Protocol Title: A Phase I/II Trial of CHOEP Chemotherapy plus Lenalidomide as Front Line Therapy for Patients with Stage II, III and IV Peripheral T-Cell Non-Hodgkin's Lymphoma

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Lenalidomide: **Celgene Reference Number:** RV-CL-PTCL-PI-003858
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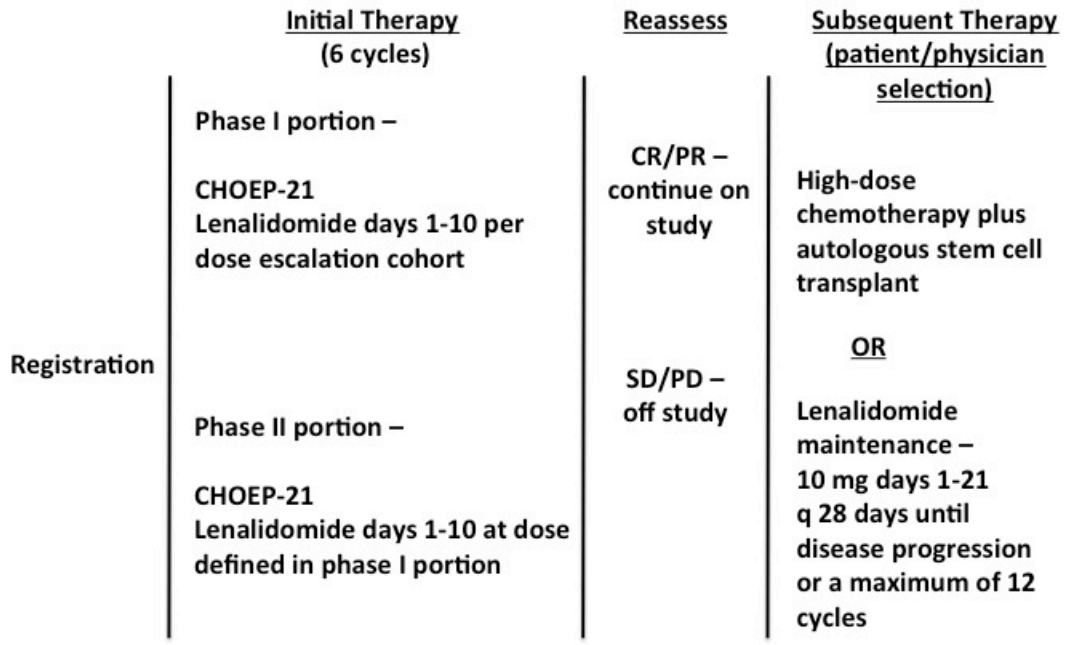
SCHEMA


Initial Therapy
(6 cycles)
Reassess
Subsequent Therapy
(patient/physician selection)
Registration
Phase I portion –
CHOEP-21
Lenalidomide days 1-10 per dose escalation cohort
Phase II portion –
CHOEP-21
Lenalidomide days 1-10 at dose defined in phase I portion
CR/PR – continue on study
SD/PD – off study
High-dose chemotherapy plus autologous stem cell transplant
OR
Lenalidomide maintenance – 10 mg days 1-21 q 28 days until disease progression or a maximum of 12 cycles

ABSTRACT

Title: A Phase I/II Trial OF CHOEP Chemotherapy Plus Lenalidomide as Front Line Therapy for Patients with Stage II, III and IV Peripheral T-Cell Lymphoma

This is a multi-center phase I/II dose escalation study testing the feasibility, tolerability and efficacy of lenalidomide in combination with CHOEP chemotherapy (cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone) as front line therapy for patients with stage II, III and IV peripheral T-Cell lymphoma (PTLC) not otherwise specified (NOS), anaplastic large cell lymphoma (ALK negative) (ALK positive if IPI 3, 4, or 5), angioimmunoblastic T-cell lymphoma, enteropathy associated T-cell lymphoma or hepatosplenic gamma delta T-cell lymphoma. In the phase I portion of the trial, a 3+3 dose escalation design will be used to determine the optimal dose of lenalidomide that can be administered with CHOEP. The primary endpoint of the phase I portion of the study is to determine the maximum tolerated dose (MTD) of lenalidomide given with CHOEP chemotherapy. This will be followed by a phase II portion of the study in which patients will be treated with CHOEP in combination with lenalidomide at the dose defined in the phase I portion of the study. In the Phase I and II portions of the trial, patients will be treated with the combination for 6 cycles. Responding patients will then receive either an autologous stem cell transplant and no further therapy, or maintenance lenalidomide therapy either until disease progression or for a maximum of 12 cycles (1 year). Therapy will be based on physician or patient choice. The primary endpoint of the phase 2 portion of the study is efficacy, defined as complete response (CR) rate after 6 cycles. Secondary endpoints of both phases of the trial will be assessment of toxicity, overall response rate (ORR), progression free survival (PFS), PFS rate at 2 years, and overall survival (OS).

1.0 STUDY OBJECTIVES

1.1 Primary Objective

1.1.1 To assess the safety and efficacy of lenalidomide in combination with standard induction therapy (CHOEP - cyclophosphamide, doxorubicin, etoposide, vincristine and prednisone) in patients with newly diagnosed stage II, III and IV peripheral T-Cell lymphoma not otherwise specified (NOS), anaplastic large cell lymphoma (ALK negative) (ALK positive if IPI 3, 4, or 5), Nodal PTCL with TFH phenotype or angioimmunoblastic T-cell lymphoma, enteropathy associated T-cell lymphoma or hepatosplenic gamma delta T-cell lymphoma.

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

1.1.3 **Phase II trial:** To assess the efficacy (complete response rate) of this combination.

1.2 Secondary Objectives

1.2.1 To evaluate overall response rate (CR+PR) of the combination of lenalidomide and CHOEP chemotherapy.

1.2.2 To evaluate the safety and tolerability of the regimen.

1.2.3 To assess the 2 year progression free survival (PFS) and overall survival (OS) using this regimen.

2.0 BACKGROUND, SIGNIFICANCE, and PRELIMINARY STUDIES

2.1 Treatment of peripheral T-cell lymphoma.

Peripheral T-cell lymphomas (PTCLs) are a heterogeneous group of rare disorders that result from clonal proliferation of mature post-thymic lymphocytes [1,2]. In Western countries, PTCL makes up 5% to 10% of all non-Hodgkin's lymphoma cases and typically affects adults [3,4]. Most of the histologically distinct subsets share an aggressive clinical behavior, poor response to conventional chemotherapy, and poor long-term survival [5,6]. There is no current consensus on standard therapy for patients with newly-diagnosed PTCL [7]. Anthracycline-containing regimens such as CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) are commonly used but frequently result in an inadequate response or a lack of durable remission [8]. High-dose chemotherapy and ASCT have been used as consolidation, but many patients still experience disease relapse [9]. Furthermore, many high-dose chemotherapy studies have been retrospective and included only patients who actually received high-dose chemotherapy. This may overestimate the role of high-dose chemotherapy as first-line therapy because 30% or more of T-cell lymphoma patients progress or do not achieve an adequate response with conventional chemotherapy and thus will not proceed to high-dose chemotherapy and ASCT [10,11]. Improvements in initial therapy in this group of diseases are clearly needed.

2.2 CHOEP chemotherapy as initial therapy for peripheral T-cell lymphoma.

CHOP chemotherapy has been a standard treatment for PTCL [8]. Prospective and retrospective studies have reported complete response rates of 40-60%, when ALK+ anaplastic large cell lymphoma (ALCL) patients were omitted, with a 5-year overall survival of 35-45% in this patient group [12,13]. Efforts to improve the outcome with CHOP chemotherapy have evaluated adding etoposide to the combination. The German High-Grade Non-Hodgkin Lymphoma Study Group analyzed patients treated with CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone/prednisolone) or CHOP plus etoposide (CHOEP) for 6-8 cycles [14]. The 3-year event-free survival (EFS) and overall survival were 41.1% and 53.9% for PTCL-NOS (n = 70), 50.0% and 67.5% for angioimmunoblastic lymphoma (AITL; n = 28), and 45.7% and 62.1% for ALK- ALCL (n = 113). For patients ≤ 60 years, the addition of etoposide to CHOP improved the 3-year EFS (75.4% versus 51.0%, p = .003). In patients > 60 years, however, a benefit for etoposide was not seen[14].

2.3 Lenalidomide in the treatment of T-cell lymphoma.

Lenalidomide is an immunomodulatory agent that has demonstrated clinical efficacy in several hematologic malignancies. Lenalidomide has several hypothesized mechanisms of action, including direct cytotoxicity to tumor cells [15,16], and immunomodulatory effects such as cytokine modulation [17] and enhanced natural killer and T-cell function [18]. In addition, lenalidomide alters the tumor cell microenvironment to discourage the growth of tumor cells and inhibit the mitogenic signaling that supports tumor cells in the bone marrow, both by overcoming the protective role of bone marrow stromal cells [18] and through anti-angiogenic properties [20]. Lenalidomide has proven efficacy in the treatment of several

hematologic malignancies, including chronic lymphocytic leukemia [21], multiple myeloma [22], and myelodysplastic syndrome [23].

Two phase II trials have recently demonstrated clinical activity of lenalidomide in patients with T-cell lymphoma [24,25]. In a Canadian trial of 24 relapsed patients, the overall response rate was 30% (7 of 23); all were partial responses [24]. Two patients had stable disease for ≥5 cycles. Responses were seen in anaplastic, angioimmunoblastic, and peripheral T-cell unspecified histologies. The median PFS was 96 days (range, 8-696+ days) and the median OS was 241 days (range, 8-696+ days). This study was updated at the 2013 American Society of Hematology Annual meeting and the results of 39 eligible patients were reported [25]. The ORR of all patients was 10/39 (26%); 3 (8%) were complete responses and 7 were partial responses. Responses occurred in anaplastic, angioimmunoblastic, and PTCL-NOS histologies. Three additional patients had SD ≥5 cycles. The median OS was 12 months (range <1-69+ months), median PFS was 4 months (range, <1-50+ months) and the median DoR was 13 months (range 2-37+ months), including 5 responses lasting greater than 1 year.

The study also enrolled patients with untreated T-cell lymphoma who were not candidates for combination chemotherapy. The ORR of this subpopulation of previously untreated patients who were not eligible for combined chemotherapy (n=8) was 43%, median OS was 22 months (range, <1-38+ months), median PFS was 2 months (range, <1-38+ months), and median DoR was 21 months (range 5-28+ months).

In a separate recent multicenter French trial [26], 54 relapsed or refractory PTCL patients were treated and an overall response rate of 22% was seen (11% CR). The median PFS was 2.5 months and the median duration of response was 3.6 months. Lenalidomide was felt to exhibit single agent activity and combination approaches were recommended.

In most of these studies, 25 mg of lenalidomide was given for 21 days every 4 weeks. In the proposed trial in which lenalidomide will be combined with CHOEP chemotherapy, this dose is not likely to be achieved. We plan to escalate the lenalidomide to a maximum of 20 mg for 10 days very 3 weeks. In the maintenance portion of the study, our goal is to have patients remain on the drug. A flat lower dose of 10 mg for 21 days every 4 weeks will be administered.

2.4 Phase I/II Study of CHOEP-21 in combination with lenalidomide.

An initial phase I dose escalation portion of the study will be done testing the feasibility and tolerability of lenalidomide in combination with standard CHOEP chemotherapy. We will use a 3+3 dose escalation design (see dose level escalation table in treatment details section) to determine the optimal dose of lenalidomide that can be administered with CHOEP.

This will be followed by a phase II portion of the study in which patients with peripheral T-cell lymphoma will be treated with CHOEP in combination with lenalidomide at the dose defined in the phase I portion of the study. Patients will be treated with the combination every 21 days (+/- 2 days) for 6 cycles. The primary efficacy endpoint of the phase 2 portion of the study is complete response rate after 6 cycles.

Responding patients will then receive either an autologous stem cell transplant and no further therapy, or maintenance lenalidomide therapy either until disease progression or for a maximum of 12 cycles (1 year). The decision between transplant or maintenance therapy will be based on physician or patient choice. While there are no data on maintenance lenalidomide in PTCL patients, previous studies using lenalidomide continued the drug to progression [25,26]. It this therefore anticipated that lenalidomide will well tolerated for 1 year in those who select maintenance therapy.

3.0 ELIGIBILITY CRITERIA

3.1 Inclusion Criteria

3.1.1 Histologically confirmed new diagnosis of Stage II, III and IV Peripheral T-cell Non-Hodgkin's lymphoma not otherwise specified (NOS), Anaplastic large cell lymphoma (ALK negative) (ALK positive if IPI 3, 4, or 5), Nodal PTCL with TFH phenotype or Angioimmunoblastic T-cell lymphoma, Enteropathy associated T-cell lymphoma, Hepatosplenic gamma delta T-cell lymphoma.

Note: As part of the eligibility criteria review, either the 2008 OR 2016 WHO classifications of these diagnoses will be recognized and accepted.

3.1.2 Pathology material: H&E stain and IHC slides or a representative FFPE tissue block along with the pathology report from initial diagnosis, should be sent to be reviewed, and the diagnosis confirmed by Mayo Clinic department (retrospective diagnostic review: treatment may commence prior to the Mayo Clinic review).

3.1.3 No prior therapy with the exception of prior prednisone alone, at the discretion of the investigator based on current diagnosis and clinical condition. This prednisone treatment will not count toward the 6 cycles of treatment given in the study.

3.1.4 Age 19 years or older (the age of consent in Nebraska); Age 18 years or older (applicable to states where the age of majority is 18).

3.1.5 Expected survival duration of > 3 months.

3.1.6 Karnofsky Performance Status > 70. (Appendix A)

3.1.7 Laboratory status as follows:

• ANC > 1000 cells/mm3, unless cytopenias due to NHL (i.e., bone marrow involvement or splenomegaly)
• Platelet Count > 100,000 /µL or > 75,000 /µL if BM involvement or splenomegaly
• Total bilirubin ≤1.5 x upper normal limit, or ≤ 3 x upper normal limit if documented hepatic involvement with lymphoma, or ≤ 5 x upper normal limit if history of Gilbert's Disease.
• Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper normal limit (≤ 5 x upper normal limit if documented hepatic involvement with lymphoma).
• Serum creatinine < 2.0 mg/dL or calculated creatinine clearance (CrCl) > 45 mL/min (Cockcroft-Gault, Appendix B)
• PT or INR, and PTT ≤ 1.5 x upper limit of normal unless patient is receiving anticoagulants. If patient is on warfarin therapy, levels should be within therapeutic range.

3.1.8 If currently not on anticoagulation medication, willing and able to take aspirin (81 or 325 mg) daily. If aspirin is contraindicated, the patient may be considered for the study if on therapeutic dose warfarin or low molecular weight hep Patients unable to take any prophylaxis are not

eligible.

3.1.9 Patients with measurable disease. Patients with non-measurable but evaluable disease may be eligible after discussion with the PI. Baseline measurements and evaluations must be obtained within 6 weeks of registration to the study. Abnormal PET/CT scans will not constitute evaluable disease, unless verified by the CT scan portion, CT scan, or other appropriate imaging.

3.1.10 Patients with measurable disease must have at least one objective measurable disease parameter. A clearly defined, bi-dimensionally measurable defect or mass measuring at least 1.5 cm in diameter on the CT portion of a PET/CT or CT scan or MRI (if appropriate) will constitute measurable disease. Proof of lymphoma in the liver is required by a confirmation biopsy. Skin lesions can be used as measurable disease provided bi-dimensional measurements are possible.

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

3.1.12 Women must not be pregnant or breast-feeding due to teratogenic effects of lenalidomide and chemotherapy.

• Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS™ program.
• All females of childbearing potential must have a blood test within 2 weeks prior to registration to rule out pregnancy.
• Pregnancy testing is not required for post-menopausal or surgically sterilized women.

3.1.13 Male and female patients of reproductive potential must agree follow accepted birth control measures.

3.1.14 Patient must be able to adhere to the study visit schedule and other protocol requirements.

3.1.15 Patients must be willing to give written informed consent, and sign an institutionally approved consent form before performance of any study-related procedure not part of normal medical care as noted in 3.1.3 above; with the exception of 1 cycle of chemotherapy based on current diagnosis and clinical condition, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

3.1.16 No serious disease or condition that, in the opinion of the investigator, would compromise the patient's ability to participate in the study.

3.2 Exclusion Criteria

3.2.1 Pregnant or breast feeding females.

3.2.2 Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients who are seropositive (i.e. hepatitis B core antibody positive; quantitative DNA negative) are eligible with appropriate prophylaxis.

3.2.3 Major surgery as defined by the institutional PI within 2 weeks of study drug administration.

3.2.4 Prior malignancies within the past 3 years with exception of adequately treated basal cell, squamous cell skin cancer, or thyroid cancer; carcinoma in situ of the cervix or breast; prostate cancer of Gleason Grade 6 or less with stable PSA levels.

3.2.5 Patients with a diagnosis of other PTCL subtype histologies other than those specified in the inclusion criteria. Large cell transformation of mycosis fungoides is excluded.

3.2.6 Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all anticoagulation and antiplatelet options, or antiviral drugs.

3.2.7 Any other clinically significant medical disease or condition laboratory abnormality or psychiatric illness that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.

3.2.8 Known hypersensitivity to thalidomide, pomalidomide, or lenalidomide.

3.2.9 The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide, lenalidomide or similar drugs.

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

NOTE:
All questions regarding eligibility for **UNMC potential subjects** should be directed to the UNMC Coordinator at 402-559-9053.

All questions regarding eligibility for **Participating Site** potential subjects should be directed to the sponsor PI by contacting the UNMC **Fred & Pamela Buffett** Cancer Center Research Project Coordinator at 402-559-4596.

NOTE: UNMC and Participating Sites should complete the eligibility checklist (Appendix C) as source documentation if it has been reviewed, signed, and dated prior to registration by the treating physician. The eligibility checklist must be accompanied by all other source documents that evidence the subject's eligibility (i.e., dictation, pathology, radiology, laboratory, etc.)

4.0 REGISTRATION PROCEDURES

Patients, who are referred to the Nebraska Medical Center (NMC) / UNMC, or other IRB approved participating sites, with the following histologies: newly diagnosed Stage II, III and IV peripheral T-cell non-Hodgkin's lymphoma not otherwise specified(NOS), anaplastic large cell lymphoma (ALK negative) (ALK positive if IPI 3, 4, or 5), angioimmunoblastic T-cell lymphoma, enteropathy associated T-cell lymphoma, hepatosplenic gamma delta T-cell lymphoma may be eligible for this trial.

Screening eligibility based on standard clinical care will be performed by the treating physician at the time of encounter. On initial presentation, a history and physical examination are performed, laboratory data obtained, and performance status is assessed. Imaging studies obtained include PET/CT; a high-resolution multi-detector computed tomography (CT) of the chest, abdomen and pelvis may be necessary if measurements cannot be made off the CT portion of the PET/CT. Further imaging studies will be obtained as clinically indicated. Pathology material must be reviewed, and the diagnosis confirmed by Mayo Clinic pathology department (retrospective) (See section 5.7 and Appendix F for details). The patient's primary oncologist will make the decision as to screened eligibility of the candidate based on the eligibility criteria listed above, prior to offering consent.

If the patient is screened as potentially eligible, he/she will then be offered the option to participate. An informed consent will be signed by the patient after thorough review of the study is completed by the physician and his/her designee.
Some insurance carrier's may decline to cover the costs of usual medical care if the patient is participating in a clinical trial. The patient will be provided assistance by the research nurse coordinator or designated staff in determining if the insurance carrier will decline coverage. Insurance carriers may or may not pay for study related expenses. The patient can then decide if they wish to participate.

4.1 Eligibility Verification/Registration:

Before patients are registered to the study, an eligibility checklist (Appendix C) must be completed and source documents provided to UNMC to verify the subject meets the eligibility criteria.

Date of Enrollment: The date of consent will be considered the date of enrollment. Within 24 hours of consent, the following information should be submitted to UNMC project coordinator:

- copy of the signed and dated consent form for the subject enrolled in the protocol
- Protocol Number
- Patient Identification: Patient initials and site id
- Patient demographics: gender, birth date (mm/dd/yyyy), race, ethnicity, insurer information

Registration Date: Eligibility verification and notification of assigned subject number (by UNMC) to Participating Sites will be known as the registration date.

First study-related Treatment Date: All eligibility criteria do not need to be met until the date of the first study related treatment (defined for this protocol as the initiation of Cycle 1 CHOEP or as noted in 3.1.3 above; “with the exception prior radiation therapy and of 1 cycle of chemotherapy based on current diagnosis and clinical condition”.

Patients will be registered through the sponsor PI by contacting the UNMC Fred & Pamela Buffett Cancer Center Research Project Coordinator and the UNMC Fred & Pamela Buffett Cancer Center Protocol Review and Monitoring System Office (PRMS). All Study personnel from UNMC and non-UNMC IRB approved sites will contact the UNMC Research Project Coordinator if a patient appears to meet the eligibility criteria. They will email the completed eligibility checklist (Appendix C) and de-identified relevant source documents to the Research Project Coordinator, at (ph: 402-559-4596) to verify the subject meets the eligibility criteria. The eligibility check list will be maintained in the study file. If the UNMC Research Project Coordinator confirms that the patient meets criteria, and target accrual has not been met, approval for the patient will be given. A confirmation of registration will be forwarded by the UNMC Research Project Coordinator.

In the event of an after-hours potential enrollment (i.e., clinic coast time differences), or an immediate need-to-treat based on potential subject condition, registration can be accomplished by contacting the sponsor PI Dr. Matthew Lunning directly by email: mlunning@unmc.edu (response required) or by phone/pager 402-559-4000 or 402-888-3837. The UNMC Research Project Coordinator must be notified in order to meet UNMC Protocol Review Monitoring System (PRMS) Office requirements.

The UNMC Fred & Pamela Buffett Cancer Center Protocol Review & Monitoring System (PRMS) Office Audit Committee defines a *Participating Site* as: a hospital clinic, or other provider of medical services who has agreed to participate in a therapeutic trial that has been designed and developed by a University of Nebraska Medical Center/Nebraska Medical Center (UNMC/NMC) investigator and is sponsored by UNMC.

The UNMC Research Project Coordinator will provide the following listed information to the UNMC Fred & Pamela Buffett Cancer Center PRMS office (obtained from participating sites which have local *and* UNMC IRB approval, and have met all other criteria to enroll). The listed information for subjects enrolled at participating sites will be provided to the PRMS office within one week of enrollment as applicable:

- UNMC and Participating Site Protocol Numbers
- Investigator/Participating Site Identifier (ID)
- Subject ID: Assigned by UNMC [Site ID followed by subject number (##-###)]
- Consent Date: Date subject signed consent
- Patient demographics: gender, birth date (mm/dd/yyyy), race, ethnicity
- Re-consent Date: (If applicable)
- Ineligibility Status: (If known)
- Off Study Date: (If applicable)

4.2 Pathology Requirements

Pathological materials are to be submitted as indicated in section 3.1.2. “Pathology material: H&E stain and IHC slides or a representative FFPE tissue block along with the pathology report from initial diagnosis, should be sent to be reviewed, and the diagnosis confirmed by Mayo Clinic department (retrospective review)”. Please NOTE: the diagnostic H&E slide and IHC slides will be returned after review.

See Biospecimen Section 5.7.1 for details of the required pathological materials for retrospective diagnosis.

4.3 Instructions for Patients Who Do Not Start Assigned Protocol Treatment

If a patient does not receive any assigned protocol treatment, enrollment data will still be collected and must be submitted according to the instructions in the protocol. Documentation of the reason for not starting protocol treatment should be noted on the enrollment forms.

4.4 Requirements for Submitting Regulatory Documents UNMC and Participating Institutions:

Before an institution may enroll patients, all site activation criteria must be met by submitting required protocol specific regulatory documents to the study project manager at UNMC Fred & Pamela Buffett Cancer Center).

4.5 Required Protocol Specific Regulatory Documents

1. Confirmation that the UNMC Team Designee(s) conducted an initial Site Visit/Teleconference prior to opening a protocol to accrual at the participating site, and that the UNMC and Site PI have documented that questions posed by the Site PI regarding the conduct of the protocol have been answered/resolved.

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. 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

5.0 TREATMENT PLAN

5.1 Drug Administration

5.1.1 Body Surface Area (BSA) Calculations
Dosage calculations will be based on the patient's BSA, at baseline. Actual height and weight should be used in determining body surface area. (Appendix B) Dose adjustments at the beginning of each cycle do not need to be made unless there has been a >10% weight gain or loss.

5.1.2 Requirement for Venous Access
Central venous access is suggested for protocol participation, but not mandated. A previously placed central venous access device that is functioning properly (free infusion of saline, unimpeded blood return, good condition of external appliance, no recent history of device infection or thrombosis) can be used. Should the patient require a central venous access, an implanted port central venous access device will be placed (e.g. Power Port) after appropriate informed consent has been obtained. Other aspects of catheter/port management will be in accordance with standard nursing clinic central venous port procedures.

5.1.3 Prophylaxis - Pre and post medications as prescribed by the treating physician.

5.1.3.1 CNS prophylaxis: Not required by the protocol. Patients should be treated per institutional guidelines

5.1.3.2 Tumor lysis precaution, per institutional guidelines. Patients considered to be at risk for tumor lysis should be well hydrated and consider to be treated with allopurinol or a suitable alternative for 12-24 hours prior to the first infusion of chemotherapy.

5.1.3.3 Prophylactic Anti-Emetic Premedication: Standard antiemetic prophylaxis will be given per institutional guidelines.

5.2 Treatment Schedule.

5.2.1 **Phase I Cohort:** Lenalidomide plus CHOEP regimen.

NOTE: Patients will receive 6 cycles of therapy before having an autologous stem cell transplant or receiving maintenance lenalidomide. Each cycle will be 21 days with a +/- 2 day start window. All 10 pills of lenalidomide must be taken to be consider eligible for DLT assessment for cycle 1; replacement doses if lost/misplaced can be obtain if within days (1-10).

DRUG	***DOSE***	***FREQUENCY***	***# of CYCLES***	***Administration***
Cyclophosphamide[1]	750 mg/m^2	Day 1	6 cycles	IV
Doxorubicin[2]	50 mg/m^2	Day 1	6 cycles	IV
Vincristine[3]	1.4 mg/m^2	Day 1	6 cycles	IV
Etoposide[4]	100 mg/m^2	Days 1-3	6 cycles	IV
Prednisone	100 mg	Days 1-5	6 cycles	PO
Lenalidomide NOTE: To provide a means of ensuring oral route of medication adherence to subjects while participating in this clinical trial. Please see: **Appendix E- Oral, Sublingual, and/or Buccal Route Medication Adherence Standard Procedure**	As determined in phase I, see dose escalation table (section 5.3.1)	Day 1-10	6 cycles; additional 12 cycles (given day 1-21 every 28 days) or until disease progression or a maximum of 12 cycles if chooses maintenance therapy (see section 5.2.3.1 for maintenance dosing)	PO
Pegfilgrastim (Neulasta)[6] 6mg	Pegfilgrastim (Neulasta) 6mg	Day 4, 5 or 6 5	6 cycles	SQ
Aspirin[5]	81mg or 325mg	Daily	During active treatment	PO

1. Cyclophosphamide dose may be rounded to nearest 50 mg
2. Doxorubicin dose may be rounded to nearest 5 mg
3. Vincristine must be capped at 2 mg
4. Etoposide dose may be rounded to nearest 5 mg. Substituting oral etoposide for intravenous is permitted on days 2 and 3 at 200 mg/m^2 and must be document in the notes section of medication diary in Appendix E

5. See Ancillary Treatment section 5.5 regarding anticoagulation recommendations.
6. Neulasta, on-body injectors are acceptable. Neupogen can be substituted per institutional policy. One dose per cycle of Neulasta including on-body injectors.

5.2.2 **Phase 2 Cohort:** Lenalidomide plus CHOEP regimen (at MTD from phase I). Patients will receive 6 cycles of therapy. Each cycle will be 21 days with a +/- 2 day start window.

NOTE: Patients will receive 6 cycles of therapy before having an autologous stem cell transplant or receiving maintenance lenalidomide.

DRUG	***DOSE***	***FREQUENCY***	***# of CYCLES***	***Administration***
Cyclophosphamide[1]	750 mg/m^2	Day 1	6 cycles	IV
Doxorubicin[2]	50 mg/m^2	Day 1	6 cycles	IV
Vincristine[3]	1.4 mg/m^2	Day 1	6 cycles	IV
Etoposide[4]	100 mg/m^2	Days 1-3	6 cycles	IV
Prednisone	100 mg	Days 1-5	6 cycles	PO
Lenalidomide NOTE: To provide a means of ensuring oral route of medication adherence to subjects while participating in this clinical trial. Please see: **Appendix E- Oral, Sublingual, and/or Buccal Route Medication Adherence Standard Procedure**	MTD dose	Day 1-10	6 cycles; additional 12 cycles (given day 1-21 every 28 days) or until disease progression if chooses maintenance therapy (see section 5.2.3.1 for maintenance dosing)	PO
Pegfilgrastim (Neulasta)[6] 6mg	Pegfilgrastim (Neulasta) 6mg	Day 4, 5 or 6	6 cycles	SQ
Aspirin[5]	81mg or 325mg	Daily	During active treatment	PO

1. Cyclophosphamide dose may be rounded to nearest 50 mg
2. Doxorubicin dose may be rounded to nearest 5 mg
3. Vincristine must be capped at 2 mg
4. Etoposide dose may be rounded to nearest 5 mg. Substituting oral etoposide for intravenous is permitted on days 2 and 3 at 200 mg/m^2 and must be document in the notes section of medication diary in Appendix E.
5. See Ancillary Treatment section 5.5 regarding anticoagulation recommendations.
6. Neulasta, on-body injectors are acceptable. Neupogen can be substituted per institutional

policy. One dose per cycle of Neulasta including on-body injectors.

5.2.3 Maintenance lenalidomide or autologous stem cell transplantation

Responding patients after 6 cycles of lenalidomide plus CHOEP may then be treated either an autologous stem cell transplant and no further therapy, or maintenance lenalidomide at 10 mg for 21 days of a 28 day cycle (with a +/- 2 day start window) either until disease progression or for a maximum of 12 cycles (1 year). Therapy will be based on physician or patient choice.

5.2.3.1 Administration Schedule for lenalidomide maintenance

• Lenalidomide 10 mg PO days 1 through 21 on a 28-day cycle.

To provide a means of ensuring oral route of medication adherence to subjects while participating in this clinical trial. Please see: ***Appendix E- Oral, Sublingual, and/or Buccal Route Medication Adherence Standard Procedure***

NOTE: The dose of lenalidomide to be given as maintenance therapy is a fixed dose of 10mg PO days 1-21 on a 28 day cycle and is independent of the dose received in combination with CHOEP chemotherapy.

NOTE: The first cycle of lenalidomide will start 8 weeks (+/- 1 week) after day 1 of cycle 6 of induction. Patients who, due to unacceptable lab values or other reasons, are unable to start consolidation within 16 weeks after the start of Cycle 6 of CHOEP/lenalidomide will be withdrawn from study treatment. The patient should remain on the study and should be followed for subsequent events.

NOTE: Prior to starting lenalidomide continuation and subsequent cycles at time points referenced in study calendar, the ANC must be > 1000 cells/mm3 (1.0 x 109/L) and the platelet count must be > 75,000 cells/mm3 (75 x 109/L).

NOTE: Creatinine clearance (CrCl) should be calculated prior to the first dosing of lenalidomide. If CrCl < 30 ml/min, or for patients on dialysis, lenalidomide should not be given.

NOTE: All patients receiving lenalidomide based continuation therapy must complete the lenalidomide pill diary for each cycle/dose of lenalidomide

Anticoagulation - All subjects receiving lenalidomide maintenance therapy will be **required** to have deep vein thrombosis (DVT) prophylaxis every day during lenalidomide therapy. Subjects with a history of a thrombotic vascular event are required to have therapeutic doses of low molecular weight heparin or warfarin with a goal to maintain an INR between 2.0–3.0. Oral anti-Xa or direct thrombin inhibitors are not allowed. All subjects without a history of a thromboembolic event are required to take a daily aspirin (81mg or 325 mg) for DVT prophylaxis. Subjects who are unable to tolerate aspirin should receive prophylactic doses of low molecular weight heparin therapy or

warfarin treatment per institutional policy.

Of note, if patients' platelets decline to < 50,000/mm3 (50 x 109/L), prophylactic anti-coagulation should be stopped (in addition to holding lenalidomide as below in Section 5.4). If/when lenalidomide is restarted (with return of platelet toxicity to ≤ Grade 2 as in Table 5.4.2 in Section 5.4), then prophylactic anti-coagulation should also be restarted.

5.2.3.2 Hematopoietic Stem Cell Transplantation

Administration of Standard Preparative Regimen (in patients who have a CR or PR as per investigator's discretion) followed by HSCT (as per institutional guidelines) regimen optional ex: BEAM

Subjects going on to receive transplant per standard/institutional guidelines will only be followed for PFS.

Hematopoietic Stem Cell Collection: Peripheral blood stem cells will be collected as per the discretion of the treating physician until an adequate number of CD34+ cells/kg have been collected (as per existing institutional guidelines).

The timing of stem cell collection will be at the discretion of the treating physician and as per institutional guidelines. However, it is recommended that delays in administering CHOEP plus lenalidomide be avoided.

<u>Suggested optional preparative regimen - BEAM:</u>

Day – 6	Day – 5	Day - 4	Day - 3	Day - 2	Day - 1	Day 0
BCNU 300mg/m^2	Etoposide 100mg/m^2 BID Cytarabine 100mg/m^2 BID	Etoposide 100mg/m^2 BID Cytarabine 100mg/m^2 BID	Etoposide 100mg/m^2 BID Cytarabine 100mg/m^2 BID	Etoposide 100mg/m^2 BID Cytarabine 100mg/m^2 BID	Melphalan 140mg/m^2	Stem Cell Infusion

Dose Modifications for Suggested Optional BEAM Regimen -
The dose of BEAM will remain constant for each subject throughout the study. No adjustments in doses for post-screening changes in body surface area will be made.

NOTE: The preparative regimen above is a suggested option. The exact combination and dosing should be as per institutional standards.

5.2.3.3 Reason as to why patients do not proceed to transplant:

Physicians will be required to document the reason why patients did not proceed to an autologous transplant - i.e., comorbidities, advanced age, inability to mobilize, patient decision, and physician decision.

5.3 Phase I dose escalation and determination of MTD.

5.3.1 Dose escalation of lenalidomide

Dose level	Dose	Day of the 21-day cycle
-1	Lenalidomide 5 mg	Day 1-10
1 (starting dose level)	Lenalidomide 10 mg	Day 1-10
2	Lenalidomide 15 mg	Day 1-10
3	Lenalidomide 20 mg	Day 1-10

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

5.3.1.2 Investigators are to contact the UNMC collaborators soon as any dose-limiting toxicity occurs.

5.3.2 Definitions of Dose Limiting Toxicity (DLT)

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

Toxicity	Definition
Hematologic	Either: 1. PLT <25,000 for ≥7days **or** platelet nadir <10,000 at anytime 2. Failure to recover counts to PLT ≥ 75,000 and/or ANC ≥1500 by day 28 after initiation of cycle 1 treatment.
Infection	Grade 4 per NCI Common Terminology Criteria for Adverse Events v4.0* (life threatening).
Non-hematologic	Either: 1. ≥ grade 3 as per NCI Common Terminology Criteria for Adverse Events v4.0* 2. Any toxicities that caused dose delay of > 1 week of the intended next dose

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

5.3.3 Maximal Tolerated Dose (MTD) Determination

The MTD in this study will be defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of patients (at least 2 of a maximum of 6 new patients). This will be defined on cycle 1 data; however, toxicity data will be collected during all cycles and monitored for cumulative toxicity. Based on the cumulative toxicity data, additional patients may be added to cohorts to further investigate and cohorts may not be investigated at the discretion of the investigators if a cumulative toxicity signal is seen.

5.3.4 Dose Escalation

5.3.4.1 Three patients will be treated at a given dose level combination and observed at least until day 1 of cycle 2to assess toxicity.

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

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

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

5.3.5 Dose De-escalation from Dose Level 1

If 2 treatment-related DLTs are observed at the starting dose level, patients will be accrued to level -1. The accrual rules based on observed DLT will be as outlined in Section 5.3.4. If 2 treatment-related DLTs are observed at dose level -1, the study will be suspended.

5.3.6 If a patient in phase I cohort fails to complete cycle 1 for reasons other

than toxicity, the patient will be regarded as non-evaluable and will be replaced for DLT assessment but will remain eligible for further toxicity and efficacy assessment.

5.4 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 CHOEP plus lenalidomide study treatment agents have been discontinued will remain on study unless all CHOEP plus lenalidomide study treatment agents are discontinued. Patients in whom all the CHOEP plus lenalidomide study treatment agents were discontinued will proceed to event monitoring.

Table 5.4.1 Dose Levels (Based on Adverse Events in Table 5.4.2)

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

Table 5.4.2 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/ etoposide	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, etoposide and ADR by 25% and follow standard dosing guidelines.
Cardiac General	Left ventricular systolic dysfunction ≥ grade 3	ADR	Discontinue ADR.
Renal/ Genitourinary	Cystitis ≥ grade 2	CTX	Omit CTX until resolution of cystitis. Decrease CTX 50% of preceding dose for next cycle of treatment. If subsequent cycle is well tolerated and there is no grade ≥2 renal/GU adverse events, increase CTX to 100% of the original dose.
Neurology	Neuropathy – motor Grade 2	VCR	Omit VCR until neuropathy < grade 2 and resume at 50% dose reduction.
	Neuropathy – motor Grade ≥ 3		Discontinue VCR.
	Neuropathy – sensory Grade 3		Omit VCR until neuropathy <grade 2 and resume at 50% dose reduction.
	Neuropathy – sensory Grade 4		Discontinue VCR
Allergy/Immunology	Allergic reaction or hypersensitivity: Grade 2	Lenalidomide	Omit treatment until ≤ grade 1 and restart with prophylaxis. If questions, call study chair.
	Allergic reaction or hypersensitivity: Grade 3		Omit therapy; treat the reaction and restart at MD discretion.
	Allergic reaction or hypersensitivity: Grade 4		If attributable to lenalidomide, discontinue treatment with lenalidomide.
Vascular	Venous thrombosis/embolism Grade 3 or 4		Discontinue lenalidomide.

ADR-doxorubicin, CTX – cyclophosphamide, VCR - vincristine

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/ CHOEP	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/ VCR	Initiate bowel regimen and continue lenalidomide and VCR. Omit lenalidomide until grade 2, initiate bowel regimen and restart lenalidomide. Decrease VCR by 25%
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 than 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/ CHOEP	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%, etoposide 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.

ADR-doxorubicin, CTX – cyclophosphamide, VCR - vincristine

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/ CHOEP	Hold drugs until toxicity has resolved to grade 2 or baseline grade then restart drugs. If questions, contact the study chair.

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

Use Common Terminology Criteria for Adverse Events (CTCAE) v4.0 unless otherwise specified			
CTCAE CATEGORY	ADVERSE EVENT	AGENT	DOSAGE CHANGE
AT TIME OF RETREATMENT			
Blood/Bone marrow	ANC<1500 PLT< 75,000	Lenalidomide/ CHOEP	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, PLT ≥75,000		Decrease lenalidomide to the next lowest dose level, continue 100% CHOEP. If lenalidomide at the lowest dose level, discontinue. If not recovered continue to hold.
	Day 36 and beyond: ANC ≥1500, PLT ≥75,000		Discontinue lenalidomide; resume CHOEP with 25% ADR, 25% etoposide and 25% CTX dose reduction. Future dose modifications of CHOEP should follow standard CHOEP guidelines.
Other non-hematologic	Grade ≥ 3*		Hold drugs until toxicity has resolved to grade 2 or baseline grade then restart lenalidomide at next lower dose level. If lenalidomide is at lowest level, discontinue. If next cycle is delayed by ≥ 2 weeks, contact study chair.

*Nausea and vomiting of grade 3 or 4 after full anti-emetic therapy will then follow dose reduction guidelines.
ADR-doxorubicin, CTX – cyclophosphamide, VCR - vincristine

5.5 Ancillary Treatment

5.5.1 Patients who are not already on anticoagulation should receive aspirin (81 mg or 325 mg) daily. This should be discontinued if platelets are <50,000 or if the patient is intolerant of aspirin or develops bleeding complications irrespective of the platelet count. If aspirin is contraindicated for other reasons – call study chair.

5.5.2 Patients should be considered for proton pump inhibitor while on aspirin or other prophylaxis per physician discretion.

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

5.5.4 Tumor lysis syndrome prophylaxis should be considered 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. Growth colony stimulating factor (GCSF) support will be given with each cycle. Treat as needed.

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.

5.5.7 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 Assessments

5.6.1 Course Assessment Schedule

A dedicated CT response assessment will be done after cycles 2. A PET/CT scan is done at the end of therapy to confirm the response.

PET/CT is preferred as part of the initial staging evaluation. Dedicated CT is necessary if measurements cannot be made for the CT portion of the PET/CT. PET/CT is optional after initial response evaluation and at the end of cycle 6. If the patient elects to undergo autologous transplant at D+100 response evaluation with CT or PET/CT is at the discretion of the investigator but PET/CT would be preferred if not in a CR after cycle 6.

A restaging bone marrow biopsy may be done if a staging bone marrow biopsy was previously positive or if symptoms suggest involvement. Restaging may also include MRI; if clinically indicated. (See Section 7.0.)

Patients with stable disease after 6 cycles are off study. Patients with progressive disease (PD) at any time are off study and will discontinue study treatment.

Patients achieving PR/CR after 6 courses, and if transplant eligible, as per investigator's discretion, proceed to HDT per institutional guidelines (See Section 5.2.3.2).

Patients achieving PR/CR after 6 courses, and who are not transplant eligible or elect not to proceed to autologous transplant, as per investigator's discretion, proceed to maintenance therapy with lenalidomide either until disease progression or for a maximum of 12 cycles (1 year). (See Section 5.2.3).

NOTE: Assessments during the first year after completing 6 cycles of CHOEP plus lenalidomide should be as per section 7.0. Assessments in year 2 post transplant or at the completion of maintenance therapy is per institutional guidelines.

5.6.2 Post Trial Assessments

Patients who go off study treatment at any time during the trial will be followed for 30 days after the last day of treatment or until other disease-related treatment begins. For all patients, drug-related SAEs and AEs will be followed until baseline or ≤ grade 1 levels. Patients who responded or maintained stable disease during the study will be followed for date of disease progression. Patients will be assessed after cycle 2 and 6 as outlined in treatment plan as well as at 100 days and 1 year post transplant. Patients may refuse to participate in the post-trial assessments.

5.7 Biospecimens

One 6 mL EDTA tube will be collected for serum, plasma and DNA at baseline, and after study treatment completion (4-6 weeks after cycle 6 day1). Serum and plasma will be used to measure serum cytokines. Any leftover serum, plasma and DNA specimens will be stored until the end of the study..

5.7.1 Required Pathological Materials for Retrospective Diagnosis

Baseline standard of care diagnostic pathology samples will be done as clinically indicated. Pathological materials are to be submitted as indicated in sections 3.1.2 and 4.2. “Pathology material: H&E stain and IHC slides or a representative FFPE tissue block along with the pathology report from initial diagnosis,), should be sent to be reviewed, and the diagnosis confirmed by Mayo Clinic department (retrospective diagnostic review: treatment may commence prior to the Mayo Clinic review)”.

Please NOTE: the diagnostic H&E slide and IHC slides will be returned after review.

Initial diagnostic materials should be submitted within 1 month of patient registration. A copy of the pathology report should be sent when the sample is shipped.

5.7.2 Correlative Studies Related to the Research - Plasma Cytokines and DNA analysis

Rationale: Recent data have suggested that increased levels of serum or plasma cytokines pretreatment correlate with prognosis in patients with lymphoma. We wish to determine whether the proposed treatment combination results in changes in the cytokine profile.

Method: We will measure the plasma levels of a variety of inflammatory cytokines, using a multiplex ELISA. Thirty cytokines, including pro-inflammatory, Th1 and Th2 associated cytokines, will be analyzed for each time point. Multiple cytokine analysis kits will be used. Assays will be run in duplicate according to the manufacturers’ protocol. Data will be collected using the Luminex system and data analysis will be performed using a multiplex expression analysis software platform such as the MasterPlex QT or Bio-Plex system. A five-parameter regression formula will be used to calculate the sample concentrations from the standard curves and a change of 50% from the baseline value will be considered significant.

EDTA Tube Processing: Centrifuge for 15 minutes at room temperature at 1500 RPM within 30 minutes of collection. For cytokine analysis – Remove and aliquot the top 2 ml of plasma from the EDTA tube. Store 1 ml aliquots in two (2) properly labeled polypropylene tubes for cryopreservation. Store samples in the freezer at ≤ -20°C until they are shipped for analysis.

For DNA analysis – Remove and aliquot the top 1 ml of cells from the EDTA tube. Store the 1 ml aliquot in a properly labeled polypropylene tube for

cryopreservation. Store the sample in the freezer at ≤ -20°C until it is shipped for analysis.

Shipping: All specimens pathology and EDTA serum and DNA samples are to be sent to the Mayo Clinic, to the contact and address listed below. Send blood samples overnight on ice Monday through Thursday only; do not send the day before a holiday. (See Appendix F)

Please contact Tammy Price-Troska, Hematology Research, at (507) 284-3805, or pricetroska.tammy@mayo.edu, to advise of planned shipments, and to discuss appropriate procedures in the event a sample collection must be drawn on a Friday or before a holiday.

Shipping Address:
Tammy Price-Troska
Hematology Research – Stabile 6-13
Mayo Clinic
200 First Street SW
Rochester MN 55905
Phone: (507) 284-3805
Email: pricetroska.tammy@mayo.edu

6.0 MEASUREMENT OF EFFECT

6.1 Response to therapy

Response to therapy will be classified as complete response (CR), partial response (PR), stable disease (SD), progressive disease (PD), early death, or not evaluable. Response to therapy will be determined after cycles 2 and 6 as outlined in treatment plan.

Patients with a global deterioration of health status requiring permanent discontinuation of study treatment (taken off study) without objective evidence of disease progression will be counted as progressive disease. Every effort should be made to document the objective progression even after discontinuation of treatment. Deaths will be counted as treatment failure.

Patients will be analyzed with respect to overall survival (OS) and progression-free survival (PFS). Overall survival is defined as time from the first chemotherapy administered on trial until death from any cause. For subjects who are still alive at the time of the study analysis or are lost to follow-up, survival will be censored at the last recorded date that the subject was known to be alive. Progression-free survival is defined as time from therapy until relapse, progression, or death from any cause. Response will be determined by the principal investigator or the co-principal investigators.

CR rate is at the end of 6 cycles of the CHOEP/lenalidomide.

Definitions for clinical response for patients with lymphoma are from the Cheson et al. Revised Response Criteria for Malignant Lymphoma[27]. Lymph node measurements should be taken from CT, CT portion of the PET/CT if possible, or MRI scans where applicable. Measurement of lymphadenopathy will be determined by adding the sum of the products of the maximal perpendicular diameters of measured lesions (SDP). Measurable extranodal disease should be assessed in a manner similar to that for nodal disease. For these recommendations, the spleen is considered nodal disease. Disease that is only assessable (eg, pleural effusions, bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative.

Response is based on both the CT component of PET/CT taking into consideration avidity of targets, CT alone, or MRI where applicable.

Response criteria, modified from Cheson et al. 2007 [27]. Peripheral T-cell lymphomas are considered FDG avid.

Response Category	Definition	Nodal Masses	Spleen, liver	Bone Marrow
CR	Disappearance of all evidence of disease.	Mass of any size permitted if PET negative; Deauville 3 or less	Not palpable, nodules disappeared	Infiltrate cleared on repeat biopsy; if indeterminate by morphology, immunohistochemistry should be negative
PR	Regression of measurable disease and no new sites	≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes **and** one or more PET positive (Deauville 4) at previously involved site	≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen	Irrelevant if positive prior to therapy; cell type should be specified
SD	Failure to attain CR/PR or PD	PET positive (Deauville 4) at prior sites of disease and no new sites on CT or PET		
Relapse/ Progressive disease	Any new lesion or increase by ≥ 50% of previously involved sites from nadir	Appearance of a new lesion(s) > 1.5 cm in any axis, ≥50% increase from nadir in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node > 1 cm in short axis. The lesions referred to above are required to be PET positive (Deauville 5). X lesion by	> 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement

		PET/CT are not to be considered progression unless biopsy confirmed		

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

6.2 Complete Response (CR)

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

6.2.2 T-cell lymphomas are FDG-avid lymphomas: in patients with no pretreatment PET/CT scan or when the PET/CT scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative (Deauville 3 or less).

6.2.3 The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination, CT scan, or CT portion of the PET/CT should not be palpable on physical examination and should be considered normal size by imaging studies, and avid nodules related to lymphoma should disappear or should acquire a Deauville score of 3 or less. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma. Therefore residual splenomegaly if felt not to be avid by PET/CT at subsequent response evaluation Similarly, other organs considered to be enlarged before therapy due to involvement by lymphoma, such as liver and kidneys, must have decreased in size.

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

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

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

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

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

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

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

6.3.5 Bone marrow assessment is irrelevant for determination of a PR if the sample was positive before treatment. However, if positive, the cell type should be specified\.Patients who achieve a CR by the above criteria, but who have persistent morphologic bone marrow involvement will be considered partial responders.

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

6.3.6 No new sites of disease should be observed.

6.3.7 For patients with no pretreatment PET/CT scan or if the PET/CT scan was positive before therapy, the post-treatment PET/CT should be positive in at least one previously involved site and considered a Deauville 4.

6.4 Criteria for Stable Disease (SD)

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

6.4.2 The PET should be positive at prior sites of disease with no new areas of involvement on the post-treatment PET/CT Deauville 4.

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

6.5.1 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/CT without histologic confirmation.

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

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

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

7.0 STUDY PARAMETERS - Test Schedule for both Phase 1 and 2 patients

Tests and procedures	Active Monitoring Phase				
		Combination treatment			Post-transplant or during maintenance therapy
	≤ 14 days prior to day 1 of cycle 1	Prior to (-2 days) subsequent treatment (cycles 2-6)	During interval between cycles	After completion of therapy (4-6 weeks after day 1 of cycle 6)	Every 3 months for year 1[17]
History and exam, weight,	X	X		X	X
Adverse event assessment	X	X		X	X
Height, Karnofsky Scale PS	X				
Registered in the Revlimid REMS™ program	X[14]	X[14]	X[14]	X[14]	Monthly[14]
Serum or urine pregnancy test[1]	X[1]	X[1]	X[1]	X[1]	
Tumor tissue sample for confirmation of diagnosis	X[2]				
Hematology group CBC (HgB, WBC, Differential, PLT)	X	X	Weekly	X	X
Chemistry group Total bilirubin, AST, Alkaline Phosphatase, LDH, Creatinine, Sodium, Potassium, Calcium	X	X		X	X
Direct bilirubin, PT/INR[4], PTT	X				
HIV HBV, HCV screen	X[3]				
Tumor Measurement/Evaluation of indicator lesions (CT chest,	X[12]	Before cycle 3		X	X[16]

Tests and procedures	Active Monitoring Phase				
		Combination treatment			Post-transplant or during maintenance therapy
	≤ 14 days prior to day 1 of cycle 1	Prior to (-2 days) subsequent treatment (cycles 2-6)	During interval between cycles	After completion of therapy (4-6 weeks after day 1 of cycle 6)	Every 3 months for year 1[17]
abdomen, pelvis; other CT and/or MRI when indicated)[10]					
PET/CT scan	X[15]	Before cycle 3[11]		X[5]	
Bone marrow aspirate and biopsy (unilateral or bilateral)	X[13]	Before cycle 3[6]		X[6]	
Electrocardiogram	X[15]				
Left ventricular function measurement	X[7, 15]				
Cerebrospinal fluid analysis	X[8]				
Research blood samples[R]	X[R]			X[R]	

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). Screening pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days as required by Revlimid REMS™). Per protocol inclusion criteria, screening pregnancy test must be serum; all other testing can be serum or urine. Female subjects must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy (see Appendix G: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
2. Central review of pathology is required for confirmation of diagnosis. Completion of central pathology review is not required prior to registration for patients; however materials for central review must be submitted within 1 month after registration.

3. Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV; see eligibility) or hepatitis C virus (HCV). Actual testing is not mandatory for participation in this trial. Patients who are seropositive because of hepatitis B virus vaccine are eligible.
4. PT/INR assessment frequency for patient on coumadin per investigator discretion to keep in therapeutic range
5. If positive after the completion of cycle 6, a biopsy of PET positive area may be done at MD discretion.
6. Repeat bone marrow only required to confirm CR if initial bone marrow or post cycle 2 bone marrow was positive.
7. MUGA or ECHO.
8. A lumbar puncture and cytologic examination of the cerebrospinal fluid is not required, but should be performed if clinically indicated.
9. Pathology material: H&E stain and IHC slides or a representative FFPE tissue block from initial diagnosis . Please NOTE: the diagnostic H&E slide and IHC slides will be returned after review.

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10. Measurements can be done off the CT images of a PET/CT; however a dedicated CT or MRI; must be done by dedicated CT if that demonstrates the lesion more clearly. The image number should be included with the measurements. If there are questions, call the UNMC collaborative investigator.
11. PET/CT is mandatory pre- and post-treatment. It is optional after 2 cycles; however, if PET/CT is used for the measureable lesion then it should be strongly considered before cycle 3.
12. Imaging must be done ≤ 6 weeks prior to study registration.
13. Bone marrow must be done ≤ 6 weeks prior to study registration.
14. For patients receiving maintenance lenalidomide - All unused lenalidomide must be returned as instructed through the Revlimid REMS™ program.
15. Must be done ≤ 28 days prior to study registration.
16. A PET/CT scan should be considered a D+100 post autologous transplant. If PET negative CR then CT may be substituted per investigator choice. The interval should remain every 3 months (+/- 14 days until 1 year post transplant. In patients who do not undergo autologous transplant a PET/CT if not achieved a PET/CT CR or CT can be substituted for PET negative CR should be done every 3 months (+/-14 days) for 1 year after completing the 6 cycles of CHOEP plus lenalidomide. Imaging thereafter is at the discretion of the treating physician.
17. Follow up in year 2 and beyond is as per institutional guidelines.

R. Research funded study. Please note, if a subject is unable to complete study treatment through cycle 6, then the research sample after completion of cycle 6 would not be collected.

8.0 DRUG FORMULATION AND PROCUREMENT

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

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

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

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

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

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

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

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

8.15 Pharmacokinetic information:
a) Absorption – Lenalidomide is rapidly absorbed following oral administration to subjects with multiple myeloma or MDS, with maximum plasma concentrations occurring between 0.5 and 6 hours post-dose. Co-administration with a high-fat and high-calorie meal in healthy subjects reduced the extent of absorption, resulting in an approximately 20% decrease in AUC and 50% decrease in Cmax in plasma. In the pivotal MM and MDS registration trials where the efficacy and safety were established for lenalidomide, the drug was administered without regard to food intake. Thus, lenalidomide can be administered with or without food. Multiple dosing (up to 100 mg BID) did not cause marked drug accumulation. Systemic exposure (AUC) of lenalidomide in MM and MDS patients with normal or mild renal function (CLcr ≥ 60 mL/min) is approximately 60% higher as compared to young healthy male subjects.
b) Distribution – In vitro (14C)-lenalidomide binding to plasma proteins

binding to plasma proteins is approximately 30%.
c) Metabolism – Lenalidomide undergoes limited metabolism. Unchanged lenalidomide is the predominant circulating component in humans. Two identified metabolites are hydroxy-lenalidomide and N-acetyl-lenalidomide; each constitutes less than 5% of parent levels in circulation.
d) Excretion – Elimination is primarily renal. Approximately 65% to 85% of lenalidomide is eliminated unchanged through urinary excretion in subjects with normal renal function. The half-life of elimination is approximately 3 to 4 hours at the clinically relevant doses (5 to 50 mg/day). Steady-state levels are achieved within 4 days.

8.16 Potential Drug Interactions: Results from human in vitro metabolism studies and nonclinical studies show that lenalidomide is neither metabolized by nor inhibits or induces the cytochrome P450 pathway suggesting that lenalidomide is not likely to cause or be subject to P450-based metabolic drug interactions in man. In vitro studies demonstrate that lenalidomide is not a substrate of multidrug resistance proteins MRP1, MRP2, or MRP3 or a substrate of organic anion and cation uptake transporters OAT1, OAT3, OATP1B1 or OCT1. In vitro, lenalidomide is a substrate, but is not an inhibitor of P-glycoprotein (Pgp). Patients taking concomitant therapies such as erythropoietin stimulating agents or estrogen containing therapies may have an increased risk of venous thromboembolism (VTE). Periodic monitoring of digoxin plasma levels is recommended due to increased Cmax and AUC with concomitant lenalidomide therapy. Close monitoring of PT and INR is recommended in multiple myeloma patients taking concomitant warfarin.

8.17 Known potential toxicities:

Pregnancy Warning: Lenalidomide is structurally related to thalidomide, a known human teratogen. Therefore, in an effort to prevent to the greatest extent possible any chance of fetal exposure, lenalidomide is available through a controlled distribution program, specifically a pregnancy prevention program called REMS™ . It is contraindicated in women who are or may become pregnant. Female subjects of childbearing potential are required to submit to regular pregnancy testing, and to agree to use effective forms of birth control as outlined in study protocols. Male subjects, even those who have had a vasectomy, must agree to use a condom during sexual contact with a pregnant woman or a woman who can become pregnant.

Very Common AEs (≥ 10%): peripheral edema, fatigue, insomnia, fever, dizziness, headache, pruritus, rash, dry skin, hyperglycemia, hypokalemia, diarrhea, constipation, nausea, weight loss, dyspepsia, anorexia, taste perversion, abdominal pain, urinary tract infection, thrombocytopenia, neutropenia, anemia, myelosuppression, muscle cramp, weakness, arthralgia, back pain, tremor, paresthesia, limb

pain, blurred vision, naso-pharyngitis, cough, dyspnea, pharyngitis, epistaxis, upper respiratory infection, pneumonia.
Common (≥ 1% and < 10%): edema, deep vein thrombosis, hypertension, chest pain, palpitation, atrial fibrillation, syncope, hypoesthesia, pain, depression, bruising, cellulitis, erythema, hypothyroidism, hypomagnesemia, hypocalcemia, vomiting, xerostomia, loose stools, dysuria, leukopenia, febrile neutropenia, granulocytopenia, lymphopenia, pancytopenia, ALT increased, myalgia, rigors, peripheral neuropathy, sinusitis, rhinitis, bronchitis, pulmonary embolism, respiratory distress, hypoxia, pleural effusion, pneumonitis, pulmonary hypertension, night sweats, diaphoresis, and sepsis.

Uncommon, limited to important or life-threatening (< 1%): acute febrile neutropenia, dermatitis, acute leukemia, acute myeloid leukemia (AML), adrenal insufficiency, angioedema, atrial flutter, azotemia, Basedow's disease, biliary obstruction, blindness, bone marrow depression, bradycardia, brain edema, cardiac failure, cardiogenic shock, cardiomyopathy, cardiopulmonary arrest, cerebrovascular accident, CHF, cholecystitis, chondrocalcinosis, chronic obstructive airway disease, circulatory collapse, coagulopathy, colonic polyp, dehydration, delirium, diabetes mellitus, diabetic ketoacidosis, diverticulitis, dysphagia, encephalitis, erythema multiforme, Fanconi syndrome, gout, hematuria, hemolysis, hemolytic anemia, hemorrhage, hepatic failure, hepatitis, herpes virus infection, hyperbilirubinemia, hypernatremia, hypersensitivity, hypoglycemia, hypotension, infection, interstitial lung disease, intestinal perforation, intracranial hemorrhage, ischemia, ischemic colitis, leukoencephalopathy, liver failure, abnormal liver function tests, lung cancer, lung infiltration, lymphoma, MI, myopathy, neutropenic sepsis, orthostatic hypotension, pancreatitis, peripheral ischemia, pseudomembranous colitis, pulmonary edema, refractory anemia, renal calculus, renal failure, renal mass, renal tubular necrosis, respiratory failure, secondary primary malignancies (AML, HL), septic shock, serum creatinine increased, skin desquamation, small bowel obstruction, spinal cord compression, splenic infarction, Stevens-Johnson syndrome, stomatitis, supraventricular arrhythmia, tachyarrhythmia, thrombophlebitis, toxic epidermal necrolysis, troponin I increased, tumor lysis syndrome (TLS), tumor flare reaction (TFR), urinary retention, urosepsis, urticaria, ventricular dysfunction, and wheezing.

The following additional adverse reactions have been reported in Celgene sponsored clinical studies and are considered by the company to be possibly related to the administration of lenalidomide: granulocytopenia, cataract, vision blurred, abdominal pain upper, dry mouth, gastrointestinal motility disorder, toothache, fall, herpes simplex, influenza, rhinitis, hyperuricemia, hypophosphatemia, iron overload, musculoskeletal pain, dysgeusia, headache, paresthesia, dry skin, hyperhidrosis, and pruritus.

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

8.18 Drug procurement:

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation's Revlimid REMS™ program. Per standard Revlimid REMS™ program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS™ program. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**
Any unused lenalidomide should be returned for disposition in accordance with the Revlimid REMS™ program.

Pregnancy Testing: Females must follow pregnancy testing requirements as outlined in the Revlimid REMS™ program material.

8.19 Nursing Guidelines:

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

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

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

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

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

8.196 Gastrointestinal side effects (diarrhea, constipation, nausea,

dyspepsia, anorexia, etc) are commonly seen. Manage patent symptomatically and monitor for effectiveness.

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

8.198 Upper respiratory symptoms (naso-pharyngitis, cough, epistaxis, etc.) can be seen. Manage symptomatically and monitor for effectiveness.

8.2 **Cyclophosphamide (Cytoxan, CTX, Neosar®)**

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

8.22 Known potential toxicities: Myelosuppression, hemorrhagic cystitis, alopecia, nausea, and vomiting are all common, SIADH is dose–related (more common with single doses > 2 gm/m^2), cardiac (if dose level □2 gm/m^2). Secondary leukemia, liver dysfunction, headaches, dizziness, interstitial pulmonary fibrosis, cardiac necrosis may occur. Anaphylaxis is rare.

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

8.24 Nursing guidelines

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

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

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

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

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

8.246 Report and record any complaint of lightheadedness, facial "heat sensation", or diaphoresis during administration.

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

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

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

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

8.33 Preparation, storage, and stability: Refer to package insert for complete preparation and dispensing instructions. Store intact vials at room temperature of 25ºC (77ºF); do not freeze. Protect from light. Etoposide should be diluted to a concentration of 0.2-0.4 mg/mL in D5W or NS for administration. Diluted solutions have concentration-dependent stability; more concentrated solutions have shorter stability times. Precipitation may occur with concentrations >0.4 mg/mL. Following dilution 0.9% Sodium Chloride or D5W to concentrations of 0.2-04 mg/mL, then drug is chemically stable for 96 and 24 hours at room temperature respectively.

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

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

8.36 Potential Drug Interactions:
Metabolism/Transport Effects: Substrate of CYP1A2 (minor), CYP2E1 (minor), CYP3A4 (major), P-glycoprotein; Inhibits CYP2C9 (weak), 3A4 (weak)

Ethanol/Herb/Nutraceutical Interactions: Avoid ethanol (may increase GI irritation). Avoid concurrent St John's wort; may decrease etoposide levels.

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

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

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

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

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

8.39 Nursing guidelines

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

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

8.393 Advise patient of possible mild, reversible alopecia.

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

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

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

8.397 Nausea and vomiting are usually mild. However the incidence is increased with oral administration. Pre-medicate with antiemetics as ordered and monitor for their effectiveness.

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

8.399a Monitor liver function tests.

8.399b Etoposide solution is oil based and settles to bottom of bag or drip chamber. Be sure to agitate bag to avoid reaction to concentrated solution. Reaction would include flushing, shortness of breath, back pain, and anxiety.

8.399c Advise patient that facial flushing is common and may occur even after administration.

8.399d Monitor INR closely in patients on warfarin therapy, as etoposide may increase prothrombin (PT) time.

8.399e May increase the toxicity of methotrexate or cyclosporine (cytotoxicity) when given concurrently.

8.4 **Doxorubicin (ADR)**

8.41 Preparation and storage: Doxorubicin RDF intact vials are stable protected from light at room temperature. Doxorubicin PFS vials must be refrigerated.

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

8.42 Known potential toxicities:

8.421 Hematologic: Leukopenia (dose-limiting), also thrombocytopenia and anemia. This treatment nadir is usually 10-14 days with recovery in 21 days.

8.422 Dermatologic: Alopecia, usually complete, hyperpigmentation of nail beds and dermal creases, radiation recall.

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

8.424 Cardiovascular: Arrhythmias, thrombosis/embolism, ECG changes, rarely sudden death. Congestive heart failure due to cardiomyopathy related to total cumulative dose, risk is greater with doses greater than 550 mg/m2, mediastinal irradiation, preexisting cardiac disease, advanced age, risk is reduced with weekly or continuous infusion regimens.

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

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

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

8.44 Nursing guidelines:

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

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

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

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

8.445 Beware of doxorubicin “flare” that can occur during administration. The reaction consists of an erythematous streak up the vein receiving the infusion. Adjacent veins may also

demonstrate red streaks. Urticaria and pruritus can be associated with the reaction. The use of corticosteroids and/or antihistamines has been helpful.

8.446 Administer antiemetics to minimize nausea and vomiting.

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

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

8.449a Doxorubicin may potentiate toxicity of other antineoplastic therapies. It has reportedly exacerbated cyclophosphamide-(Cytoxan, CTX) induced hemorrhagic cystitis.

8.449b Assess heart and lung sounds. Monitor vital signs (resting pulse). Be alert to early signs of cardiotoxicity, i.e., dyspnea, steady weight gain, nonproductive cough, arrhythmias, tachycardia, and pulmonary rales.

8.449c Document cumulative dose, which should not exceed maximum cumulative dose.

8.449d Advise patient of probable facial flushing for several hours after drug administration, especially if given quickly.

8.5 **Vincristine (VCR)**

8.51 Preparation and storage: Vincristine is stored in the refrigerator. No preparation is required. Vincristine should be administered according to the standard CHOEP regimen.

8.52 Known potential toxicities:

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

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

8.523 Gastrointestinal: Nausea, rarely vomiting, constipation,

abdominal cramps, anorexia, and diarrhea. Fatal ascending paralysis follows intrathecal administration.

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

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

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

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

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

8.529 Cardiovascular: Thrombosis/embolism.

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

8.54 Nursing guidelines:

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

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

8.543 Monitor bowel function and encourage use of stool softeners.

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

8.6 **Prednisone (PRED)**

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

8.62 Known potential toxicities:

8.621 Hematologic: Leukocytosis.

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

8.623 Dermatologic: Rash, skin atrophy, facial hair growth, acne, facial erythema, and ecchymosis.

8.624 Genitourinary: Menstrual changes (amenorrhea, menstrual irregularities)

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

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

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

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

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

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

8.64 Nursing guidelines:

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

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

8.643 Monitor CBC and glucose levels.

8.644 Educate patient concerning potential mood changes.

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

9.0 TOXICITY REPORTING GUIDELINES

The reporting is only for lenalidomide-CHOEP “study medication,” until 30 days after last administration of study medication.

No transplant related AE’s will be recorded or reported.

NOTE: Problems related to insurance coverage for UNMC potential subjects or enrolled subjects will be reported to the IRB as they are encountered.

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC Fred & Pamela Buffett Cancer Center Data Monitoring plan. The protocol will adhere to the institutional and FDA guidelines for the toxicity reporting.

All patients will be closely followed for toxicity from the time of informed consent until 30 days after last administration of study medication. Adverse event and serious adverse events will be followed until baseline or ≤ grade 1 levels. Toxicity will be assessed using the revised NCI CTCAE version 4.02.

All adverse events will be followed to a satisfactory conclusion. Serious adverse events should be followed until resolution, death, or until no further improvement is reasonably expected. Deaths occurring within 30 days of study treatment regardless of relationship will be reported to the UNMC IRB and UNMC DSMC.

In addition to complying with all applicable regulatory reporting laws and regulations, all serious adverse events and toxicities will be reported to the University of Nebraska Medical Center, Institutional Review Board (IRB), participating sites own IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC).

Definitions:

Adverse Event

An adverse event (AE) is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not the event is considered causally related to the use of the product.

An elective surgery or procedure that is scheduled to occur during a study will not be considered an adverse event if the surgery or procedure is being performed for a pre-existing condition and the surgery or procedure has been planned before study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*e.g.,* the surgery is performed earlier than planned), then the deterioration of the condition for which the elective surgery or procedure is being done will be considered an adverse event.

An adverse event can result from use of the drug as stipulated in the protocol or labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an adverse event. Laboratory abnormalities and changes in vital signs are considered to be adverse events if they result in discontinuation from the study, necessitate therapeutic medical intervention, meet protocol specific criteria (see Section 5.0, Treatment Plan) and/or if the investigator considers them to be adverse events. In general, if a laboratory abnormality or change in vital sign is associated with a

specific diagnosis that is being reported concurrently as an adverse event (e.g. elevated creatinine with renal failure or sinus tachycardia in febrile neutropenia) the findings that support the diagnosis do not need to be reported as separate adverse events unless the investigator feels it is appropriate.

Treatment-emergent Adverse Event
Treatment-emergent adverse event is defined as any adverse event with onset or worsening from the time that the first dose of study drug is administered until 30 days after the final dose of study drug is administered.

Unexpected Adverse Event
An unexpected adverse event is any adverse drug event that is not listed in the current labeling/Investigator's Brochure. This includes events that may be symptomatically and pathophysiologically related to an event listed in the labeling, but differ from the labeled event because of greater severity or specificity. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the labeling only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the labeling only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (i.e., included in the labeling) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

Serious Adverse Event
A serious adverse event is one that at any dose (including overdose) and regardless of causality that:

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

[1] "Life-threatening" means that the subject was at immediate risk of death at the time of the serious adverse event; it does not refer to a serious adverse event that hypothetically might have caused death if it were more severe.
[2] "Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.
[3] Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or

drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

9.1 Adverse Event Reporting and Definitions Per University of Nebraska Medical Center, IRB and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) and Celgene Drug Safety and Surveillance

This protocol will adhere to all institutional guidelines for adverse event reporting. Adverse events will be evaluated using the NCI Common Terminology Criteria for Adverse Events (CTC-AE) version 4.02.

9.1.1 IRB REPORTING

All internal serious adverse events (AE) must be reported to the local IRB promptly per institutional policy and in no case later than two (2) business days following PI notification that the event occurred *if* the principal investigator determines that conditions A, B, and C are met:

a. **The AE is unexpected, *AND***
b. **The AE is related to, or possibly related to, the drug, biologic, device, or other research intervention, *AND***
c. **The AE is more than minor in nature which is defined as requiring treatment from a health professional.**

All *unexpected*, internal, fatal AEs must be reported promptly to the local IRB per institutional policy, but no later than *24 hours* following PI notification that the event occurred. If documentation is still pending, the IRB office must be notified by a telephone call or e-mail.

All *expected*, internal, fatal AEs (i.e., due to progressive disease or which reflect a risk currently found in the consent form) must be reported to the local IRB per institutional policy no later than ten (10) business days following PI notification that the event occurred.

9.1.2 FRED & PAMELA BUFFETT CANCER CENTER DATA AND SAFETY MONITORING COMMITTEE (DSMC) REPORTING

All adverse events > grade 3 (expected or unexpected, regardless of attribution) will be reported to the University of Nebraska Medical Center, Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) in accordance with DSMC guidelines.

Attribution of AE: The likelihood of relationship of the AE to the study drugs will be determined by the investigator based on the following definitions:

Not related: The subject was not exposed to the study treatment or another cause is obvious.

Probably not related: The AE is most likely explained by another cause, and the time of occurrence of the AE is not reasonably related to the study treatment.

Possibly related: Study treatment administration and AE occurrence reasonably related in time, and the AE is explained equally well by causes other than study treatment, or treatment administration and AE occurrence are not reasonably related in time, but the AE is not obviously a result of other causes.

Probably related: Study treatment administration and AE occurrence are reasonably related in time, and the AE is more likely explained by study treatment than by other mechanisms.

Definitely related: There occurrence and timing of the AE are clearly attributable to the study treatment.

Severity Grade of AE. The severity of events reported on the AE case report form will be determined by the principal investigator according the NCI Common Toxicity Criteria (CTC version 4.02).

AEs will be collected from the time the subject signs the consent form and ending 30 days following the final chemotherapy. All AEs will be followed until resolution or a cause is identified. Prescription medication taken to relieve symptoms of the AE will be recorded in addition to the outcome.

AEs judged by the investigator as not related or probably not related to the treatment will NOT be followed beyond the 30 days after the final chemotherapy.

Transplant related Adverse Experiences (AE's) or Serious Adverse Experiences (SAE's) will NOT be collected.

Copies of the AE report will be submitted to the IRB as indicated in Section 9.1.1.

Detailed policy and procedures for this section may be reviewed at: http://www.unmc.edu/cancercenter/clinical/prms.html

9.1.3 FOOD AND DRUG ADMINISTRATION (FDA) REPORTING

This study has been determined by the FDA to be IND Exempt. The participating site investigator may utilize the FDA MedWatch Form (Appendix D) for the reporting of serious adverse events and follow up information to those events to meet Celgene reporting requirements. The form can be found at the following URL: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf The SAE information will be routed to the UNMC PI who will further evaluate the SAE.

SAE reporting instructions are reiterated and further outlined in the Participating Site Study Manual.

Additionally, serious adverse events will be reported to CELGENE, the IRB, SRC, Audit Committee and the Data Safety Monitoring Committee by the Investigator as described further within Section 9.0.

9.1.4 CELGENE REPORTING REQUIREMENTS:

All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (e.g. mild, moderate, severe), relationship to drug (e.g. probably

related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

Serious Adverse Event (SAE) Reporting -

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

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

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

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

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

Expedited reporting by investigator to Celgene

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

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form (see Appendix D) of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-CL-PTCL-PI-003858) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Pregnancies

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

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate

method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

Male Subjects

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

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com

Investigator Reporting Responsibilities
The conduct of the study will comply with all FDA safety reporting requirements.

IND Annual Reports
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Affairs Operations
Connell Corporate Park
400 Connell Drive Suite 700
Berkeley Heights, NJ 07922

9.2 Auditing

The UNMC Fred & Pamela Buffett Cancer Center Scientific Review Committee (SRC) will review this protocol on at least an annual basis.

This study will undergo audit on at least a quarterly basis by the UNMC Fred & Pamela Buffett Cancer Center Audit Committee.

For participating site(s) that are NCI Cancer Centers, the protocol specific finding of the participating site's Audit Committee will be submitted to the UNMC Audit Committee for review on a schedule to be determined by the UNMC Audit Committee. For participating site(s) that are not NCI Cancer Centers, the audit process will be established by the UNMC Audit Committee on a site-by-site basis. All adverse events whether internal or external, will be reported to the UNMC Fred &

Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) as noted in Section 9.1.2. In its initial review, the DSMC will make a recommendation for the frequency of DSMC monitoring based on an assessment of risk associated with study-associated therapy, per DSMC policy.

Detailed policy and procedures for this section may be reviewed at: http://www.unmc.edu/cancercenter/clinical/prms.html.

9.3 Monitoring

9.3.1 Various methods will be implemented by the sponsor (UNMC) to exchange information with participating sites:

- Site Initiation/Orientation
- Regular Teleconferences including group wide progress within the agenda
- Investigator meetings as feasible (remote or TBA, possibly in conjunction with larger meetings)
- Email distributions/reports as needed
- Celgene, Lenalidomide Safety Updates (Sent direct to site PI from Celgene)

9.3.2 Ongoing safety monitoring for all the subjects in this study:

All participating sites are required to execute a data compliance policy agreement. UNMC will monitor the data of participating sites in adherence to applicable research regulations, the protocol, and the policy agreement. De-identified source documents which support data entered must be provided to the sponsor by mail, fax, or electronic means for centralized compliance monitoring.

10.0 STATISTICAL CONSIDERATIONS

This study will determine the efficacy and toxicity of a combination of lenalidomide and CHOEP in patients with peripheral T-cell lymphoma. In phase I, a standard 3+3 study design will be effective in determining the MTD. In phase II, a Simon two-stage design with an interim analysis will be utilized to determine the complete response rate. The intent to treat analysis will be conducted for all eligible patients (Please refer to Section 10.6 Evaluable Patient).

10.1 Primary Objective
Phase 1 part: Determine the maximum tolerated dose (MTD).
Phase 2 part: Complete response (CR) rate

10.2 Secondary objectives
Toxicity assessment, Overall response rate (ORR), Progression free survival (PFS), PFS rate at 2 years, and overall survival (OS).

10.3 Efficacy Endpoints

Overall response rate (ORR) and progression free survival (PFS)

10.4 Sample Size

Total: 54 patients - Per Group: Up to 20 in phase I, 34 in phase II
This study is expected to require a minimum of 9 and a maximum of 18 evaluable patients in the phase I dose escalation. (If a patient in phase I cohort fails to complete cycle 1 for reasons other than toxicity, the patient will be regarded as non-evaluable and will be replaced.) An additional 31 evaluable patients will be accrued in the phase II portion. It is anticipated that 5 additional patients will be accrued (2 phase I, 3 phase II) to account for ineligibility, cancellation, major treatment violation, or other reasons. Therefore, the overall sample size will be a maximum of 54 patients.

10.5 Stopping Rules

In the phase I portion of the study, the DLT criteria will be used to halt dose escalation and confirm safety of the MTD. In the phase II portion, a Simon two-stage design with an interim analysis will be utilized. The interim analysis will be conducted after the first 19 patients are evaluable for response, where at least 9 complete responses must be seen to continue accrual.

10.6 Evaluable Patient

If a patient in phase I cohort fails to complete cycle 1 for reasons other than toxicity, the patient will be regarded as non-evaluable for toxicity and will be replaced.

Every patient who fulfills all aspects of patient eligibility who receives at least 2 cycles of chemotherapy will be evaluable for the response endpoint. Patients with a global deterioration of health status requiring permanent discontinuation of study treatment (taken off study) without objective evidence of disease progression will be counted as progressive disease. Every effort should be made to document the objective progression even after discontinuation of treatment. Deaths will be counted as treatment failure. CR rate is at the end of the lenalidomide-CHOEP (6 cycles).
Every patient who fulfills all aspects of patient eligibility who receives a partial or complete cycles of chemotherapy will be evaluable for toxicity after cycle 1 in the phase I and evaluable for efficacy if remains without prior evidence of progression of disease. Any exclusion, for any reason, must be specified by the responsible investigator on the flow sheets.

10.7 Primary Analysis

<u>Phase I:</u>

MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of patients (at least 2 of a maximum of 6

new patients). A dose level must have a total of 6 patients treated with ≤1 DLTs seen to be called the MTD.

Toxicity Profile: The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by dose level and patient will be explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

Phase II:

The primary endpoint of this trial is the proportion of complete responses. A success is defined to be an objective status of CR after completion of 6 cycles of treatment. All patients meeting the eligibility criteria who have signed a consent form and have begun treatment will be evaluable for response. The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. A 95% confidence interval for the true overall CR rate will be calculated according to the method of Duffy and Santner. [28]

The toxicity profile will be further assessed based on phase II patients.

The ORR will be estimated by the total number of patients who achieve a PR or CR at the end of six cycles of treatment divided by the total number of evaluable patients. Exact binomial 95% confidence intervals for the true ORR will be calculated.

The progression-free survival (PFS) time is defined as the time from registration to progression or death due to any cause. The distribution of PFS will be estimated using the method of Kaplan-Meier. [28] The PFS rate at 2 years will be estimated. A 2-year PFS rate of 60% will be considered of interest.

The overall survival time is defined as the time from registration to death due to any cause. The distribution of overall survival will be estimated using the method of Kaplan-Meier. [29]

10.8 Statistical Power Calculation

In the phase II portion, a Simon optimum two-stage design will be utilized to assess the efficacy and tolerability of the combination of lenalidomide-CHOEP in patients with peripheral T-cell lymphoma. The primary endpoint is complete response rate, where a success is defined to be an objective status of CR at the end of 6 cycles of treatment. We are interested in testing the null hypothesis that the CR rate in this population is 40%. The study will have 9%

Type I error and 85% power to detect an effective treatment using a two-stage design with an interim analysis based on a Simon optimum design.[30] If the true proportion of patients who achieve a complete response is at least 60% versus the null hypothesis that the true complete response rate is at most 40%. The 6 patients treated at the MTD in phase I will also be included in the phase II portion. An additional 13 or 31 evaluable patients will be enrolled for up to 37 evaluable patients overall in the phase II portion. An interim analysis will be conducted after the first 19 patients are evaluable for response, where at least 9 successes must be seen to continue accrual. Accrual will however continue while the interim analysis is performed. For the final analysis, if 18 or fewer successes are observed in all 37 evaluable patients accrued, we will consider this regimen ineffective in this patient population. If 19 or more successes are observed, this will be considered sufficient evidence that this treatment may be recommended for further testing in subsequent studies.

11.0 RECORDS TO BE KEPT

Information regarding the actual treatments, adverse effects, radiographic and laboratory information, and pathology are to be recorded on appropriate forms. See attached Data forms. De-identified source documents which support data entered must be provided to the sponsor by mail, fax, or electronic means for centralized compliance monitoring. Serious adverse events, when noted, will be recorded on site via the standard serious adverse effects form.

11.1 Quality assurance:

Complete records must be maintained in a research chart on each patient treated on the protocol. These records should include primary documentation (e.g., lab. report slips, X-ray reports, scan reports, pathology reports, physician notes, etc.) which confirm that:

- The patient met the eligibility criteria.
- Signed informed consent was obtained prior to treatment.
- Treatment was given according to protocol (dated notes about doses given & reasons for any dose modifications).
- Toxicity was assessed according to protocol (laboratory report slips, etc.).
- Response was assessed according to protocol (x-ray, scan, lab reports, dated notes on measurements & clinical assessment, as appropriate).

11.2 Electronic Data Capturing (EDC) System

Data will be stored electronically for this study on the Forte secure server. Data forms will not differ from the paper versions with the exception of an electronic format containing the UNMC Fred & Pamela Buffett Cancer Center and Forte logo.

Forte EDC provides for remote data collection that meets FDA 21 CFR Part 11 requirements as well as HIPAA and other regulatory requirements designed to enhance data security and protect patient confidentiality. Authorized users log into Forte through a secure connection and must provide a valid username, password, and database ID. This data may be made available to the public at large.

12.0 PATIENT CONSENT

12.1 Human Subjects Research Protection Training

All personnel involved in this research project will have completed the OHRP-approved computer based training course on the Protection of Human Research Subjects. All clinical and correlative research included in this application will have approval by the institutional review board.

12.2 Study Population

Patients are from all socio-economic groups and will be entered into the study without bias with respect to gender or race. Attempts will be made to recruit minorities. No vulnerable subjects will be included in the study.

12.3 Sources of Material

Pathology material (as stated in Section 5) must be reviewed, and the diagnosis confirmed by Mayo Clinic pathology department (retrospectively) as outlined in the protocol.

12.4 Recruitment and Informed Consent

Patients with histologically confirmed new diagnosis of Stage II, III and IV Peripheral T-cell Non-Hodgkin lymphoma (PTCL) not otherwise specified (NOS), Anaplastic large cell lymphoma (ALK negative), Angioimmunoblastic T-cell lymphoma, Enteropathy associated T-cell lymphoma, Hepatosplenic gamma delta T-cell lymphoma for whom this therapy would be appropriate will be available for recruitment. These patients will be informed of the nature of this study, and will be asked to participate on a voluntary basis after informing them of the possible risks and benefits of the study. A number of public registries may be accessible to health care providers and prospective subjects as listed below.

National Library of Medicine - http://clinicaltrials.gov (NCT02561273)
National Cancer Institute - http://www.cancer.gov (NCI-2015-00088)

12.5 Subject Competency

Subjects will be eligible to participate in the study only if they are competent to give informed consent. A subject that the investigators judges to be incompetent will not be enrolled.

12.6 Process of Informed Consent

If the patient chooses to be a participant in this study, informed consent will be obtained by the investigators. The study and procedures involved including the risks will be explained in detail to each subject. It will be clearly explained to the subject that this is a research study and that participation is entirely on a voluntary basis. Subjects will be given the option to discuss the study with a family member, friend, counselor or, another physician. The participating investigators will be available to discuss the study with them.

12.7 Subject/Representative Comprehension

When the process of informed consent is completed, the subject will be asked to state in his/her own words, the purpose of the study, the procedures that will be carried out, potential risk, potential benefits to the subject, the alternatives and the right to withdraw from the study. If there is any indication that a given subject's comprehension is anything less than accurate, the points of confusion will be discussed and clarified.

12.8 Information Purposely Withheld.

The results of the tests done solely for research purposes will not be disclosed to the subject. No other information will be purposely withheld from the subject.

12.9 Potential Benefits of the Proposed Research to the Subjects

It is hoped that the use of protocol therapy in this patient population may result in tumor shrinkage or stabilization of disease.

12.10 Potential Benefits to Society.

Information obtained from this study may help other cancer patients by Identifying proper doses of lenalidomide used in combination with an established cancer drugs, CHOEP.

12.11 Potential Risks

The use of multiagent cytotoxic chemotherapy is associated with numerous potential risks. Multiagent chemotherapy is considered to be a valid treatment option for patients with advanced malignancies. It is believed the treatment option outlined in the study will not pose significant additional risks compared to conventional treatment that might consist of other chemotherapy drugs given alone or in combination.

12.12 Therapeutic Alternatives

If patients choose not to participate in this study they may elect to receive standard therapy as per their primary oncologist, which may include other chemotherapy drugs given alone or in combination.

12.13 Risk/Benefit Relationship

Although there are inherent risks involved because of the use of chemotherapy agents, the risk is considered to be acceptable in the setting of cancer.

12.14 Consent Form Documents

No information will be purposely withheld from the patients. The consent document used in this study will include the adult consent document. See attached consent form

13.0 REFERENCES

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14.0 Data Forms
Attached

Appendix A. Karnofsky Scale for Performance Status

Scale (%)	Description
100	Normal; no complaints
90	Able to carry on normal activities; minor signs or symptoms of disease
80	Normal activity with effort
70	Cares for self. Unable to carry on normal activity or to do active work
60	Requires occasional assistance but able to care for most of needs
50	Requires considerable assistance and frequent medical care
40	Disabled; requires special care and assistance
30	Severely disabled; hospitalization indicated though death not imminent
20	Very sick. Hospitalization is necessary. Active supportive treatment necessary
10	Moribund
0	Dead

Reference: Karnofsky DA, et al. Cancer 1:634-656, 1948.

Appendix B: Body Surface Area and Creatinine Clearance Calculations

Body surface area (BSA) should be calculated using a standard nomogram that yields the following results in meters squared (m^2)

Creatinine clearance (CrCl) can be calculated using the Cockroft-Gault equation as follows:

$$\text{CrCl (ml/min)} = \frac{(140\text{-age}) \text{ (actual wt in kg)}}{72 \times \text{serum creatinine (mg/dl)}}$$

For females use 85% of calculated CrCl value.

Appendix C: Eligibility checklist

Date Completed:	Institution:	Patient ID#:	Checklist Version #4.0 Dated: 03-14-17
IRB# 511-14 Title: A Phase I/II Trial of CHOEP Chemotherapy plus Lenalidomide as Front Line Therapy for Patients with Stage II, III and IV Peripheral T-Cell Non-Hodgkin's Lymphoma Celgene Reference #: RV-CL-PTCL-PI-003858 PI: Matthew Lunning, MD		Waiver #:	

Inclusion Criteria: **Response should be YES**	Yes No N/A
1. Histologically confirmed new diagnosis of Stage II, III and IV Peripheral T-cell Non-Hodgkin's lymphoma not otherwise specified (NOS), Anaplastic large cell lymphoma (ALK negative) (ALK positive if IPI 3, 4, or 5), Nodal PTCL with TFH phenotype or Angioimmunoblastic T-cell lymphoma, Enteropathy associated T-cell lymphoma, Hepatosplenic gamma delta T-cell lymphoma. Note: As part of the eligibility criteria review, either the 2008 OR 2016 WHO classifications of these diagnoses will be recognized and accepted.	[ ] [ ] Diagnosis: _____ Source documenting: _____
2. Pathology material: H&E stain and IHC slides or a representative FFPE tissue block along with the pathology report from initial diagnosis sent to be reviewed, and the diagnosis confirmed by Mayo Clinic department (retrospective diagnostic review: treatment may commence prior to the Mayo Clinic review).	[ ] [ ]
3. No prior therapy with the exception of prior prednisone alone, at the discretion of the investigator based on current diagnosis and clinical condition. *This prednisone treatment will <u>not</u> count toward the 6 cycles of treatment given in the study.*	[ ] [ ] [ ] Source documenting: _____
4. Age 19 years or older (the age of consent in Nebraska); Age 18 years or older (applicable to states where the age of majority is 18).	[ ] [ ] DOB: _____
5. Expected survival duration of > 3 months.	[ ] [ ] Source documenting: _____
6. Karnofsky Performance Status > 70. (Appendix A)	[ ] [ ] Source documenting: _____

7. Laboratory status as follows **(Please enter values OR WNL, as appropriate)**: _____ANC > 1000 cells/mm3, unless cytopenias due to NHL (i.e., bone marrow involvement or splenomegaly) _____ Platelet Count > 100,000 /μL or > 75,000 /μL if BM involvement or splenomegaly _____ Total bilirubin ≤1.5 x upper normal limit, or ≤ 3 x upper normal limit if documented hepatic involvement with lymphoma, or ≤ 5 x upper normal limit if history of Gilbert's Disease _____ Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 x upper normal limit (≤ 5 x upper normal limit if documented hepatic involvement with lymphoma) _____ Serum creatinine < 2.0 mg/dL or calculated creatinine clearance (CrCl) > 45 mL/min (Cockcroft-Gault, Appendix B) _____ PT or INR, and PTT ≤ 1.5 x upper limit of normal unless patient is receiving anticoagulants. If patient is on warfarin therapy, levels should be within therapeutic range	[ ] [ ] Source documenting: _____
8. If currently not on anticoagulation medication, willing and able to take aspirin (81 or 325 mg) daily. *If aspirin is contraindicated, the patient may be considered for the study if on therapeutic dose warfarin or low molecular weight heparin. Patients unable to take any prophylaxis are not eligible.*	[ ] [ ] Source documenting: _____
9. ___Patient with measurable disease. ___Patient with non-measurable but evaluable disease may be eligible after discussion with the PI. *Baseline measurements and evaluations must be obtained within 6 weeks of registration to the study. Abnormal PET/CT scans will not constitute evaluable disease, unless verified by the CT scan portion, CT scan, or other appropriate imaging.*	[ ] [ ] Source documenting: _____
10. Patient with measurable disease must have at least one objective measurable disease parameter. *A clearly defined, bi-dimensionally measurable defect or mass measuring at least 1.5 cm in diameter on the CT portion of the PET/CT or CT scan or MRI (if appropriate) will constitute measurable disease. Proof of lymphoma in the liver is required by a confirmation biopsy. Skin lesions can be used as measurable disease provided bi-dimensional measurements are possible.*	[ ] [ ] [ ] Source documenting: _____
11. Patient must be registered into the mandatory Revlimid REMS™ program, and be willing and able to comply with the requirements of the REMS™ program.	[ ] [ ] Source documenting: _____
12. Women must not be pregnant or breast-feeding due to teratogenic effects of lenalidomide and chemotherapy. _____ Female of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS™ program _____ Female of childbearing potential must have a **blood** test within 2 weeks prior to registration to rule out pregnancy _____ Pregnancy testing is not required for post-menopausal or surgically sterilized women	[ ] [ ] [ ] Source documenting: _____
13. Male and female patient of reproductive potential must agree follow accepted birth control measures.	[ ] [ ]
14. Patient must be able to adhere to the study visit schedule and other protocol requirements.	[ ] [ ]

15. Patient must be willing to give written informed consent, and sign an institutionally approved consent form before performance of any study-related procedure not part of normal medical care as noted in number 3 above; with the exception of 1 cycle of chemotherapy based on current diagnosis and clinical condition, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.	[ ] [ ] Date Consent signed: _____
16. No serious disease or condition that, in the opinion of the investigator, would compromise the patient's ability to participate in the study.	[ ] [ ]
Exclusion Criteria: **Response should be NO**	Yes No N/A
1. Pregnant or breast feeding female.	[ ] [ ]
2. Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). *Patients who are seropositive because of hepatitis B virus vaccine is eligible. A patient who is hepatitis B core antibody +; quantitative DNA (PCR) negative is eligible if appropriate prophylaxis is planned*	[ ] [ ] Source documenting: _____
3. Major surgery within 2 weeks of study drug administration.	[ ] [ ] Source documenting: _____
4. Prior malignancy within the past 3 years with exception of adequately treated basal cell, squamous cell skin cancer, or thyroid cancer; carcinoma in situ of the cervix or breast; prostate cancer of Gleason Grade 6 or less with stable PSA levels.	[ ] [ ] Source documenting: _____
5. Diagnosis of other PTCL histologies other than those specified in the inclusion criteria.	[ ] [ ]
6. Contraindication to any of the required concomitant drugs or supportive treatments, including hypersensitivity to all anticoagulation and antiplatelet options, or antiviral drugs.	[ ] [ ]
7. Any other clinically significant medical disease or condition laboratory abnormality or psychiatric illness that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.	[ ] [ ]
8. Known hypersensitivity to thalidomide or lenalidomide.	[ ] [ ]
9. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide, lenalidomide or similar drugs.	[ ] [ ]
10. Ejection fraction of <45% by either MUGA or ECHO.	[ ] [ ] Source documenting: _____

NOTE: All questions regarding eligibility for potential subjects should be directed to the UNMC Research Project Manager at 402-559-4596

Eligibility: [ ] Patient satisfies all criteria

[ ] Patient not formally eligible, but admitted to this study because (state reason):

Patient Initials: _____MR or Study ID#_____

ELIGIBILITY reviewed and confirmed.

Site Investigator Signature _____Date_____

Printed Name of Investigator: _____

ELIGIBILITY reviewed and confirmed.

Principal Investigator Signature _____Date_____

Printed Name of Investigator: _____

Appendix D: FDA MEDWATCH form

Available on-line at
http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf

Appendix E:
Oral, Sublingual, and/or Buccal Route
Medication Adherence Standard Procedure

PURPOSE

To provide a means of ensuring oral, sublingual and/or buccal routes of medication adherence to subjects while participating in a clinical trial.

1. A physician's order will be completed by study subjects or representative for oral, sublingual and/or buccal administration per IRB approved protocol.
2. To ensure the consistent and safe administration of medications not given under the direct supervision of study staff (at home), there will be a "Medication Information Sheet" and a diary to document times of drug administration.
3. To record medication adherence Study staff will document results of medication reconciliation and or medication return in the subject's chart.
4. Maintain documentation of medications returned or sent to for destruction (if applicable).

PROCEDURE

1. Subjects will be given a monthly "Medication Diary". The diary will have a place for the subject to record the time that the medication(s) were taken. (See Form A for example)

2. The research nurse will review the subject's "Medication Diary" for adherence to the study regimen for oral medication administration. Adherence will be noted in the subject's chart. All unused Revlimid® (lenalidomide) capsules should be returned to the research center for disposition in accordance with the Revlimid REMS™ program. If any study drug is lost or damaged, its disposition should be documented in the source documents.

Medication Diary (Form A)

Medication Lenalidomide Diary

CYCLE________________ Date___________

Your prescribed dose is _________________.

- If you miss a dose please add the comment “missed dose” on the corresponding date.
- If your Study Doctor has asked you to change your dose, please add the new dosage on the corresponding date.
- Return all study drug bottles, any unused drug and completed diaries to the Study Coordinators at the study site.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
Date:_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM
Date:_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM
Date:_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM
Date:_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM
Date:_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM	**Date:**_________ Revlimid® at: _______AM / PM
		Notes:				

Appendix F:
Blood and Tissue Sample Processing and Shipping

Description of Sample Collection:

One 6 mL EDTA tube will be collected for serum, plasma and DNA at baseline, and at re-staging. The serum, plasma and DNA specimens will be stored until the end of the study. The tumor biopsy at the time of diagnosis will be reviewed and slides returned to sites after review. (See protocol section 5.7 for details) *No therapeutic intervention will be undertaken and the results of these studies will not have any influence on the medical management of the subjects.*

Facility	Sample	Contact Person(s)	Date and Time Points
Hematology Research Mayo Clinic	Pathology material: H&E stain and IHC slides or a representative FFPE tissue block along with the pathology report from initial diagnosis, Please NOTE: the diagnostic H&E slide and IHC slides will be returned after review.	Tammy Price-Troska Phone: (507) 284-3805 Email: pricetroska.tammy@mayo.edu Shipping Address: Hematology Research – Stabile 6-13 Mayo Clinic 200 First Street SW Rochester MN 55905	☐ Diagnostic Baseline Tissue Date: ___/___/____ Submit within 1 month of patient registration. A copy of the pathology report should be sent when the sample is shipped. Diagnostic H&E slide and IHC slides will be returned Provide Return Shipping contact, address and phone # : _____ _____ _____
Hematology Research Mayo Clinic	Research blood specimen: One 6 mL EDTA tube at baseline and at re-staging. EDTA Tube Processing: Centrifuge for 15 minutes at room temperature at 1500 RPM within 30 minutes of collection. For cytokine analysis – Remove and aliquot the top 2 ml of plasma	Tammy Price-Troska Phone: (507) 284-3805 Email: pricetroska.tammy@mayo.edu Shipping Address: Hematology Research – Stabile 6-13 Mayo Clinic 200 First Street SW Rochester MN 55905	☐ Baseline Blood Sample Date: ___/___/____ ☐ Re-staging Blood Sample Date: ___/___/____

	from the EDTA tube. Store 1 ml aliquots in two (2) properly labeled polypropylene tubes for cryopreservation. Store samples in the freezer at ≤ -20°C until they are shipped for analysis. For DNA analysis – Remove and aliquot the top 1 ml of cells from the EDTA tube. Store the 1 ml aliquot in a properly labeled polypropylene tube for cryopreservation. Store the sample in the freezer at ≤ -20°C until it is shipped for analysis.		

Please contact Tammy Price-Troska, Hematology Research, at (507) 284-3805, orpricetroska.tammy@mayo.edu, to advise of planned shipments, and to discuss appropriate procedures.

Appendix G:

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

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryo fetal development study in animals indicates that lenalidomide produced malformations in the offsprings of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

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

Criteria for females of childbearing potential (FCBP)

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

The investigator must ensure that:

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

Contraception

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

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

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

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

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

<u>Pregnancy testing</u>

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

† A female of childbearing potential is a sexually mature woman 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).

Before starting study drug:

Female Subjects

- FCBP must have two (2) negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The subject may not receive lenalidomide 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.

During study participation and for 28 days following discontinuation from the study:

Female Subjects

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

Male Subjects

- Must practice complete abstinence or use a condom during sexual contact with pregnant female or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy. If pregnancy or a positive pregnancy test does occur in the partner of a male study subject during study participation, the investigator must be notified immediately.
- Male subjects should not donate semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.

Additional precautions

- Subjects should be instructed never to give lenalidomide to another person.
- Subjects should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.
- Any unused lenalidomide must be returned as instructed through Revlimid REMS™ program.