hydration and fluid balance. Patients receiving larger doses should force fluids up to 2 liters above normal intake for 72 hours after administration. Instruct patients to void more frequently to minimize occurrence of hemorrhagic cystitis. For high-dose therapy MESNA may be used.
4. Premedicate with antiemetics.
5. Observe for possible phlebitis at injection site.
6. Administer antiemetics as indicated.

NOTE: Please refer to the commercially-available package labeling for more information.

8.4.13 References

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2. Cytoxan package insert, Princeton, NJ: Mead Johnson Oncology Products 1998; July
3. Micromedex Inc. Vol. 101; 1999.

4. USPDI Volume1 1999:1128-1134.
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6. Cazin B., Gorin NC, LaPorte JP. Cardiac complications after bone marrow transplantation: A Report of a series of 63 consecutive transplants. Cancer 1986;57:2061-2069.
7. Gryn et.al., Pentostatin increases the acute toxicity of high dose cyclophosphamide. Bone Marrow Transplantation 1993;12:217-220.
8. Pedersen-Bjergaard J, Ersboll J, Sorenson HM. Risk of acute nonlymphocytic leukemia and preleukemia in patients treated with cyclophosphamide for non- Hodgkin's lymphoma. Ann Intern Med 1985;103:195-200.
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10. Zucchero FJ, ed. Evaluation of drug interactions. St. Louis:Professional Drug Systems, 1997:2/35, 12/21.
11. Hansten PD, ed. Drug interactions analysis and management. Applied Therapeutics, Inc., Vancouver, WA: 1998:185-186.
12. Trastuzumab package insert, South San Francisco, CA: Genentech, Inc. 1998;September Date/Reviewer: July 1999/Robert K. Sylvester, Pharm.D. (701) 234-5154

8.5 Vincristine

8.5.1 Other names

Oncovin R, Vincasar PFS R, vincristine sulfate, VCR, leucocristine, LCR.

8.5.2 Classification

Vinca alkaloid (tubulin inhibitor).

8.5.3 Mode of Action

Vincristine binds to tubulin, a protein that forms microtubules, thus interfering with spindle formation during metaphase and causing cessation of cellular mitosis.

8.5.4 Storage and Stability

Vincristine is stored in the refrigerator.

8.5.5 Dose Specifics

Commonly used doses range from 0.5-1.4 mg/m^2 every 1-4 weeks. Dose modifications are necessary in patients with hepatic insufficiency.

8.5.6 Preparation

Doses for continuous infusion are further diluted with normal saline or 5% dextrose in water.

8.5.7 Administration

Usually given by IV push using extravasation precautions. Occasionally it is administered by continuous IV infusion over 96 hours.

8.5.8 Incompatibilities

Furosemide; some in-line filters; polysiloxan containers used in portable delivery devices.

8.5.9 Compatibilities

Chemically stable in normal saline or 5% dextrose for at least 4 days, alone or mixed with doxorubicin, at room temperature in either glass or PVC containers. Also compatible with bleomycin, cytarabine, fluorouracil, methotrexate, and metoclopramide.

8.5.10 Availability

Vincristine is commercially available in a concentration of 1 mg/ml in 1, 2, and 5 mg vials and 1 mg and 2 mg syringes (Hyporets).

8.5.11 Side Effects

1. Hematologic: Leukopenia (mild and rare), thrombocytopenia (rare), anemia.
2. Dermatologic: Alopecia; skin and soft tissue damage if extravasated (the manufacturer recommends subcutaneous injection of hyaluronidase and application of heat to help disperse the drug); rash.
3. Gastrointestinal: Nausea, vomiting (rare); constipation (see neurological side effects); abdominal pain (cramps); anorexia; diarrhea. Fatal ascending paralysis follows intrathecal administration.
4. Hepatic: Elevations of SGOT and SGPT (mild and transient).
5. Neurologic: Peripheral neuropathy (loss of deep tendon reflexes, paresthesias, paralysis); autonomic neuropathy (constipation, paralytic ileus, urinary retention, orthostasis); ataxia; myalgias; cortical blindness; headache; seizures.
6. Pulmonary: Bronchospasm (acute shortness of breath), more common when administered with mitomycin.
7. Ocular: Diplopia; ptosis; photophobia; cortical blindness (see neurologic); optic atrophy.
8. Other: Severe pain in the jaw, pharynx, bones, back and limbs following injection; syndrome of inappropriate antidiuretic hormone (SIADH); fever; pancreatitis (rare).

8.5.12 Nursing Implications

1. Vesicant - do not extravasate. Refer to extravasation protocol if inadvertent infiltration occurs.
2. Monitor for neurotoxicities - numbness, tingling, ataxia, loss of deep tendon reflexes, etc.

3. Monitor for constipation and treat promptly. May require prophylactic laxatives.
4. Precautions should be taken to prevent inadvertent intrathecal injection.

NOTE: Please refer to the commercially-available package labeling for more information.

8.5.13 References

Byrd RA, Rohrbaugh TM, Raney RB, Norris DG. Transient cortical blindness secondary to vincristine therapy in childhood malignancies. Cancer 47:37-40, 1981.

McRae MP, King JC. Compatibilities of antineoplastic, antibiotic and corticosteroid drugs in intravenous admixtures. Am J Hosp Pharm 33:1010-1013, 1976.

Chauncey TR, Shanel JL, Fox JH. Vincristine neurotoxicity. JAMA 254:507, 1985. ECOG 2/91

8.6 Prednisone

8.6.1 Other Names

Deltasone, Orasone, Medicorten, Panasol-S, Liquid-Pred, others

8.6.2 Classification

Adrenal corticosteroid.

8.6.3 Mode of Action

Prednisone is a potent synthetic glucocorticoid that affects almost every body system. It has antiinflammatory, immunosuppressant, and minimal mineralocorticoid activity, and antineoplastic properties. As an antineoplastic agent, prednisone may bind to specific proteins (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatin alters mRNA and protein synthesis within the cell.

8.6.4 Storage and Stability

The drug is stored at room temperature in a dry place.

8.6.5 Dose Specifics

Common regimens include: 40 mg/m^2/day x 14 days, repeat every 28 days; and 100 mg/m^2/day x 5 days, repeat every 3-4 weeks; 20mg/m^2 x 7 days.

8.6.6 Administration

Prednisone is taken orally. Pill calendar to be provided to patients. See Appendix III.

8.6.7 Availability

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

8.6.8 Side Effects

1. Gastrointestinal: Nausea, vomiting, anorexia; increased appetite and weight gain; peptic ulceration.
2. Dermatologic: Rash; skin atrophy; facial hair growth, acne, facial erythema; ecchymoses.
3. Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities), urinary frequency.
4. Neurologic: Insomnia; muscle weakness; euphoria, psychosis, depression; headache, vertigo, seizures.
5. Cardiovascular: Fluid retention and edema; hypertension.
6. Ocular: Cataracts; increased intraocular pressure; exophthalmos.
7. Metabolic: Hyperglycemia; decreased glucose tolerance; aggravation or precipitation of diabetes mellitus; adrenal suppression; Cushingoid features; hypokalemia.
8. Hematologic: Leukocytosis.
9. Other: Osteoporosis (and resulting back pain); serious infections including herpes zoster, varicella zoster, fungal infections, pneumocystis carinii, tuberculosis; muscle wasting; delayed wound healing; suppression of reactions to skin tests.

8.6.9 Nursing Implications

1. Instruct patients to take prednisone after meals. Should not be taken too close to bedtime to avoid insomnia. A mild sedative may be required.
2. GI symptoms should be treated symptomatically.
3. Monitor blood glucose levels.
4. Educate patient concerning potential mood swings.
5. Gradual tapering of doses after 14 days of therapy should be employed.

NOTE: Please refer to the commercially-available package labeling for more information.

8.6.10 References

Pickup ME: Clinical pharmacokinetics of prednisone and prednisolone. Clin Pharmacokinet 4:111-128, 1979.

The Boston Collaborative Drug Surveillance Program: Acute reactions to prednisone in relation to dosage. J Clin Pharmacol 13:694-698, 1972.

Ling MHM, Perry PJ, Tsuang MT: Side effects of corticosteroid therapy: Psychiatric aspects. Arch Gen Psychiatry 38:471-477, 1981.

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9. Statistical Considerations

This is a randomized phase II study to evaluate the efficacy of adding Lenalidomide (Revlimid) to RCHOP therapy for patients with newly diagnosed Diffuse Large B-Cell Lymphoma. A total of 283 evaluable patients will be randomized at 1:1 ratio (141 evaluable patients per arm) to the control arm (RCHOP) and the experimental arm (R2CHOP), stratified on IPI (2-3 vs. 4-5), age (< 60 yrs. Vs > 60 yrs).

The primary objective is to determine whether R2CHOP improves progression-free survival (PFS) compared to RCHOP. With the planned sample size and follow-up time, the study will have 89% power to detect a 41% reduction in the PFS hazard rate in R2CHOP arm compared with RCHOP arm, at an one-sided 0.1 significance level. A subset analysis within patients with ABC subtype is planned, and 102 eligible ABC patients will be accrued and randomized. The study will have 82% power to detect a 48% reduction in the PFS failure rate in R2CHOP arm compared with RCHOP arm within ABC subtype, at an one-sided 0.125 significance level (log-rank test).

The secondary objectives include evaluating response rate (RR), complete remission rate (CR) defined by PET-CT criteria and overall survival (OS). The correlative objectives will investigate the impact of DLBCL molecular subtype on outcome and the relation between interim PET scan and study outcome. A maximum of 300 patients will be enrolled to the study.

9.1 Accrual

Based on our previous experience with E4494, we expect to enroll 12-15 patients/month. With an anticipated 10% ineligible rate based on previous experience in large co-operative DLBCL trail, we will accrue a total of 220 patients over 15-18 months and follow-up for additional 24 months.

The study was suspended on May 22, 2015, with a total of 219 patients enrolled at a rate of 15-20 patients/month. Pathology review has been done for 107 patients, and 30 cases (28%) were rejected. The primary reasons for rejections were: alternative diagnosis (not DLBCL or de novo DLBCL) in 20 (19%) patients and poor quality of pathology material submitted not allowing confirmation of diagnosis in 10 (9%) patients. While some IHC is still pending, the great majority of remaining 77 cases will be confirmed DLBCL cases based on the initial review. Of these 53 patients had IHC classification performed already and the first group of 36 patients was selected for GEP using Lymph2CX on the Nanostring platform. And 31 out of 36 patients have COO results. There were 18 (58%) GCB, 1(3%) unclassifiable, and 12 (39%) ABC. For the five samples that did not give CCO, results are being re-analyzed.

If the study continues as written, we assume that the pathology ineligibility rate will continue at the same level (28%) for the remaining 113 patients of the original accrual goal (220) predicting 158 (72%) eligible patients. We estimate that of the confirmed DLBCL cases, about 90% will have enough tissue after pathology review for GEP processing and 40% of the processed cases will have ABC subtype, a total of 57 ABC-DLBCL will be accrued.

To increase the proportion of eligible cases going forward, we propose a “real time” central pathology eligibility screening process. Patients deemed INELIGIBLE for either reason (alternative diagnosis or poor quality of pathology material submitted) will not be permitted to enroll in E1412. We expect that

pathology eligibility rate will be reduced to near 0%, and expect GEP by Nanostring to render GEP results in 90% of tumor samples after screening for adequacy. We expect ABC DLBCL in 40% of cases. Therefore, an additional 125 patients will be accrued to the study (total accrual of 345 cases) to generate 45 (125*0.9*0.4) proven ABC DLBCL cases. As a result, a total of 283 eligible DLBCL cases are expected to be enrolled to the study, of which 102 cases are ABC-DLBCL. Assuming the accrual rate of 12-15 patients/month, it will take 9-13 months to finish enrollment.

9.2 Primary Objective and Sample Size Calculation

The primary objective of this study is to determine whether R2CHOP improves progression-free survival (PFS) compared to RCHOP. PFS is defined as the time from randomization to the earliest of documented disease progression, new primaries of the same type or death without progression. Cases with incomplete follow-up or without adequate disease evaluation will be censored at the date last documented to be progression free.

Because a percentage of long-term cures have been observed with this patient population, we use a cure rate model for this PFS endpoint. It is expected that 2-year PFS rate will be 64%, and cure rate is about 60% for the RCHOP arm. Assuming exponential distribution for the PFS in the non-cure group, this translates into a median of 7.2 months (monthly failure rate of 0.096) in the non-cure group. The study will target a 13% increase in 2-year PFS rate from 64% to 77% in the R2CHOP arm. With proportional hazard rate assumption, this difference corresponds to a hazard ratio of 0.59 and a 41% reduction in the PFS failure rate in the R2CHOP arm compared with the RCHOP arm. Thus, the cure rate is hypothesized to be 74% under the R2CHOP arm. With a total accrual of 283 evaluable (eligible and treated) patients and total information of 89 failures (additional 24 months follow-up); the study will have 89% power to detect a 41% reduction in the PFS hazard rate, at one-sided 0.1 significance level. Considering 9-13 months for additional accrual and 24 months follow-up, it is anticipated that the study will reach full information 33-37 months from study re-opening. The following table lists the difference in 2-yerar PFS rate and hazard ratio that can be detected with the same power (89%, HR=0.59) at one-sided 0.1 significance level, under a series of 2-year PFS rates and cure rates under the control arm.

2-year PFS rate (RCHOP)	2-year PFS rate (R2CHOP)	Difference in 2-year PFS
60%	74.0%	14.0%
64%	76.8%	12.8%
68%	79.6%	11.6%

An inferior outcome has been reported in patients with ABC subtype, with an estimated 56% 2-year PFS rate and about 47% cure rate with RCHOP therapy. Assuming exponential distribution for the PFS in the non-cure group, this translates into a median of 9.4 months (monthly failure rate of 0.074) in the non-cure group. With the addition of lenalidomide, we expect to have as 18% improvement to 74% 2-year PFS rate for patients with ABC subtype. With proportional hazard rate assumption, this difference corresponds to a hazard ratio of 0.52 and a 48% reduction in the PFS failure rate. It is estimated that 40% of the eligible patients will have ABC subtype. With 52 ABC patients on each arm

and total 40 failures, the study will have 81% power to detect a 48% reduction in the PFS failure rate with the addition of lenalidomide to RCHOP, at one-sided 0.125 significance level (log-rank test). The following table lists the difference in 2-yerar PFS rate and hazard ratio that can be detected with 81% power (HR=0.52) at one-sided 0.125 significance level, under a series of 2-year PFS rates and cure rates for the ABC subtype under the control arm.

2-year PFS rate (RCHOP)	2-year PFS rate (R2CHOP)	Difference in 2-year PFS
52%	71.2%	19.2%
56%	74.0%	18.0%
60%	76.7%	16.7%

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An early look at PFS outcome will be performed when 20 events (progression and death) have occurred . All available information will be used, and overall hazard ratio (HR) among all patients will be calculated. The study will continue if HR (R2CHOP vs. RCHOP) is less than 1, indicating the study is going in the direction as expected. The study will be suspended in the case of overall HR > 1, and waiting for GEP results to calculate the HR within ABC subtype. If HR is > 1 in the ABC subset, the study will be terminated. If HR is less than 1 in the ABC subset, the study team will discuss with CTEP regarding how to proceed (whether continue accrual only in ABC subset) in the best interest of patients.

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An additional interim analysis will be taken at the time when the last enrolled patient have had end of induction therapy efficacy assessment, which is approximately at 6-months after the last patient is enrolled to the study. The current projected enrollment closure date is approximately by end of 2016, therefore data will be mature for this interim analysis around end of June 2017.The analysis will be conducted on all patients as well as on patients with ABC subtype (randomized and eligible) with all available data on the study. The analysis will be focused on the primary study endpoint, progression-free survival (PFS), and decisional rules will be applied for all patients and within ABC subtype. Other endpoints will also be evaluated including: overall response rate and CR rate, response at the end of induction therapy, event-free survival (EFS), and OS by Kaplan Meier estimate and hazard ratio based on Cox proportional regression model. EFS is defined as the time from randomization to the earliest of documented disease progression, new primaries of the same type, non-protocol anti-tumor therapy or death without progression. Cases with incomplete follow-up or without adequate disease evaluation will be censored at the date last documented to be progression free.

For all evaluable patients, the estimated number of PFS events will be about 72 events with 6 month additional follow-up, which will be approximately 80% information time. We will calculate HR(R2CHOP/RCHOP) and together with conditional power, the trial will be stopped futility if the observed HR >=0.9 and conditional power <=20%. This additional interim look has no impact on overall study significance level (remain 0.10) and study power (remains 89%).

For patients with ABC subtype, the estimated number of PFS events will have 29 events with 6 month additional follow-up, which will be at approximately 72.5% information time. We will calculate HR(R2CHOP/RCHOP) and together with conditional power, the trial will be stopped futility if the observed HR >=0.93 and

conditional power <=20%. This additional interim look has minimal impact on overall study significance level and study power, which will be one-sided 0.12 and 80%, respectively

The decision to move to a phase III study will depend on many factors, including the strength of our data as well as emerging data on other treatment strategies. For the proposed treatment strategy, we suggest that if either the overall test was significant at the 0.1 level, or the ABC subtype was significant at the 0.125 level, then there would be promising evidence for a consideration of a phase III. When the overall test is significant, we will evaluate each cell-of-origin subtype separately and would drop GCB subtype from phase III consideration if the estimated hazard ratio was not at least 0.8 within this subset.

The primary analysis of PFS will be performed including all randomized elgible patients using a one-sided log-rank test stratified on IPI (2-3 vs. 4-5), age (<60 yrs. Vs ≥ 60 yrs) and molecular subtype (GCB vs. ABC).An analysis based on intent to treat (ITT) principal including all randomized patients will also be performed. Cox proportional hazards models will be used to assess possible effects of baseline clinical and biological characteristics on outcome, including age, gender, disease stage, and IPI. Treatment and covariate interactions will also be examined.

9.3 Secondary Objectives

The secondary endpoints include overall response rate (RR), complete remission (CR) and overall survival (OS). Response will be determined based on PET-CT scan. The comparison of RR and CR between two arms will be performed with Cochran-Mantel-Haenszel (CMH) test, stratified on IPI (2-3 vs. 4-5), age (<60 yrs. Vs ≥ 60 yrs) and molecular subtype (GCB vs. ABC). Exploratory logistic regression will be used to assess possible effects of baseline clinical and biological characteristics on outcome, including age, gender, disease stage, and IPI. Treatment and covariate interactions will also be examined.

Overall survival (OS) is defined as the time from randomization until death due to any cause. The method of Kaplan and Meier will be used to estimate overall survival, and stratified log-rank test will be used to compare OS between two arms. Analysis will include all randomized eligible patients, and analysis based on intent to treat (ITT) principal including all randomized patients will also be performed.

9.4 Safety Monitoring

Toxicity will be assessed and report on all patients who received any protocol treatment regardless of eligibility status. Interim analyses of toxicity are performed twice yearly for all ECOG-ACRIN studies. Reports of these analyses are made available to the ECOG-ACRIN Principal Investigator or Senior Investigator at the participating institutions. Expedited reporting of certain adverse events is required, as described in Section 5.2.

As per NCI CTCAE Version 4.0, the term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. The maximum grade for each type of toxicity will be recorded for each patient, and frequency tables will be reviewed to determine toxicity patterns. In addition, we will review all adverse event data that is graded as 3, 4, or 5 and

classified as either "unrelated or unlikely to be related" to study treatment in the event of an actual relationship developing.

9.5 Gender and Ethnicity

Based on previous data from ***E3402*** the anticipated accrual in subgroups defined by gender and race is:

Ethnic Category	**Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	1	7	8
Not Hispanic or Latino	138	199	337
Ethnic Category: Total of all subjects	139	206	345
Racial Category			
American Indian or Alaskan Native	1	1	2
Asian	1	7	8
Black or African American	3	7	10
Native Hawaiian or other Pacific Islander	1	1	2
White	133	190	323
Racial Category: Total of all subjects	139	206	345

9.6 Correlative Objectives

DLBCL molecular subtype on outcome

Tumor specimens will be analyzed for lymphoma molecular subtype e.g. GCB vs. ABC DLBCL vs. non-classifiable based on previously identified gene expression classifiers (see G. Wright et al, PNAS, 2003). The primary analysis will be based on classification by GEP from paraffin-embedded tissue. The tissue will be archived for GEP to be performed after target enrollment is met for molecular classification and analysis including orthogonal technologies including established immunohistochemistry (IHC) algorithms. The outcome measures including PFS and RR rates will be compared between the DLBCL types. GEP will be performed in collaboration with Dr. Randy Gascoyne's laboratory from paraffin embedded tissue utilizing the Affymetrix platform (see Williams et al, J MolDiag, 12(5): 680-686, 2010). The submission of paraffin blocks and/or 20 micron scrolls from tumor biopsies is mandatory. Although Affymetrix gene expression profiling represents the current gold-standard for determinin the cell-of-origin subtypes for DLBCL, we recognize unprecedented technological progress in this regard, and an alternative promising platform (like NanoString) could be used if sufficiently validated by the time GEP is ready to be performed. Although we encourage fresh frozen tissue collection and FFT will be banked where available, we do not mandate fresh frozen tissue submission for GEP, due to i) logistical difficulties which will likely negatively affect accrual and ii) recent developments in GEP from paraffin tissue.

We hypothesize that lenalidomide can overcome poor outcome of patients with DLBCL ABC type. While we believe that addition of lenalidomide improves outcomes of both DLBCL types, the magnitude of benefit may be higher in non-GCB subtype partially due to poorer outcome in this group and potentially partially due to higher activity of lenalidomide in this subset. In this regard,

retrospective analysis of outcomes of patients with GCB versus DLBCL treated with salvage lenalidomide at 4 academic institutions was recently performed (Hernandez-Ilizaliturri, Deeb 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); complete response rate was 23.5% versus 4.3%. Median progression-free survival was 6.2 versus 1.7 months (P = .004), although no difference in OS was observed.

PFS and RR will be compared between the molecular DLBCL types determined by GEP classification. Stratified on the IPI (2-3 vs. 4-5),age (<60 yrs. Vs ≥60 yrs) and treatment arm (RCHOP vs. R2CHOP), a stratified log-rank test and Cochran-Mantel-Haenszel (CMH) test will be used to compare PFS and RR between two molecular subtypes, respectively. Other secondary outcomes, including ORR and OS will be compared using similar methods.

Similar analysis will also be performed between molecular subtypes with other algorithms including Hans, Tally Choi methods.

9.7 Imaging Central Reader Study

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Three standard practice ^{18}F-FDG Whole Body PET/CT imaging studies (pre-therapeutic baseline [PET0], interim PET after 3 cycles of therapy [PET3], and PET after 6 cycles of therapy [PET6]) scans will be archived and centrally reviewed at the American College of Radiology (ACR) Imaging Core Laboratory by ACRIN. Our primary imaging aims are as follows:

Imaging Aim 1: To evaluate the association between a binary score of baseline SUV and PFS.

Imaging Aim 2: To evaluate the association between the binary score of % change in SUVs (from PET3 to baseline) and PFS.

Imaging Aim 3: To compare % change in SUVs from PET3 to baseline between R2CHOP and RCHOP arms.

Exploratory analyses are planned to evaluate correlation of imaging findings with therapeutic response and survivorship:

a) **Measurement of a Single Time Point:**

1) Correlation of baseline scan (PET0) SUVs, tumor metabolic volume measurements, and CT-based tumor volumes with therapy response, PFS, OS, IPI, and Ann Arbor staging.

2) Correlation of baseline PET0, PET3, and PET6 qualitative and quantitative imaging parameters with molecular analysis (e.g. GCB vs ABC).

b) **Measurements Between any Two PET Time Points:**

1) Impact of change in SUVs (as a % reduction) with respect to response, PFS, and OS

2) Impact of changes in metabolic tumor volume measurements and CT-based tumor volumes with respect to response, PFS, and OS

c) **Comparisons Between Treatment Arms.** Comparison of PET3 and PET6 qualitative and quantitative imaging parameters between treatment arms; in this regard, it has been suggested that mild persistent uptake can be seen more commonly in R2CHOP arm due to lenalidomide's impact on microenvironment.

d) **Comparison with Other Studies' Results.** Comparison of results with other prospective studies with comparable data, when and if available (e.g E3404-NCT00274924, Nordic trial after one cycle-NCT00286832).

Analysis plans

Imaging Aim 1: To evaluate the association between the binary score of baseline SUV and PFS.

We will create binary SUV scores (high or low SUV) for the baseline SUV_{max} measurements. To determine the optimal cutoff point for the high SUV_{max}, ROC analysis will be performed. The PFS curves between the two SUV groups (high or low) will be obtained using the Kaplan-Meier method and will be compared by a log-rank test. We will also fit a Cox regression model in which the response will be PFS and the predictors will be a binary score of baseline SUV_{max}, treatment (RCHOP, R2CHOP) as a binary variable, interaction between treatment and PET marker, adjusting for important covariates including patient characteristics.

Imaging Aim 2: To evaluate the association between the binary score of % change in SUVs (from from PET3 to baseline) and PFS.

We will conduct a similar analysis to Imaging Aim 1. This time, the % change in SUVs from PET3 and baseline will be used and two groups (small and high SUV changes) will be created.

Imaging Aim 3: To compare % change in SUVs from PET3 to baseline between R2CHOP and RCHOP arms.

We will conduct a two-sample t-test to evaluate whether the %change in SUVs of R2CHOP arm is greater than that of RCHOP arm.

Analysis plans for exploratory imaging aims are as follows.

Prediction of Therapeutic Response: The endpoint for this analysis is response status at the end of chemotherapy (binary variable). The semi-quantitative measurement of primary interest will be SUV_{max}. Other available SUV-based metrics and tumor metabolic volume (e.g., tumor metabolic volume measurements and CT-based tumor volumes) also will be considered.

Measurement at a Single Time Point. For the analysis of prediction of response by an imaging marker involving a measurement at a single time point, at pre-therapeutic baseline (PET0), after 3 cycles of therapy (PET3), or after 6 cycles of therapy (PET6), logistic regression will be used to estimate the odds ratio for response (dichotomized as responders vs not). Specifically, the predictors in the logistic regression models will include each imaging marker, treatment (binary: RCHOP or R2CHOP), interaction between imaging marker and treatment, and other covariates of interest. Additionally, ROC curves and their associated Area under the ROC Curves (AUC) will be estimated for each imaging marker; First,

the AUC will be calculated for each (raw) marker, and second, the covariate-adjusted AUC will be calculated using a parametric distribution free approach such as Pepe (1997) or Alonzo and Pepe (2002) where covariates will include patients characteristics measured at baseline. ROC curves for different markers will be compared using non-parametric methods appropriate for correlated data.

Measurement Between Any Two PET Time Points. For markers involving measurements at two time points, such as PET0 and PET3, change in SUVs (as a % reduction) will be considered. Logistic regression models and ROC analysis will be used as described above.

Prediction of Survivorship:

For the analysis of prediction of PFS, we will use a Cox proportional hazards model for each PET maker in which the response is PFS and the predictors will include an imaging marker, treatment, interaction between an imaging marker and treatment, and additional covariates measuring relevant patient characteristics measured at baseline. Significance of each marker will be determined by a Wald test and estimated survival functions between the two arms will be compared.

Second, each PET predictor will be assessed using time-dependent ROC curve at pre-specified time points (e.g. 36mos). In the first step, we will divide the data into training and test data sets, and fit a Cox proportional hazards model adjusted by covariates including baseline patient characteristics using the training data set. Then, we will derive a linear predictor of the (covariates-adjusted) imaging marker using the test dataset where the weight of each predictor will be obtained from the estimated Cox regression coefficient. In the second step, the time-dependent ROC curve and its corresponding AUC at a specific time point will be estimated for the derived covariate-adjusted imaging marker using methods proposed by Heagerty et al. (2000) or Heagerty and Zheng (2005).

Next, we will repeat similar analyses for predicting OS.

Comparisons Between Treatment Arms**.** Comparison of PET3 and PET6 qualitative and quantitative imaging parameters between treatment arms;

To test the difference between two arms, we will use two-sample t-tests or Wilcoxon rank sum tests for quantitative PET imaging parameters; and use Fisher's exact tests for qualitative PET imaging parameters.

Sample Size and Power considerations for imaging aims

The statistical power for imaging aim 1 is calculated using 283 eligible patients. Since the measurements of the PET 3 imaging markers are optional, the sample sizes for these two aims are calculated at a pre-specified power. For aims 1 and 2, it is assumed that the study lasts for 3 years of which patient accrual occurs in the first 2 years. All computations were carried out using PASS 12 (Hinze J. [2008] PASS, NCSS, LLC, Kaysville, Utah).

Imaging Aim1: We assume that 2 year PFS in high and low SUV groups are 51% and 79%, respectively based on a prior study by Lin et al. (2007). A two-sided log-rank test with an overall sample size of 283 patients achieves 99.9% power at a 5% significance level to detect a hazard ratio of 0.3501.

Imaging Aim2: A one-sided log-rank test with an overall sample size of 88 patients (44 in each arm) achieves 90.0% power at a 5% significance level to

detect a hazard ratio of 0.4243 when the proportion progression-free surviving at year 2 in the small SUV reduction group is 0.3.

Sample Size for Imaging Aim 2, at a significance level of 5% and power 90%

SUV Change (-)	SUV Change (+)	Total size	Hazard Ratio	S1	S1
22	22	45	.3174	.2000	.6000
14	15	29	.2216	.2000	.7000
9	10	19	.1386	.2000	.8000
44	***44***	***88***	***.4243***	***.3000***	***.6000***
24	24	48	.2962	.3000	.7000
14	15	29	.1853	.3000	.8000
103	103	206	.5575	.4000	.6000
44	44	88	.3893	.4000	.7000
22	22	45	.2435	.4000	.8000

SUV Change (-): Sample size of the small SUV reduction group

SUV Change (+): Sample size of the high SUV reduction group

S1 (S2): rate of PFS at year 2 in the small (high) SUV reduction group

Imaging Aim 3: To compare % change in SUVs from PET3 to baseline between R2CHOP and RCHOP arms.

We target to find a 15% difference between the two arms with respect to the % change in SUV from PET 3 to baseline. Group sample sizes of 70 and 70 achieve 91% power to detect a difference of -15.0 between the null hypothesis that the means in both arms are 60.0 and the alternative hypothesis that the mean of R2CHOP arm is 75.0 with estimated group standard deviations of 30.0 and 30.0 using a one-sided two-sample t-test.

Sample Size for Imaging Aim 3, at a significance level of 5% and power 90%

N1	N2	Total	Mean1	Mean2	S1	S2
32	32	64	60.0	75.0	20.0	20.0
51	51	102	60.0	75.0	20.0	30.0
51	51	102	60.0	75.0	30.0	20.0
70	*70*	*140*	*60.0*	*75.0*	*30.0*	*30.0*

N1 (N2): number of patients sampled from RCHOP (R2CHOP) arm

Mean1: mean of arms 1 and 2 under the null hypothesis of equality

Mean2: mean of arm 2 under the alternative hypothesis

S1 (S2): population standard deviations in RCHOP (R2CHOP) arm

In summary, all 283 eligible patients in the study will have PET measurements at baseline, and the sample size achieve 99.9 % power for evaluating Imaging Aim 1. Based on the power calculation for Imaging Aims 2 and 3, we expect to have at least 70 PET measurements in each arm at PET 3.

10. Imaging Studies

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ECOG-ACRIN plan to archive PET/CT image data collected during the course of the study at the central ACR Imaging Core Laboratory. A central reader study evaluating imaging in relation to therapeutic response, PFS, OS, differences among therapeutic arms, and histologic biology will be performed by ACRIN. For the ECOG-ACRIN E1412 trial, we plan to evaluate specific clinical data elements to associate images with treatment milestones. In the future, the de-identified image archive may be used for additional research, such as retrospective reviews of disease or software validation. Patient identifiers will never be included in future research and no patients will be named in publications related to future research.

10.1 Standard-of-Care Imaging Time Points and Minimum Preferred Phases

10.1.1 All standard-of-care imaging studies (including CT, MRI, PET, or any combination), including all phases completed, will be submitted to ACRIN per Section 10.3 instructions.

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10.1.2 Standard practice imaging studies for the trial per E1412 procedures include:

- Pre-treatment baseline scan ^{18}F-FDG Whole Body PET0;
- Interim ^{18}F-FDG Whole Body PET3 after cycle 3/before cycle 4 of treatment.
- ^{18}F-FDG Whole Body PET6 after cycle 6 of treatment.

10.1.3 Preferably, a minimum of three (3) image phases will be submitted (see below), as well as any perfusion CT sequences that may be performed as standard institutional practice:

- Preferred:
  - Late arterial phase through the abdomen;
  - Portal venous phase through the abdomen and pelvis;
  - Delayed (equilibrium) phase through the abdomen at 3 to 4 min after contrast administration;
- If performed per standard institutional practice:
  - Perfusion CT sequences of an area of interest is optional and should be performed according to site specific specifications if available at the participating institution.

10.2 Central Reader Study

OVERVIEW OF READER STUDY – Please refer to Section 9.7 for the Imaging Central Reader Study.

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10.3 Images Submission

TRIAD 4.0 Submission: The method of image transfer employed by the E1412 trial is TRIAD v4.0, a software application that ACRIN provides for installation on a site's PC. One or several computers of choice within the institutional "firewall" and on the institutional network may be equipped with TRIAD 4.0 software; Internet access is also required. The TRIAD application can then be configured

as a DICOM destination on either scanner(s) and/or PACS system for direct network transfer of study related images into the TRIAD directory. When properly configured, the TRIAD software anonymizes, encrypts, and performs a lossless compression of the images before they are transferred to the ACRIN image archive in Philadelphia. Once equipment-readiness has been determined, imaging personnel from ACRIN will coordinate installation and training for the software. At study start-up sites will receive TRIAD 4.0 software registration and installation information. This information is included in the appendices of this document.

TRIAD 4.0 Installation Information and User Guide are available at: https://triadinstall.acr.org/triadclient/

Questions and general inquiries regarding TRIAD 4.0 can be sent to: triad-support@acr.org. Please include "E1412 Trial" in the subject line of all inquiries.

The submission of image data on media will not be accepted for the E1412 trial.

All image-related forms are found in the iMedidata Rave database used for the trial.

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11. Biological Specimen Submissions

Following pre-registration, diagnostic material from previously collected tissue must be submitted to MAYO CLINIC – ROCHESTER for central diagnostic review and quality assessment (QA) for adequacy for the mandatory defined laboratory research studies described in Section 12. The site will be notified with two (2) working days of receipt of the tissue of the eligibility of the patient. Patients deemed INELIGIBLE for either reason will not be permitted to enroll in E1412.

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Peripheral blood is to be submitted from consenting patients for future undefined laboratory research studies.

The IRB approved consent must allow patients the option to provide samples for use in the optional laboratory research studies and/or for undefined future research studies. Failure to allow this option will result in a major violation at the time of an audit.

It is **required** that all samples submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (see Section 11.4). An STS shipping manifest form is to be included with every submission.

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All samples must be labeled clearly with the ECOG-ACRIN protocol number (E1412), ECOG-ACRIN patient sequence number, patient's initials, date of collection and sample type.

11.1 Sample Collection and Submission Schedule

Samples are to be submitted as follows:

- Diagnostic pathology samples are to be submitted following pre-registration (Step 0). See Section 11.2.
- Randomization (Step 1): Peripheral blood samples are to be submitted as outlined in Section 11.3 on the day of collection. Samples are to be collected at the following time points:
  - Baseline, prior to treatment
  - Before cycle four (4)
  - After completion of therapy

11.2 Pre-Registration Tissue Submissions

Submitting pathologist and clinical research associate may refer to Appendix I which outlines the Pathology Submission Guidelines. Submission of pathology samples from all patients is mandatory for determination of patient eligibility.

Questions are to be directed to the Mayo-Clinic Division of Haematology, Dr. William Macon or Dr. Rebecca King (507) 284-1198 OR Kim Henderson at (507) 284-3805 or Henderson.Kimberly@mayo.edu.

The tissue samples are to be labeled with the institution's assigned pathology ID as well as the information above.

11.2.1 Required Materials

Forms: Must be submitted with all tissue submissions.

- STS generated shipping manifest form.
- Copy of the pathology report.

- Completed *Patient Information Form* (Appendix I) - provide the contact to be notified of patient eligibility based on the results of the central pathology diagnostic and QA review. If patient is ineligible for the trial, the submitted pathology materials will be returned to the site in care of this same contact.

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Pathological Material Submission:

- Representative diagnostic FFPE tumor tissue block

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NOTE: If a block is unavailable for submission, slides are to be submitted. All slides must be adequately labeled, and numbered sequentially in the order cut. Alternative submission requirements:

Adequately label every slide submitted.

- One (1) H&E slide, and
- Twenty (20) 4 µm unstained air-dried plus slides,

11.2.2 Shipping Procedures

Pathology materials are to be shipped at ambient temperature following pre-registration (Step 0).

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Ship using the CBPF's FedEx account using the FedEx on-line Ship Manager

Access to the shipping account for shipments to the CBPF can only be obtained by logging into fedex.com with an account issued by the CBPF. For security reasons, the account number will no longer be given out in protocols, over the phone, or via email. If your site needs to have an account created, please contact the CBPF by email at eacbpf@mdanderson.org.

Ship to:

Kim Henderson
Mayo Clinic Lymphoma Laboratory
613 Stabile
224 4th Avenue Southwest
Rochester, MN 55905
Phone: (507) 284-3805
Email: Henderson.Kimberly@mayo.edu

11.3 Submissions from Patients Randomized to Step 1

Blood samples should be shipped the day they are drawn. If you have any questions concerning sample collection and shipment, please contact Kim Henderson at (507) 284-3805 or Henderson.Kimberly@mayo.edu at the Mayo Clinic Lymphoma Laboratory.

Submit from patients who answer "Yes" to "I agree to provide additional blood for research."

11.3.1 Sample Preparation Guidelines

Kits are available to order for the collection of the samples, and will contain the supplies and instructions for collecting, processing, and

shipping the samples. To order kits contact Kim Henderson at (507) 284-3805 or Henderson.Kimberly@mayo.edu Include the name of the contact person, phone number, and address where the kits should be shipped, ECOG-ACRIN protocol number, the number of kits needed, and if the kits need to be shipped priority overnight, otherwise kits will arrive in three to four working days.

The following CBC information must be entered into STS with each time point: WBC and lymphocyte count.

Blood samples should be shipped the day they are drawn at room temperature (do not freeze). Samples from multiple patients can be shipped together, but must be placed in separately labeled tubes and bags.

All samples must be clearly labeled with the ECOG-ACRIN protocol number E1412, the patient's initials (last name, first name), the patient's ECOG-ACRIN sequence number (If available), date of collection, and type of sample (PB).

- Peripheral blood: Draw 7mL of whole blood into each of three (3) ACD yellow top tubes (provided in the kit) at each time point. Ship day of collection.
- Peripheral blood: Draw 10mL of whole blood into one (1) EDTA purple top tube (provided in the kit) at each time point. Ship day of collection.
- Peripheral blood: Draw 10mL of whole blood into one (1) red top tube (provided in the kit) at each time point. Ship day of collection.

11.3.2 Shipping Procedures

Blood samples should be mailed the day they are obtained and shipped overnight to arrive during normal working hours. The laboratory is open to receive shipments Monday through Friday. Follow packing guidelines listed in the kit. If samples are sent late in the week and will arrive on the weekend, please note "Saturday Delivery" on the Federal Express form.

FRIDAY AND PRE-HOLIDAY SHIPMENTS SHOULD BE AVOIDED.

- Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
- Place the filled specimen bag in the Styrofoam container.
- Loosely pack with paper toweling.
- Place the Styrofoam container and the Sample Tracking System Shipping Manifest Form within the cardboard mailing sleeve.
- Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Air Bill and adhere to the exterior lid of the box. Ship samples priority overnight delivery the same day collected.
- Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

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The blood samples in prepared kits should be shipped to the following:

Kim Henderson
Mayo Clinic Lymphoma Laboratory
613 Stabile
Rev. 1/17 224 4th Avenue Southwest
Rochester, MN 55905

An STS shipping manifest form must be generated and shipped with all sample submissions.

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11.4 ECOG-ACRIN Sample Tracking System

It is **required** that all specimens submitted on this trial be entered and tracked using the ECOG-ACRIN Sample Tracking System (STS). The software will allow the use of either 1) an ECOG-ACRIN user-name and password previously assigned (for those already using STS), or 2) a CTSU username and password.

When you are ready to log the collection and/or shipment of the specimens required for this study, please access the Sample Tracking System software by clicking https://webapps.ecog.org/Tst.

Important: Please note that the STS software creates pop-up windows, so you will need to enable pop-ups within your web browser while using the software. A user manual and interactive demo are available by clicking this link: http://www.ecog.org/general/stsinfo.html Please take a moment to familiarize yourself with the software prior to using the system.

An STS generated shipping manifest form must be shipped with all specimen submissions.

Please direct your questions or comments pertaining to the STS to ecog.tst@jimmy.harvard.edu.

Study Specific Notes

Generic Specimen Submission Form (#2981), along with the Patient Information Form (Appendix VII, for submissions to Mayo Clinic) are required to be submitted with the shipments if STS is unavailable at time of sample submission. Indicate the appropriate Lab on the submission form:

- Mayo Clinic Lymphoma Laboratory

If your shipment was not logged into the ECOG-ACRIN STS **call Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu to notify the laboratory when samples are being shipped**. Indicate the ECOG-ACRIN protocol number, the FedEx tracking number, and name and phone
Rev. 1/17 number of the contact person.

It is mandatory to enter the specimen collection and shipping information when STS is available.

11.5 Use of Specimens in Research

Pathological materials from patients deemed eligible by the central review will be distributed to investigators for the laboratory research studies defined in Section

12 and remaining tissue to the ECOG-ACRIN Central Biorepository and Pathology Facility to be stored for future research studies. Tissue from patients determined to be ineligible based on central pathology and QA assessments will be returned to the site.

Specimens from patients who consented to allow their specimens to be used for future ECOG-ACRIN approved research studies will be retained in an ECOG-ACRIN designated central repository.

Specimens submitted will be processed to maximize their utility for current and future research projects. Tissue processing may include, but not limited to, extraction of DNA and RNA and construction of tissue microarrays (TMAs). DNA and plasma (if appropriate) will be isolated from the submitted peripheral blood specimens.

Any residual blocks will be available for purposes of individual patient management on specific written request.

If future use is denied or withdrawn by the patient, the specimens will be removed from consideration for use in any future research study. Pathology materials may be retained for documentation purposes or returned to the site. All other specimens will be destroyed per guidelines of the respective repository.

11.6 Sample Inventory Submission Guidelines

Inventories of all samples submitted from institutions will be tracked via the ECOG-ACRIN STS and receipt and usability verified by the receiving laboratory. Inventories of samples forwarded and utilized for approved laboratory research studies will be submitted by the investigating laboratories to the ECOG-ACRIN Operations Office – Boston on a monthly basis in an electronic format defined by the ECOG-ACRIN Operations Office – Boston

12. Correlative Studies

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12.1 Pathology Review (MANDATORY)

The tumor tissue samples will be forwarded to William Macon, MD and Rebecca King, MD for central diagnostic review and classification to confirm the diagnosis, and identify material to be used for the research studies described below.

The site will be notified with two working days of receipt of the tissue of the eligibility of the patient. Patients deemed INELIGIBLE will not be randomized to treatment (Step 1) on E1412.

The received tissue will be reviewed in order to assess quality for GEP. Patients with a central pathology review inconsistent with DLBCL or materials are inadequate for the mandatory GEP assessments are considered ineligible. The final determination for the specific GEP platform will be selected to represent the most accurate platform with the highest possible correlation to fresh frozen tissue at the time of analysis.

Material from eligible patients will be distributed for the research studies below. Residuals will be forwarded to the ECOG-ACRIN CBPF as described in Section 11.5

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12.2 Gene Expression Profiling (GEP) Analysis (MANDATORY)

This mandatory laboratory research study will utilize tumor tissue samples selected by Dr. Macon as adequate for GEP analysis based on cellularity and quality. The selection of best material for GEP will be done during central pathology review (see 12.1). The GEP platform is described in Appendix XIV and is selected to represent the most accurate platform with the highest possible correlation to fresh frozen tissue.

The GEP analysis will be performed by Dr. Randy Gascoyne, at the British Columbia Cancer Agency.

12.3 Immunohistochemical (IHC) Classification, FISH Cmyc Analysis (MANDATORY)

This laboratory research study will utilize tumor tissue samples.

This analysis will be performed at Mayo Clinic under the direction of Dr. William Macon, in collaboration with Dr. Rebecca King.

12.4 Lab Data Transfer Guidelines

The data collected on the above mentioned laboratory research studies will be submitted electronically using a secure data transfer to the ECOG-ACRIN Operations Office – Boston by the investigating laboratories on a quarterly basis or per joint agreement between ECOG-ACRIN and the investigator.

13. Electronic Data Capture

Please refer to the ***E1412*** Forms Completion Guidelines for the forms submission schedule. Data collection will be performed exclusively in Medidata Rave.

This study will be monitored by the CTEP Data Update System (CDUS) version 3.0. Cumulative CDUS data will be submitted quarterly from the ECOG-ACRIN Operations Office – Boston to CTEP by electronic means.

CDUS reports are due January 31, April 3, July 31 and October 31.

14. Patient Consent and Peer Judgment

Current FDA, NCI, state, federal and institutional regulations concerning informed consent will be followed

15. References

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Randomized Phase II Open Label Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

Appendix I

Pathology Submission Guidelines

The following items are included in Appendix I:

1. List of Required Materials for E1412
2. Instructional memo to submitting pathologists

Rev. 10/15

3. Patient Information Form

Rev. 1/15

4. ECOG-ACRIN Generic Specimen Form (#2981v3)

List of Required Material

E1412 Randomized Phase II Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

Rev. 10/15 The following materials are to be submitted following pre-registering (Step 0):

Rev. 1/14, 1/15

1. Pathology materials (MANDATORY):
   - Representative diagnostic tumor tissue block

     NOTE: If a block is unavailable for submission, slides are to be submitted. All slides must be adequately labeled, with slides numbered sequentially in the order cut. Alternative submission requirements:

     Adequately label every slide submitted.
     - One (1) H&E slide, and
     - Twenty (20) 4 µm unstained air-dried plus slides, and
2. Forms and Reports:

   The following items are to be included with the pathology materials:
   - Institutional Pathology Report
   - ECOG-ACRIN Sample Tracking System (STS) Shipping Manifest Form
   - **Completed Patient Information Form**

   NOTE: Adequate patient identifying information must be included with every submission. It is strongly recommended that full patient names be provided. The information will be used only to identify patient materials, and will help to expedite any required communications with the institution (including site pathologists).
3. Mail pathology materials to:

   Kim Henderson
   Mayo Clinic Lymphoma Laboratory
   613 Stabile
   200 First Street Southwest
   Rochester, MN 55905

If you have any questions concerning the above instructions contact Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu

ECOG-ACRIN
cancer research group
Reshaping the future of patient care

Robert L. Comis, MD, and Mitchell D. Schnall, MD, PhD
Group Co-Chairs

MEMORANDUM

TO: _____

(Submitting Pathologist)

FROM: Stanley Hamilton, M.D., Chair ECOG-ACRIN Laboratory Science and Pathology Committee

DATE: _____

SUBJECT: *Submission of Pathology Materials for E1412:* Randomized Phase II Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

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The patient named on the attached ECOG-ACRIN Generic Specimen Submission Form has been entered onto an ECOG-ACRIN protocol by _____ (ECOG-ACRIN Investigator). This protocol requires the submission of pathology materials for central pathology review and laboratory research studies.

Please complete PART B of the Submission Form. Keep a copy for your records and return the completed Submission Form, the surgical pathology report(s), the slides and/or blocks and any other required material (see List of Required Material) to the Clinical Research Associate (CRA).

Rev. 10/15 The CRA will forward all required pathology material to the Mayo Clinic Lymphoma Laboratory in Rochester, MN.

Blocks and slides submitted for this study will be retained at the ECOG-ACRIN Central Biorepository and Pathology Facility for undefined future research studies. Paraffin blocks will be returned upon written request for purposes of patient management.

Please note: Since blocks are being used for laboratory research studies, in some cases the material may be depleted, and, therefore, the block may not be returned.

If you have any questions regarding this request, please contact Kimberly Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu.

The ECOG-ACRIN CRA at your institution is:

Name: _____

Address:_____

Phone:_____

Thank you.

Rev. 10/15

Patient Information Form

Specimen Date: / /

Institution/Affiliate:

Physician:

Patient Initials (last name, first name):

Hospital ID or Social Security #:

ECOG-ACRIN Protocol #: E1412

ECOG-ACRIN Patient Sequence #:

Contact Person[1]:

Institution:

Address:

City State Zip

Phone #:

FAX #:

1 For pre-registration tissue submissions, provide the contact to be notified of patient eligibility based on the results of the central pathology diagnostic and QA review. If patient is ineligible for the trial, the submitted pathology materials will be returned to the site in care of this same contact.

Please indicate which specimens are being shipped at this time:

1. **Pre-registration – Mandatory Tissue Submissions**
2. Baseline
3. Before Cycle Four (4)
4. After Completion of Therapy

Any questions concerning these specimens or to obtain blood collection kits for the E1412 study, please contact:

Kim Henderson
Mayo Clinic Lymphoma Laboratory
(507) 284-3805
Henderson.Kimberly@mayo.edu

ECOG-ACRIN Generic Specimen Submission Form

Form No. 2981v3

Institution Instructions: This form is to be completed and submitted with **all specimens** ONLY if the Sample Tracking System (STS) is not available. **Use one form per patient, per time- point.** All specimens shipped to the laboratory must be listed on this form. Enter all dates as MM/DD/YY. Keep a copy for your files. Retroactively log all specimens into STS once the system is available. **Contact the receiving lab to inform them of shipments that will be sent with this form.**

Protocol Number _____ **Patient ID** _____ **Patient Initials** Last _____ First _____

Date Shipped _____ **Courier** _____ **Courier Tracking Number** _____

Shipped To (Laboratory Name) _____ **Date CRA will log into STS** _____

FORMS AND REPORTS: Include all forms and reports as directed per protocol, e.g., pathology, cytogenetics, flow cytometry, patient consult, etc.

Required fields for all samples				**Additional fields for tissue submissions**				**Completed by Receiving Lab**
Protocol Specified Timepoint:								
Sample Type (fluid or fresh tissue, include collection tube type)	**Quantity**	**Collection Date and Time 24 HR**		**Surgical or Sample ID**	**Anatomic Site**	**Disease Status** (e.g., primary, mets, normal)	**Stain or Fixative**	**Lab ID**

Fields to be completed if requested per protocol. Refer to the protocol-specific sample submissions for additional fields that may be required.					
Leukemia/Myeloma Studies:	**Diagnosis**	**Intended Treatment Trial**	**Peripheral WBC Count (x1000)**	**Peripheral Blasts %**	**Lymphocytes %**
Study Drug Information:	**Therapy Drug Name**	**Date Drug Administered**	**Start Time 24 HR**	**Stop Time 24HR**	
Caloric Intake:	**Date of Last Caloric Intake**		**Time of Last Caloric Intake 24HR**		

CRA Name _____ **CRA Phone** _____ **CRA Email** _____

Comments

9/12/14

Randomized Phase II Open Label Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

Rev. 6/14

Appendix II

Patient Thank You Letter

We ask that the physician use the template contained in this appendix to prepare a letter thanking the patient for enrolling in this trial. The template is intended as a guide and can be downloaded from the ECOG web site at http://www.ecog.org. As this is a personal letter, physicians may elect to further tailor the text to their situation.

This small gesture is a part of a broader program being undertaken by ECOG-ACRIN and the NCI to increase awareness of the importance of clinical trials and improve accrual and follow-through. We appreciate your help in this effort.

[PATIENT NAME] [DATE]

[PATIENT ADDRESS]

Dear [PATIENT SALUTATION],

Thank you for agreeing to take part in this important research study. Many questions remain unanswered in cancer. With the participation of people like you in clinical trials, we will improve treatment and quality of life for those with your type of cancer.

We believe you will receive high quality, complete care. I and my research staff will maintain very close contact with you. This will allow me to provide you with the best care while learning as much as possible to help you and other patients.

On behalf of ***[INSTITUTION]*** and the ECOG-ACRIN Cancer Research Group, we thank you again and look forward to helping you.

Sincerely,

[PHYSICIAN NAME]

Randomized Phase II Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

Appendix III

Patient Medication Calendar

Medication Calendar Directions

1. Take your scheduled dose of each medication.
2. If you forget, the missed medication will not be taken later.
3. Please bring the empty bottle or any leftover medication and your calendar to your next clinic visit.

Patient Medication Calendar - Lenalidomide

This is a calendar on which you are to record the time and number of capsules you take each day. You should take your scheduled dose of each medication. **Note the times and the number of capsules that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused capsules and your completed medication calendar to your doctor's visits.

DAY	Date Month Day Year			Time capsule taken		Number of capsules taken		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								

Patient Medication Calendar - Aspirin

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each medication. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed medication calendar to your doctor's visits.

DAY	Date Month Day Year			Time tablet taken		Number of tablets taken		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								
14								
15								
16								
17								
18								
19								
20								
21								

Patient Medication Calendar - Prednisone

This is a calendar on which you are to record the time and number of tablets you take each day. You should take your scheduled dose of each medication. **Note the times and the number of tablets that you take each day.** If you develop any side effects, please record them and anything you would like to tell the doctor in the space provided. Bring any unused tablets and your completed medication calendar to your doctor's visits.

DAY	Date Month Day Year			Time tablets taken		Number of tablets taken		Use the space below to make notes about things you would like to tell the doctor (including unusual symptoms you experience, other medicine you have taken and anything else you think would be of interest.)
1								
2								
3								
4								
5								

Randomized Phase II Open Label Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

Appendix IV

CRADA/CTA

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industry) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing investigational Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.
2. For a clinical protocol where there is an investigational Agent used in combination with (an)other investigational Agent(s), each the subject of different collaborative agreements , the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data."):
    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NIH, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.
    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own investigational Agent.
    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own investigational Agent.
3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available exclusively to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order. Additionally, all Clinical Data and Results and Raw Data will be collected , used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   Executive Plaza North, Suite 7111
   Bethesda, Maryland 20892
   FAX 301-402-1584
   Email: anshers@ctep.nci.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

Randomized Phase II Open Label Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

Appendix V

ECOG Performance Status

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

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Appendix VI

International Prognostic Index

- Age older than 60
- Lactate dehydrogenase level higher than normal
- ECOG performance status score of 2 or greater (Appendix V)
- Stage III or IV disease
- More than one involved extranodal disease site

International Prognostic Index (IPI), gives one point for each of the above characteristics, for a total score ranging from zero to five.

Randomized Phase II Open Label Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

Appendix VII

Blood Collection Kit Mayo Clinic Lymphoma Laboratory

Specimen Checklist and Shipping Instructions

****PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

Kit Contents:

- Small Styrofoam box and cardboard mailing sleeve
- Rev. 10/15 Patient Information Form (copy provided in Appendix I of E1412)
- FedEx Air Bill with pre-printed return address
- 7ml ACD (yellow top) collection tubes
- 10ml EDTA (purple top) collection tube
- 10ml Red Top collection tube
- Absorbent tube holder
- Zip lock specimen bag

Packing and Shipping Instructions:

1. Collect the following specimens:
    1. Peripheral blood – Draw:
        - 21ml into three (3) ACD tubes
        - 10ml in one (1) EDTA tube
        - 10ml in one (1) Red Top tube
2. All specimens are to be clearly labeled with the ECOG-ACRIN protocol number E1412, the patient's initials (last, first, middle), ECOG-ACRIN sequence number (if available) and date of collection.
3. Place the tubes in the absorbent holder and seal in the zip lock specimen bag.
4. Place the filled specimen bag in the Styrofoam container.
5. Loosely pack with paper toweling.
6. Rev. 10/15 Place the Styrofoam container and the Sample Tracking System Shipping Manifest Form and the completed Patient Information Form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Complete the sender portion of the return FedEx Air Bill and adhere to the exterior lid of the box. Ship specimens via priority overnight delivery (next day delivery by 10am) the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location.

Rev. 6/14 **The ECOG-ACRIN Sample Tracking System will automatically contact the Mayo Clinic Lymphoma Laboratory. If you did not use the ECOG-ACRIN Sample Tracking System**

please call Kim Henderson at (507) 284-3805 or e-mail Henderson.Kimberly@mayo.edu to notify the laboratory when samples are being shipped.

Indicate the ECOG-ACRIN protocol number, the Fed Ex tracking number, name and phone number of the contact person. The blood specimens in prepared kits should be shipped to the following:

Kim Henderson
Mayo Clinic Lymphoma Laboratory
613 Stabile
200 First Street Southwest
Rochester, MN 55905

Affiliates who anticipate participating in this study should please call in advance for kits.

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Appendix VIII

Lenalidomide Education and Counseling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Patient Name (Print): _____ DOB: _____/_____/_____(mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

□ FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months)

□ NOT FCBP

Male: □

Do Not Dispense study drug if:

The patient is pregnant.

No pregnancy tests were conducted for a FCBP.

The patient states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to treatment, during treatment and during dose interruption].

FCBP:

I verified that the required pregnancy tests performed are negative.

I counseled FCBP regarding the following:

Potential risk of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.

Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to treatment, during treatment, during dose interruption and 28 days after discontinuation of lenalidomide].

That even if she has amenorrhea she must comply with advice on contraception

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

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

Pregnancy tests before, during, and after treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10 to 14 days and the second within 24 hours of the start of study drug.

Frequency of pregnancy tests to be done:

Rev. 1/14
- Every week during the first 21 days of this study and a pregnancy test every 21 days during the patient's participation in this study if menstrual cycles are regular or every 10 days if cycles are irregular.
- If the patient missed a period or has unusual menstrual bleeding.
- When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

Provide Lenalidomide Information Sheet to the patient.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

I counseled the female NOT of child bearing potential regarding the following:

- Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP)

- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not break, chew, or open study drug capsules
- Return unused study drug capsules to the study doctor.

Provide Lenalidomide Information Sheet to the patient.

MALE:

I counseled the Male patient regarding the following:

- Potential risks of fetal exposure to lenalidomide (Refer to item #2 in FCBP).
- To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.
- Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant.
- NEVER share study drug with anyone else.
- Do not donate blood, semen or sperm while taking study drug and for 28 days after stopping study drug.
- Do not break, chew, or open study drug capsules.
- Return unused study drug capsules to the study doctor.

Provide Lenalidomide Information Sheet to the patient.

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____

Maintain a copy of the Lenalidomide Education and Counseling Guidance Document in the patient records.

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Appendix IX

Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

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

Criteria for females of childbearing potential (FCBP)

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

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding

- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

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

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

Contraception

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

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

Highly effective methods:

- Intrauterine device (IUD)
- Hormonal (birth control pills, injections, implants)
- Tubal ligation
- Partner's vasectomy

Additional effective methods:

- Male condom
- Diaphragm
- Cervical Cap

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

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Patients:

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

Male Patients:

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

During study participation and for 28 days following study drug discontinuation

Rev. 1/14 *Female Patients:*

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 21 days of study participation and then every 21 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 21 days and then every 10 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 21 days.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Rev. 1/14 *Male Patients:*

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 21 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.

- Female patients should not donate blood during treatment and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during treatment or for at least 28 days following discontinuation of lenalidomide.

Only enough study drug for 28 days or one cycle of therapy (whichever is shorter) may be dispensed with each cycle of therapy.

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Appendix X

Lenalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

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

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

Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby. Lenalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Lenalidomide has not been tested in pregnant women but may also cause birth defects. Findings from a monkey study indicate that lenalidomide caused birth defects in the babies of female monkeys who received the drug during pregnancy.

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

Do not take study drug if you are pregnant or plan to become pregnant

Either do not have sexual intercourse at all or use two reliable, separate forms of effective birth control at the same time:

- for 28 days before starting lenalidomide
- while taking lenalidomide
- during dose interruptions of lenalidomide
- for 28 days after stopping lenalidomide

Rev. 1/14 **You must have pregnancy testing done at the following times:**

- within 10 to 14 days and again 24 hours prior to the first dose of lenalidomide
- weekly for the first 21 days
- every 21 days after the first month or every 10 days if you have irregular menstrual periods
- if you miss your period or have unusual menstrual bleeding
- When the patient is discontinued from lenalidomide and 28 days after the last dose of lenalidomide (14 and 28 days after the last dose if menstrual periods are irregular)

Stop taking study drug if you become pregnant during treatment

- If you suspect you are pregnant at any time during the study, you must stop lenalidomide immediately and immediately inform your study doctor. Your study doctor will report all cases of pregnancy to the National Cancer Institute and the pharmaceutical collaborator, Celgene Corporation.

Do not breastfeed while taking study drug

The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

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

If you are a man:

Lenalidomide is detected in trace quantities in human semen. The risk to the fetus in females of child bearing potential whose male partner is receiving lenalidomide is unknown at this time.

Men (including those who have had a vasectomy) must either abstain from sexual intercourse or use a condom during sexual contact with a pregnant female or a female that can become pregnant:

- While you are taking lenalidomide
- During dose interruptions of lenalidomide
- For 28 days after you stop taking lenalidomide

Men should not donate sperm or semen while taking study drug and for 28 days after stopping lenalidomide.

If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to the National Cancer Institute and the pharmaceutical collaborator, Celgene Corporation. Your partner should call their healthcare provider immediately if she gets pregnant.

Restrictions in sharing lenalidomide and donating blood:

Do not share lenalidomide with other people. It must be kept out of the reach of children and should never be given to any other person.

Do not donate blood while you take lenalidomide and for 28 days after stopping study drug.

Do not break, chew, or open study drug capsules.

You will get no more than a 28-day supply of lenalidomide at one time.

Return unused study drug capsules to your study doctor.

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

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Appendix XI

Site Counselor Identification Form

- **Please identify at least two (2) counselors and fax back to 888-314-2392**
- **Use one form per counselor.**
- **Identified counselors must be licensed healthcare professionals (e.g. RN, PA, RPh, PhD, LPN, CNP, or MD) and must not be the principal investigator.**
- **If you have any questions, please email (coop_ma@celgene.com)**

General Information

Principal Investigator: _____ Institution Name: _____

Counselor Information

CTEPpersonID: _____ CTEPsiteID: _____

First Name: _____ Middle Initial: ____ Last Name: _____

License Type: (circle one) MD PhDPA CNP RN LPN RPh Other: _____

Email Address: _____

Phone: _____

Fax: _____

Institution Street Address:

_____

City: _____ State/Region: _____

Zip/Post Code: _____ Country:

_____

Previously approved as a Counselor? □ No □ Yes

If no, please list all the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) that you *plan to provide* counseling for:

If yes, please list the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) *for protocols Celgene has already associated you with*:

Protocol#:	CTEPsiteID	Institution

Document A _Version 2.1 May 17, 2011

Randomized Phase II Open Label Study of Lenalidomide R-CHOP (R2CHOP) vs RCHOP (Rituximab, Cyclophosphamide, Doxorubicin, Vincristine and Prednisone) in Patients with Newly Diagnosed Diffuse Large B Cell Lymphoma

Rev. 1/14. 6/14

Appendix XII

Instructions for Reporting Pregnancies on a Clinical Trial

What needs to be reported?

All pregnancies and suspected pregnancies (including a positive or inconclusive pregnancy test regardless of age or disease state) of a female patient while she is on Lenalidomide, or within 28 days of the patient's last dose of Lenalidomide must be reported in an expeditious manner. The outcome of the pregnancy and neonatal status must also be reported.

How should the pregnancy be reported?

The pregnancy, suspected pregnancy, or positive/inconclusive pregnancy test must be reported via CTEP's Adverse Event Reporting System (CTEP-AERS) (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/adverse_events.htm)

When does a pregnancy, suspected pregnancy or positive/inconclusive pregnancy test need to be reported?

An initial report must be done within 24 hours of the Investigator's learning of the event, followed by a complete expedited CTEP-AERS report within 5 calendar days of the initial 24-hour report.

What other information do I need in order to complete the CTEP-AERS report for a pregnancy?

- The pregnancy (fetal exposure) must be reported as a Grade 3 "Pregnancy, puerperium and perinatal conditions – Other (pregnancy)" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions"
- The pregnancy must be reported within the timeframe specified in the Adverse Event Reporting section of the protocol for a grade 3 event.
- The start date of the pregnancy should be reported as the calculated date of conception.
- The potential risk of exposure of the fetus to the investigational agent(s) or chemotherapy agent(s) should be documented in the "Description of Event" section of the CTEP-AERS report.

What else do I need to know when a pregnancy occurs to a patient?

- The Investigator must follow the female patient until completion of the pregnancy and must report the outcome of the pregnancy and neonatal status via CTEP-AERS.
- The decision on whether an individual female patient can continue protocol treatment will be made by the site physician in collaboration with the study chair and ECOG-ACRIN Operations Office – Boston. Please contact the ECOG-ACRIN Operations Office – Boston to ask for a conference call to be set up with the appropriate individuals.
- It is recommended the female subject be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

How should the outcome of a pregnancy be reported?

The outcome of a pregnancy should be reported as an amendment to the initial CTEP-AERS report if the outcome occurs on the same cycle of treatment as the pregnancy itself. However, if

the outcome of the pregnancy occurred on a subsequent cycle, a new CTEP-AERS report should be initiated reporting the outcome of the pregnancy.

What constitutes an abnormal outcome?

An abnormal outcome is defined as any pregnancy that results in the birth of a child with persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital anomalies, or birth defects. For assistance in recording the grade or category of these events, please contact the AEMD Help Desk at aemd@tech-res.com or 301-897-7497, for it will need to be discussed on a case by case basis.

Rev. Add9 **Reporting a Pregnancy Loss**

A pregnancy loss is defined in CTCAE as "A death in utero."

It must be reported via CTEP-AERS as Grade 4 "Pregnancy loss" under the System Organ Class (SOC) "Pregnancy, puerperium and perinatal conditions".

A fetal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Rev. Add9 **Reporting a Neonatal Death**

A neonatal death is defined in CTCAE as "A death occurring during the first 28 days after birth" that is felt by the investigator to be at least possibly due to the investigational agent/intervention. However, for this protocol, any neonatal death that occurs within 28 days of birth, without regard to causality, must be reported via CTEP-AERS AND any infant death after 28 days that is suspected of being related to the in utero exposure to Lenalidomide must also be reported via CTEP-AERS.

It must be reported via CTEP-AERS as Grade 4 "*Death Neonatal*"under the System Organ Class (SOC) "General disorder and administration site conditions".

A neonatal death should **NOT** be reported as a Grade 5 event as currently CTEP-AERS recognizes this event as a patient's death.

Additional Required Forms:

When submitting CTEP-AERS reports for pregnancy, pregnancy loss, or neonatal loss, the CTEP 'Pregnancy Information Form' must be completed and faxed along with any additional medical information to CTEP (301-230-0159). This form is available on CTEP's website (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/PregnancyReportForm.pdf)

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Rev. 6/14

Appendix XIII

Modified Ann Arbor Staging System

Stage I	Involvement of a single lymph node region.
Stage II	Involvement of 2 or more lymph node regions on the same side of the diaphragm.
Stage III	Involvement of lymph node regions on both sides of the diaphragm.
Stage IV	Diffuse or disseminated involvement of one or more extra lymphatic organs or tissues, with or without associated lymph node involvement.

The subscript E (e.g., IIE or IIIE) is used to denote involvement of an extra lymphatic site primarily or by direct extension, rather than hematogenous spread, as in the case of a mediastinal mass extending to involve the lung.

The presence of (B) or absence of (A) fever, night sweats, and/or unexplained loss of 10% or more body weight in the 6 months prior to admission are denoted by the corresponding suffix letters B and A.

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Rev. 10/15

Appendix XIV

Gene ExPression Analysis

Determination of molecular DLBCL subtype by GEP is an **integral test,** necessary to conduct the E1412 trial. Although GEP data is not used for clinical decisions or stratification, the accrual goal is based on GEP. Tissue availability and submission for GEP is an eligibility criterion for the study and is **mandatory** for all patients. Dr. Randall Gascoyne's laboratory at British Colombia Cancer Agency is CLIA certified (ID Number: 99D2000767) and will perform the assessments.

1. GEP Determination

   A. Analytes, Technical Platforms, and Assay Components

   Tumor specimens will be analyzed for lymphoma molecular subtype e.g. GCB vs. ABC DLBCL vs. non-classifiable based on previously identified gene expression classifiers [3]. The initial analysis will be based on classification by GEP from paraffin embedded tissue [4]. The tissue will be archived for GEP to be performed after target enrollment is met for molecular classification and analysis including orthogonal technologies and established immunohistochemistry (IHC) algorithms. The outcome measures including PFS and RR rates will be compared between the DLBCL types. GEP will be performed from paraffin embedded tissue utilizing the Affymetrix platform [5]. The submission of paraffin blocks, core needle biopsies, and/or 20 4 micron scrolls from tumor biopsies is mandatory. See Section 3.1.4 and Section 11.

   Although Affymetrix gene expression profiling represents the current gold-standard for determining the cell-of-origin subtypes for DLBCL, we recognize unprecedented technological progress in this regard, and an alternative promising platform (like NanoString) could be used if sufficiently validated by the time GEP is ready to be performed. Although fresh frozen tissue collection is encouraged for GEP, we do not mandate fresh frozen tissue submission for GEP, due to i) logistical difficulties which will likely negatively affect accrual and ii) recent developments in GEP from paraffin tissue.

   B. Scoring Procedures

   GEP results are categorically qualitative and will be reported as a DLBCL molecular subtype e.g. GCB vs. ABC DLBCL vs. non-classifiable based on previously identified gene expression classifiers [3] utilizing the Affymetrix platform [5]. No cut-points will be used.

2. Clinical Utility of GEP Determination as an Integral/Integrated Marker in E1412

   A. Background Information that Justifies the Use of the GEP DLBCL Classification in Relation to Lenalidomide Activity and Determination of Study Accrual Targets

DLBCL is a heterogeneous disorder with 2 major molecular subtypes identified by GEP: Germinal Center B-cell type (GCB) and ABC [3, 6-9]. The latter group is often included in the non-GCB type in IHC-based classification algorithms. The ABC (non-GCB subtype) has been associated with inferior outcome in RCHOP treated patients [10]. Retrospective analysis of the outcomes of patients with GCB vs. non-GCB DLBCL treated with salvage lenalidomide at 4 academic institutions was recently performed. 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 [4]. 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 (Figure 1). 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.

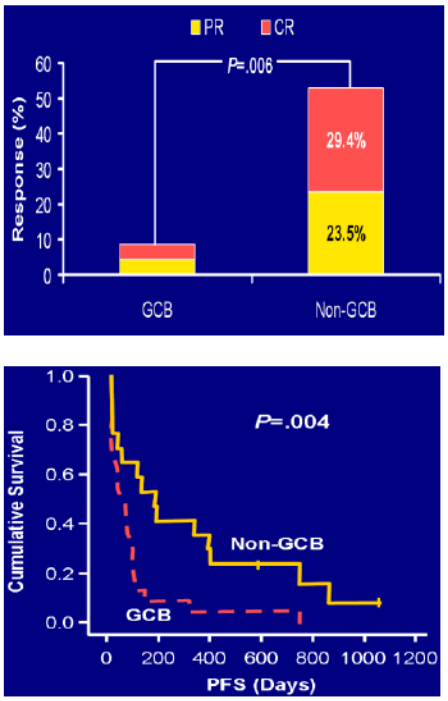

Figure 1. Lenalidomide activity in GCB vs. non-GCB subtype of DLBCL in relapsed/refractory setting. In relapsed/refractory setting, response rates (upper panel) and progression free survival (PFS) are better in patients with non-GCB subtype.

It is unknown if the DLBCL subtype has any impact on lenalidomide efficacy in upfront therapy. The recently reported results from a phase 1/2 study of R2CHOP in newly diagnosed DLBCL, indicate that addition of lenalidomide to RCHOP may overcome the negative prognostic impact of ABC DLBCL subtype [2]. In this study, the PFS of patients with non-GCB subtype of DLBCL was similar to PFS of patients with GCB DLBCL subtype (**Figure 2**). Importantly, in the case control group treated with RCHOP alone at the same institution, as expected, ABC-DLBCL patients treated with RCHOP had an inferior outcome to GCB patients. However, the small number of patients and non-randomized design precluded definite conclusions in regards to deferential activity of lenalidomide in upfront therapy of DLBCL.

Since lenalidomide appears to be particularly active in ABC molecular subtype of DLBCL, it is essential to assure that the E1412 study accrues the predefined number of patients with ABC DLBCL. Any underrepresentation of patients with ABC subtype in E1412 could result in inability to detect differences between study arms. Determination of molecular subtype of DLBCL by GEP is therefore critical to determine if the **study accrual goal** in regards to ABC patients has been met. Thus, molecular DLBCL subtype by GEP is an **integral test** necessary to conduct the E1412 trial. Potential differential activity of lenalidomide in DLBCL provides also a **strong rationale** for use of GEP classification in determination of **futility/early stopping decision** in the trial. In this regard, GEP classification of DLBCL ensures that the study is not terminated prematurely due to a lack of ABC DLBCL accrual and/or masking the improvement of outcome in this group by GCB DLBCL subtype. While we believe that addition of lenalidomide improves outcomes of both DLBCL types, the magnitude of benefit may be higher in ABC subtype partially due to poorer outcome in this group and potentially partially due to higher activity of lenalidomide in this subset.

B. Distribution of Molecular DLBCL Subtypes in Population of Patients with Newly Diagnosed DLBCL

Based on published GEP data in newly DLBCL, the two major molecular subtypes of DLBCL - GCB and ABC subtypes represent approximately 40-45% and 40-45% of patients respectively. The third group is often referred to as non-classifiable and constitutes approximately 15% of patients.

C. Access to GEP Results

Physicians and patients will not be informed of their DLBCL GEP results at any time-point throughout the course of the study because GEP results will not alter patient treatment or care decisions.

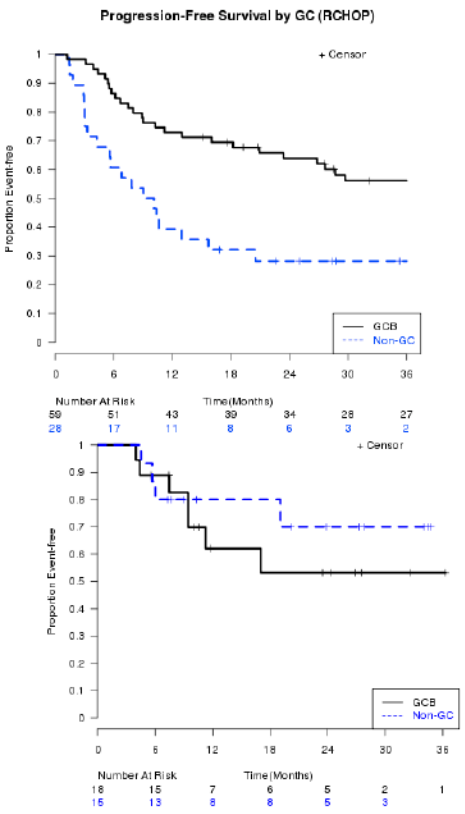

Figure 2. Progression free survival of patients treated lenalidomide RCHOP and RCHOP alone based on DLBCL subtype. While non-GCB subtype was associated with inferior outcome in RCHOP treated patients (lower panel), small number of patients with non-GCB DLBCL appear to have similar outcome in GCB patients when treated with lenalidomide/RCHOP. Nowakowski et al., ASH Dec 2012.