Protocol Title: **Phase I/II Study of Lenalidomide Maintenance Following BEAM (+/- Rituximab) for Chemo-Resistant or High Risk Non-Hodgkin's Lymphoma**

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Abstract: This is a multi-center Phase I/II trial in which up to 16 evaluable subjects with persistent or relapsed non-Hodgkin's lymphoma (NHL) (any histology) that is chemo-resistant (< a PR), has received 3 or more prior chemotherapy regimens, or for subjects with lymphomas that have a high relapse rate following autologous or syngeneic stem cell transplantation (transformed NHL, peripheral T-cell lymphoma (PTCL), mantle cell lymphoma, ALK-negative anaplastic large cell lymphoma (ALCL, alk neg), intermediate IPI or high risk IPI or subjects with a positive PET scan prior to transplant. Subjects that relapse within one year of diagnosis are also eligible. Subjects will receive the suggested transplant regimen of BEAM +/-Rituximab (Rituximab added for CD20+ NHL's) treatment and Autologous Hematopoietic Stem Cell Transplantation (AHSCT) (Standard of Care) followed by lenalidomide maintenance. Lenalidomide Phase II maintenance therapy will be started day 100, or as close as possible by treating physician's discretion and dependent on the subject's travel conditions, etc., when the ANC is $\geq$ 1000 and the plts are $\geq$ 60K. Lenalidomide was administered to four subject dose cohorts, (10 mg, 15 mg, 20 mg and 25 mg). Lenalidomide will be administered orally on days 1-21 followed by 7 days of rest (28 day cycle) for 12 cycles maintenance. Three (3) subjects will be accrued in each Lenalidomide dose cohort with enrollment starting at dose cohort 1, (10 mg). These subjects will be evaluated to establish the maximum tolerated dose of Lenalidomide that can be tolerated in following Rituximab/BEAM autologous peripheral blood stem cell transplantation. The Lenalidomide of 10 mg will be utilized for the Phase II cohort. Due to the high dropout rate of subjects and the counting of consented never treated subjects, up to 114 subjects will be enrolled to achieve the 16 evaluable at the Phase II 10 mg dose level to estimate the 1 year event-free and overall survival. Data collected will be utilized to obtain a preliminary estimate of the response rate, event-free and overall survival using this regimen.

Summary Schema:

Stem cell collection per standard protocol
Rituximab per standard care.

				Day – 6	Day - 5	Day - 4	Day - 3	Day - 2	Day - 1	Day 0
Transplantation				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

Day 100, or as close as possible by treating physician's discretion and dependent on the subject's travel conditions, etc., post-transplant*		
Phase I Cohort	**# Pts**	**Days 1-21 of a 28 day cycle for** 12 cycles after initiation of the therapy post-transplant.
#-1		Maintenance Lenalidomide 5 mg PO
#1	3	Maintenance Lenalidomide 10 mg PO
#2	3	Maintenance Lenalidomide 15mg PO
#3	3	Maintenance Lenalidomide 20 mg PO
#4	3	Maintenance Lenalidomide 25 mg PO
Phase II Cohort		**Days 1-21 of a 28 day cycle for** 12 cycles after initiation of the therapy post-transplant
	Up to 24	Maintenance Lenalidomide 10mg PO

* the first cycle of Lenalidomide should be started day 100, or as close as possible by treating physician's discretion and dependent on the subject's travel conditions, insurance approval, primary/referral oncologist approval, consolidation radiation, which may delay day 100, etc., post-transplant when the ANC is $\geq$ 1000 and the plts are $\geq$ 60K.

1.0 Objective

1.1 Primary Objective

To establish the maximum tolerated dose (MTD) of Lenalidomide given in the post- transplant setting for a 12 month maintenance period

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1.2 Secondary Objective

To obtain preliminary estimates of the 1-year response rate, event-free and overall survival using this regimen.

2.0 Background, Significance, and Preliminary Studies

Subjects with persistent or relapsed non-Hodgkin's lymphoma that is chemotherapy resistant or have received 3 or more prior chemotherapy regimens have only a 15-30% long term disease-free survival following standard high-dose chemotherapy and autologous stem cell transplantation. The major cause for failure is progressive lymphoma. However, the addition of other standard chemotherapy agents have not been found to improve the results in this difficult to treat subject population. With this in mind, we have been adding agents to the transplant protocol that have a novel mechanism of action and have demonstrated some individual activity in NHL subjects. Lenalidomide has shown single agent activity in NHL. The purpose of this proposed trial is to add on to this backbone of the BEAM (+/- Rituximab) with Lenalidomide maintenance therapy to decrease the post-transplant relapse of NHL.

2.1 High-Dose Therapy in non-Hodgkin's Lymphoma

Subjects with relapsed non-Hodgkin's lymphoma have a high complete response rate with Rituxan/BEAM and autologous stem cell transplantation. However, there are still a number of subjects who relapse following this procedure. It is hoped the addition of maintenance therapies would improve the outcomes for subjects receiving high-dose chemotherapy and stem cell transplantation for treatment of relapsed non-Hodgkin's lymphoma without excessive toxicity. A Phase I study of the addition of Lenalidomide need to be carried out due to the lack of prior studies with this treatment used as maintenance in the post-transplant setting.

Subjects who have transformed from a follicular to a diffuse large cell non-Hodgkin's are felt to have a poor prognosis with standard therapies. (Lerner and Burns, 2003; Martinez-Climent, Alizadeh, Segraves, 2003) However, if subjects have at least a partial response to salvage

chemotherapy with respect to the large cell component and then go on to receive high-dose chemotherapy and autologous stem cell transplantation, they have been found to have a similar prognosis to subjects receiving a similar transplant for follicular NHL. (Cao, Horning, Negrin, 2001; Andreadis, Schuster, Chong, 2005; Laudi, Arora, Burns, 2005) In one study by Cao et al, 17 subjects with transformed NHL who underwent autologous stem cell transplant had a 4 year estimate of overall survival of 50% (95% CI, 24% - 76%) and disease- free survival year survival of 49% (95% CI, 20% - 78%). This compares to a 4 year overall survival of 60% and a disease-free survival of 44% in subjects who were transplanted still having a follicular histology.

Rituximab (IDEC-C2B8) is a chimeric monoclonal antibody directed against the CD20 antigen. It contains human IgG1 antibody and kappa constant regions, complexed to murine variable regions. This combination seems to maximize antitumor activity while minimizing autoimmunogenicity. *In vitro* rituximab mediates antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). It appears to directly inhibit cellular proliferation and induces apoptosis. Rituximab has also demonstrated an ability to sensitize drug-resistant lymphoma cell lines to the cytotoxic effects of chemotherapy. *In vivo*, it is not clear which of these mechanisms of action predominate. In subjects with large circulating tumor burdens, rapid tumor lysis has been observed, most likely as a result of activation of the complement system. Toxicity is generally infusional, and related to acute host responses to a foreign protein (e.g., fever, chills, asthenia). Other toxicities such as acute bronchospasm/hypotension have been observed rarely, and generally respond to the agents used to treat acute hypersensitivity reactions. Such reactions tend to be minimized or detectable early by administering the drug at a controlled gradually escalating infusion rate. Responses to rituximab are seen over 1-3 months, with duration of response varying by tumor type, bulk of disease, and amount and type of prior therapy. Median durations of response in these trials were often in the range of 7-13 months. Very rarely, life threatening allergic reactions has occurred with the use or rituximab.

2.2 Early Trials of Rituximab

Maloney et al. initially evaluated Rituximab for use in subjects with relapsed non-Hodgkin's lymphoma in usual Phase I fashion, administering it as a single agent in doses ranging from 10 to 500 mg/m^2. Among 15 treated subjects, 7 responses (2 partial, 5 minimal) were seen. Therapy was in general well tolerated and no dose-limiting toxicity was observed, although the higher dose levels required that subjects undergo prolonged infusion times because of infusion-related side effects. Toxicity consisted generally of allergic/infusional symptoms, including fevers, asthenia, chills, rash and urticaria with bronchospasm, hypotension and angioedema seen less commonly. Some subjects experienced brief, clinically insignificant

hematologic nadirs. Infusion-related symptoms tended to be most severe during the first infusion and generally diminished with subsequent treatments. No increased rates of infection were observed. This is presumably because serum immunoglobulin and T-cell levels did not change significantly post therapy. The higher dose in the multi-dose study was selected as the test dose for subsequent Phase II trials. As responses appeared to be more common in subjects with relapsed indolent lymphomas, subsequent Phase II trials focused primarily on this subject population. (Maloney et al.)

McLaughlin et al. published the results of a pivotal large multicenter Phase III trial in which 166 subjects with previously treated low-grade lymphoma were enrolled. Subjects received rituximab 375 mg/m^2 weekly for 4 weeks. In the intent-to-treat analysis the response rate was 48% and the complete response rate was 6%. Response rates of 60% were seen in those with follicular lymphoma, and subjects considered chemotherapy-resistant still demonstrated a response rate of 36%. The median time to progression for responders was 13.2 months and median duration of response was 11.6 months. Again, the majority of adverse events occurred during the first infusion and was allergic/infusional in nature. Only 1 grade 4 neutropenia was observed. On the basis of these studies, rituximab was approved by the Food and Drug Administration for use in subjects with relapsed low-grade/follicular non-Hodgkin's lymphoma. Several further studies have been conducted with rituximab to evaluate other aspects of its therapeutic potential. A study by Piro and colleagues evaluated safety and efficacy of extending therapy to 8 weekly infusions. Thirty seven subjects with relapsed/refractory low-grade or follicular B-cell NHL who had relapsed or had failed primary therapy were treated. The majority of toxicity as expected was infusional, with events decreasing with subsequent infusions. No host antibody (human anti-chimeric antibody) responses were seen. Mean serum immunoglobulin levels remained within normal. On an intent-to-treat basis, 5 subjects (14%) had a complete response and 16 subjects (43%) had a partial response for an overall response rate of 57%. Among 35 evaluable subjects, the response rate was 60% (14% CR and 46% PR), and the median time to progression (TTP) and the median response duration have not been reached after 19.4+ months and 13.4+ months, respectively. The authors concluded that the safety profile appeared to compare favorably with 4 weekly injections. It is possible that the median time to progression, and median response duration with 8 weekly injections is superior to that seen with 4 weeks of treatment, but no such direct comparison has yet been carried out.

Finally, a Phase II study of 31 subjects with low grade/follicular lymphoma described response rates and duration in subjects with low grade/follicular lymphoma and bulky disease (defined as the presence of at least one tumor mass $\geq$ 10 cm). This study demonstrated an overall response rate of 40% in 28 evaluable subjects. The median time to progression and duration of

response were 8.1 months and 5.9 months, respectively. The shorter time to progression compared with studies of subjects with non-bulky disease suggests perhaps decreased penetrance of antibody in bulky disease sites. (Davis et al.)

2.3 Rituximab in Conjunction with CHOP in Subjects with Indolent non-Hodgkin's Lymphomas

A Phase II study by Czuczman et al. published in 1999 looked at the combination of CHOP chemotherapy in conjunction with rituximab in 40 subjects with low-grade/follicular non-Hodgkin's lymphoma. Subjects had to be anthracycline naïve, and had to have a WHO performance status of 0-2. Most subjects had follicular small cleaved or follicular mixed histology, and nearly 80% of subjects had received no prior therapy. CHOP was given in standard doses, at 21 day intervals for six cycles. Rituximab was given at the usual dose for six infusions. Two infusions were given prior to the initiation of CHOP; one infusion was given at weeks 5 and 11 respectively, then finally as two infusions after the completion of CHOP. The overall response rate in this group of subjects was 95%, and with a median follow-up duration of nearly two years, 75% of subjects have not experienced disease recurrence or progression. Toxicity did not appear to be different than that associated with CHOP alone, with the exception of the expected first dose effect seen with rituximab.

2.4 Rituximab in Aggressive Non-Hodgkin's Lymphoma

A prospective Phase II study by Coiffier et al. looked at the use of rituximab in 54 subjects with aggressive subtypes of non-Hodgkin's lymphoma and mantle-cell lymphoma. Subjects received 8 weekly infusions of rituximab at a dose of either 375 mg/m^2 or a dose of 375 mg/m^2 once followed by 7 weekly infusions at a dose of 500 mg/m^2. Subjects were evaluated for response 2 months after completion of therapy. In an intent-to-treat analysis, the complete response rate was 9% and the partial response rate was 22% for an overall response rate of 31%. The projected median time to progression was greater than 105 days for all subjects and greater than 246 days for responding subjects. Taking into account the observation that many of these subjects had chemorefractory disease, these data were considered encouraging for a single agent.

The potential for synergy with rituximab in conjunction with chemotherapy led to a Phase II study of CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone) in combination with rituximab in subjects with advanced stage aggressive B-cell lymphomas. Subjects received rituximab 375 mg/m2 on day one and CHOP on day 3 of each 21 day chemotherapy cycle. Thirty-one subjects were treated. The median age of subjects was 49 years. All

subjects received six cycles of therapy. The overall response rate was 94%. The complete response rate was 61%. The median time to progression had not been reached after a median follow-up of 26 months. Toxicity was predominantly hematologic, but did not appear to be different than that expected from CHOP alone. Expected side-effects associated with rituximab were seen.

The conclusion of this pilot trial was that this regimen was tolerable with serious adverse events occurring at a rate and severity similar to that seen with conventional CHOP chemotherapy. Response rates may have been higher than that with CHOP alone, but since this was a pilot Phase II trial, no control group was available for comparison. (Vose et al.)

Most recently, a randomized trial comparing CHOP to rituximab/CHOP (r-CHOP) in elderly subjects (60-80 years of age) with aggressive B-cell lymphomas was conducted by the GELA (Groupe d'Etude de Lymphomes Adultes) and the first peer reviewed results on this study were recently published. In this study 399 subjects were randomized to CHOP versus r-CHOP. For subjects receiving r-CHOP both therapies were given on day 1. Response rates were higher for r-CHOP compared with CHOP alone (86% vs 71%, P=0.007). Eighteen-month event-free survival (62% vs 43%; P=0.00012) and overall survival (73% vs 61%; P=0.0065) were superior in the r-CHOP group. This is the first published randomized trial comparing CHOP to r-CHOP. Although preliminary results of a second randomized trial are likely to be available within the next one to two years, many centers are now considering r-CHOP as standard therapy for newly diagnosed aggressive B-cell non-Hodgkin's lymphoma. (Coffier et al.)

2.5 Rituximab in Conjunction with High-Dose Therapy/Autologous Hematopoietic Stem Cell Transplantation

Since relapse is the most common cause of treatment failure in subjects with chemotherapy refractory or relapsed lymphoma, the evaluation of this combination was clearly warranted. The potential additive or synergistic benefit of rituximab in conjunction with chemotherapy led to the design and execution of three clinical trials at UNMC. Rituximab was given in conjunction with BEAM (carmustine, etoposide, cytarabine, melphalan) followed by AHSCT. The first study included subjects with chemotherapy sensitive indolent NHL receiving high-dose BEAM/PSCT. In this study rituximab was given as a pre and post-transplant agent as a possible chemosensitized and for the treatment of post-transplant minimal residual disease. This study produced a complete response rate of 88% and a 24-month failure-free survival of 84% and a 24-month overall survival of 94%. Toxicity did not appear to be greater than that expected from the BEAM regimen alone.

A second trial was conducted which enrolled subjects with chemorefractory disease prior to transplantation. This trial of BEAM in conjunction with rituximab was completed in subjects with refractory disease, multiple prior chemotherapy regimens, or mantle-cell lymphoma. In this trial, rituximab was administered twice prior to peripheral blood stem cell mobilization (preliminary information had demonstrated that at least two doses of rituximab given two weeks prior to hematopoietic stem cell collection was necessary for adequate clearing of PCR positive cells in the product to provide further cytoreductive therapy pre-transplant, as well as to act as a potential in-vivo purge prior to peripheral blood progenitor cell collection. One further dose of rituximab was administered prior to beginning conditioning with BEAM, and a fourth dose was administered post recovery from transplantation. Preliminary results of this trial have demonstrated a complete response rate of 65%, a 24-month overall survival of 88% and a 24-month event-free survival of 76%.

Investigators from Stanford presented results from a Phase II trial of rituximab as an adjuvant to high-dose therapy/AHSCT at the recent meeting of the American Society of Hematology. Subjects with relapsed/refractory B-cell lymphomas were eligible. Thirty-two subjects received CBV (cyclophosphamide carmustine, etoposide) as their conditioning regimen and three received a total body irradiation-based regimen. All subjects received a purged stem cell product. Subjects received four weekly infusions of rituximab starting at day + 40 post-transplant. Toxicity appeared to be similar to that expected with high-dose chemotherapy/ AHSCT alone. At a median follow-up of 18 months, projected two year freedom from progression is 86%, and overall survival is 85%. This result was felt by the investigators to be an improvement over that seen with conventional conditioning/transplantation only (comparison made with historical controls), and as a result a randomized intergroup trial is under development to evaluate rituximab as an adjuvant therapy further in this setting. However, for subjects with chemotherapy refractory NHL results with high-dose chemotherapy and peripheral stem cells (PSC) continue to need improvement with additional modalities to the regimen (Horowitz et al.).

2.6 Lenalidomide

Lenalidomide is a proprietary IMiD® compound of Celgene Corporation. IMiD® compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF. (Dredge et al., 2005) In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and

modulates IL-12 production. (Corral et al.,1993) Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity. (Schafer et al., 2003)

Although the exact antitumor mechanism of action of lenalidomide is unknown, a number of mechanisms are postulated to be responsible for lenalidomide's activity against multiple myeloma. Lenalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis. (Davies et al., 2001) In addition, lenalidomide has direct activity against multiple myeloma and induces apoptosis or G1growth arrest in multiple myeloma cell lines and in multiple myeloma cells of subjects resistant to melphalan, doxorubicin and dexamethasone. (Hideshima et al., 2000)

Clinical Experience in Solid Tumors with Lenalidomide

Twenty subjects with varying types of solid tumors (13 with malignant melanoma, 2 each with carcinoma of the pancreas and non-small-cell lung cancer [NSCLC], 1 each with renal carcinoma, breast carcinoma, and carcinoid-unknown primary) were enrolled in a Phase 1 study of lenalidomide conducted at the St. George Hospital, London, UK. This was a non-randomized, open-label with-in subject dose-escalation design, where subjects started on 5 mg/day for 7 days and then increased their dose every 7 days to 10 mg/day, 25 mg/day, and 50 mg/day for a total of 4 weeks on therapy. (Bartlett et al., 2004)

Clinical Experience in Multiple Myeloma with Lenalidomide

In two (2) Phase I studies in multiple myeloma, a total of 41 subjects have been treated with lenalidomide. In one study at the University of Arkansas, 15 subjects who relapsed or were refractory to high dose melphalan therapy with stem cell transplant were treated for 4 weeks in an open-label safety study and were permitted to continue therapy in an extension Phase of the trial. Subject cohorts were treated at the following daily doses: 5mg, 10mg, 25mg, and 50mg. (Zangari et al. 2001). In a similar study at the Dana Farber Cancer Institute, 27 subjects with rapidly advancing refractory multiple myeloma were enrolled. (Richardson et al., 2002)

Anti-myeloma activity was observed in each of these 2 Phase I studies. Decreases in neutrophil and platelet counts were the dose-limiting toxicities associated with lenalidomide. The maximum tolerated dose (MTD) was not reached within 28 days. Due to dose modifications associated with myelosuppression observed beyond Day 28 at the 25mg and 50mg daily dose levels, the dose schedule most widely used in future studies has been lenalidomide 25 mg on Days 1-21, repeated every 28 days.

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

A recent Phase II trial utilizing lenalidomide plus dexamethasone for newly diagnosed multiple myeloma subjects were reported by the Mayo Clinic. Lenalidomide was given orally 25 mg daily on days 1-21 of a 28-day cycle. Dexamethasone was given orally 40 mg daily on days 1-4, 9-12, 17-20 of each cycle. Objective response was defined as a decrease in serum monoclonal protein by 50% or greater and a decrease in urine M protein by at least 90% or to a level less than 200 mg/24 hours, confirmed by two consecutive determinations at least 4 weeks apart. Thirty-one of 34 subjects achieved an objective response, including 2 (6%) achieving complete response (CR), and 11 (32%) meeting criteria for both very good partial response and near complete response, resulting in an overall objective response rate of 91%. Of the 3 remaining subjects not achieving an objective response, two had minor response (MR) and one stable disease. Forty-seven percent of subjects experienced grade 3 or higher non-hematologic toxicity, most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%) and rash (6%). Revlimid®/dexamethasone is a highly active regimen with manageable side-effects in the treatment of newly diagnosed myeloma. (Rajkumar et al., 2005)

A Phase I/II trial of liposomal doxorubicin (Doxil®), vincristine, dexamethasone (DVd) and lenalidomide in heavily pretreated relapsed/refractory multiple myeloma subjects is ongoing. The MTD of lenalidomide was 10mg on Days 1-21 in combination with Doxil® 40mg/m2 IVPB on Day 1, vincristine 2mg IVP on Day 1 and dexamethasone 40mg PO on Days 1-4 cycled every 28 days. All subjects received amoxicillin, acyclovir and aspirin 81mg prophylactically. The dose limiting toxicity with lenalidomide 15mg on Days 1-21 in combination with DVd was sepsis/septic shock. (Hussin etg al., 2004) Additional Phase I trials of lenalidomide with chemotherapy in advanced malignancies are in progress.

Celgene Corporation sponsored 2 multicenter, randomized, double-blinded, placebo-controlled Phase III trials [1 U.S. (MM-009) and 1 international (MM-010)] in subjects with relapsed or refractory multiple myeloma. (Data file Celgene Corporation) More than 350 subjects were enrolled into each of

these studies. All subjects had to be considered sensitive to dexamethasone and were treated with dexamethasone 40mg daily on Days 1-4, 9-12 and 17-20. In addition to receiving dexamethasone, subjects were randomized to lenalidomide 25mg or placebo each given daily on Days 1-21. Cycles were repeated every 28 days. After 4 cycles, there was a predetermined reduction of the dexamethasone dose to 40mg daily on Days 1-4 repeated every 28 days. In both studies, a pre-specified interim analysis conducted by an Independent Data Monitoring Committee demonstrated that subjects receiving the combination of lenalidomide (Len) plus dexamethasone (Dex) had significantly longer times to progression and higher response rates than those treated with single-agent dexamethasone. These studies led to the FDA approval of lenalidomide in combination with dexamethasone for the treatment of multiple myeloma in subjects that have received at least one prior therapy.

Clinical experience in Myelodysplastic Syndromes (MDS) with Lenalidomide

An exploratory trial in 43 MDS subjects with transfusion dependent or symptomatic anemia was conducted at the University of Arizona. (List et al., 2005) Subjects received lenalidomide at doses of 25mg or 10mg per day, or of 10mg on Days 1-21, repeated every 28 days. All subjects had had no response to erythropoietin or had a high endogenous erythropoietin level. Response rates were similar across the 3 dose schedules used. Responses were observed in 24 subjects overall (56%) including 21 subjects with a major response and 20 subjects with sustained transfusion independence. Subjects with a major response reached a median hemoglobin level of 13.2 grams per deciliter, with a corresponding 5.3 grams per deciliter median increase from baseline. After a median follow-up of 81 weeks, the median duration of major response had not been reached and was more than 48 weeks. Of 20 subjects with karyotypic abnormalities, 10 (50%) subjects had a complete cytogenetic remission. The response rate was highest in subjects with a clonal interstitial deletion involving chromosome 5q31.1 (10 out of 12, 83%). Neutropenia and thrombocytopenia were the most common adverse events, and resulted in dose delays or reductions in 25 subjects (58%).

Celgene Corporation sponsored a multicenter trial (MDS-003) of 148 MDS subjects with a clonal interstitial deletion involving chromosome 5q31.1. Lenalidomide was given at a dose of 10mg on Days 1-21, repeated every 28 days, to 44 subjects, and at a dose of 10mg daily to the other 104 subjects. Transfusion independence was achieved in 93 subjects (64%), with a median hemoglobin increase of 3.9g/dl. Cytogenetic response was achieved in 76% of transfusion independent subjects with 55% achieving a cytogenetic complete response. Pathologic complete response was documented in 32 out of 110 (29%) evaluable subjects. With a median follow-up of 9.3 months, the median response duration had not been reached. Neutropenia (39%) and

thrombocytopenia (35%) were the most common adverse events requiring dose delays or reductions. (List et al., 2005

Another Celgene Corporation sponsored trial (MDS-002) in subjects with low to intermediate-1 risk MDS enrolled 215 subjects, of whom, 166 were documented to have low to intermediate-1 risk MDS. Among the subjects with documented low to intermediate-1 risk MDS, 84 subjects (51%) responded to treatment. Transfusion independence was achieved in 54 subjects (33%) and 30 subjects (18%) achieved a minor response, defined as a 50% or greater decrease in blood transfusion requirement. The median duration of transfusion-independence was 41 weeks. The median baseline hemoglobin level was 8.0g/dl, which increased by 3.2g/dl in responding subjects. Among 20 subjects evaluable for cytogenetic response, 9 subjects (45%) experienced a cytogenetic remission.

Clinical Experience with Lenalidomide and Non-Hodgkin's Lymphoma. Two Phase II studies have been performed for subjects with relapsed non-Hodgkin's lymphoma. One was for subjects with indolent NHL and the other for subjects with aggressive NHL. In the protocol treating indolent NHL, the overall response rate was 26% in subjects with multiply relapsed follicular lymphoma, small lymphocytic, and marginal zone lymphoma (Witzig et al., 2007). In the Phase II study for subjects with relapsed aggressive NHL, the overall response rate was 41% with a 50% response rate in mantle cell lymphoma and a 50% response rate in transformed lymphoma. (Wiernik et al., 2007).

Updated Information for Phase I. (Protocol V.3.8, dated 09-06-2012) Results from Phase I with 3 subjects treated at dose level I (10mg), 1 subject with dose level toxicity which resulted in expanding to 6 subjects and all 6 subjects completed 12 cycles. At dose level II (15mg), 3 subjects were treated; 1 subject completed 12 cycles and 2 subjects withdrew from study, and no dose level toxicity occurred at this level. Moving onto dose level III (20mg), 3 subjects were treated; 1 subject completed 12 cycles and 2 subjects withdrew from study, and no dose level toxicity occurred at this level. During dose level IV (25mg), 4 subjects were treated; 2 subjects completed 12 cycles, 1 subject was removed from the study after repeated delays and 1 subject was put on hold post elective surgery. Two dose level toxicities occurred at this level and level was expanded to dose level 3 with 3 additional subjects with 1 subject receiving treatment and 2 subjects withdrawn from study. All 3 additional subjects had dose level toxicity which is an indicator that all subjects will be treated with dose level II (15mg) in Phase II of the study.

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

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

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

2.7 Study Rationale

The rationale for this trial is to build upon the preliminary results with the combination of BEAM (+/- Rituxan) for subjects with relapsed NHL. The current trial will add maintenance therapy starting day 100 (+/- 7 days) when the ANC is $\geq$ 1000 and the plts are $\geq$ 60K with Lenalidomide (in four dose cohorts, 10 mg, 15 mg, 20 mg and 25 mg) administered orally on days 1-21 followed by 7 days of rest (28 day cycle) for 12 cycles after initiation of the therapy post-transplant. This trial will be in chemoresistant (< PR), subjects who have received multiple prior treatments ($\geq$ 3 regimens), or have histologies that have a known higher post-transplant relapse such as transformed lymphoma, PTCL, MCL or ALCL, alk neg, intermediate IPI or high risk IPI or subjects with a positive PET scan prior to transplant.

Phase II dose will be 10mg 1 day x 21 days of 28-day cycle.

3.0 Eligibility Criteria

3.1 Inclusion Criteria

3.1.1 Persistent, or relapsed non-Hodgkin's lymphoma (NHL) (any histology) that is chemo-resistant (< a PR), subjects who have received ≥3 prior chemotherapy regimens, or subjects with lymphomas that have a high relapse rate following autologous or syngeneic stem cell transplantation (transformed NHL, peripheral T-cell lymphoma (PTCL), mantle cell lymphoma, ALK-negative anaplastic large cell lymphoma (ALCL, alk neg), intermediate IPI or high risk IPI or subjects with a positive PET scan prior to transplant, and otherwise eligible for transplantation with adequate end-organ function.

3.1.2 Subjects that relapse within one year of diagnosis.

3.1.3 Able to collect ≥ 1.5 X 10^6 CD34+/kg cell for transplantation.

3.1.4 ANC ≥ 1000 cells/mm^3 and Platelet Count ≥ 60K when maintenance Lenalidomide is started [as close to as feasible to day 100 post-transplant].

3.1.5 Subjects must have calculated creatinine clearance ≥ 30ml/min (Appendix H).

3.1.6 Total bilirubin ≤ 1.5 x ULN

3.1.7 AST (SGOT) and ALT (SGPT) ≤ 3 x ULN.

3.1.8 Age ≥19 years.

3.1.9 Subjects who are seropositive because of hepatitis B virus vaccine

3.1.10 Subjects 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, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.

3.1.11 Able to adhere to the study visit schedule and other protocol requirements.

3.1.12 Expected survival duration of ≥ six months.

3.1.13 Karnofsky Performance Status ≥ 70. (Appendix A)

3.1.14 Subjects > age 60 or with clinical signs of heart disease must have ejection fraction ≥ 45% LVEF pre-transplant.

3.1.15 Subjects with clinical signs of pulmonary insufficiency must have DLCO to be measured at $\geq$ 50% of predicted value prior to transplant.

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

3.1.17 Disease free of prior malignancies for $\geq$ 2 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "insitu" of the cervix or breast or low risk prostate cancer after curative therapy.

3.1.18 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.

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

3.1.20 Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS ™ program.

3.1.21 Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (subjects intolerant to ASA may use warfarin or low molecular weight heparin).

3.1.22 Male subject agrees to use an acceptable method for contraception for the duration of the study.

† 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).

3.2 Exclusion Criteria

3.2.1 Chemosensitive NHL, except subjects receiving ≥ 3 prior chemotherapy regimens, or subjects having transformed NHL, PTCL, MCL, or ALCL, alk neg.

3.2.2 End-organ function not appropriate for transplantation.

3.2.3 Inability to collect adequate stem cells.

3.2.4 Known positive for HIV or infectious hepatitis, type B (HBV) or C (HCV) or active Hepatitis.

3.2.5 Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

3.2.6 Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking lenalidomide).

3.2.7 Known hypersensitivity to thalidomide or lenalidomide (if applicable).

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

3.2.9 Any prior use of lenalidomide.

3.2.10 Concurrent use of other anti-cancer agents or treatments.

3.2.11 Serum creatinine >2.0mg/dL or calculated creatinine clearance < 30ml/min (Appendix H).

3.2.12 Active infection at the start of Lenalidomide.

3.2.13 Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. (Appendix C) Prior to study entry, any ECG abnormality at Screening has to be documented by the investigator as not medically relevant.

3.2.14 History of life threatening or recurrent thrombosis/embolism. Subjects may participate if they are adequately anticoagulated during the treatment.

3.2.15 Subject has >Grade 2 peripheral neuropathy within 14 days before enrollment

4.0 Registration Procedures

Subjects who are referred to the Nebraska Medical Center (NMC) / UNMC; University of Kansas Cancer Center-Westwood, KS; University Hospitals Seidman Cancer Center-Case Western Reserve University- Cleveland, OH; or other IRB approved sites, for autologous stem cell transplant with persistent, or relapsed non-Hodgkin's lymphoma (NHL) (any histology) that is chemoresistant (< a PR), has received 3 or more prior chemotherapy regimens, or for subjects with lymphomas that have a high relapse rate following autologous or syngeneic stem cell transplantation (transformed NHL, peripheral T-cell lymphoma (PTCL), mantle cell lymphoma, ALK-negative anaplastic large cell lymphoma (ALCL, alk neg), intermediate IPI or high risk IPI or subjects with a positive PET scan prior to transplant may be eligible for this trial. The pre-conditioning regimen will be at the discretion of the treating physician. Screening eligibility 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 will be obtained as clinically indicated. The subject's primary oncologist will make the decision as to eligibility of the candidate based on the eligibility criteria listed above.

If the subject is found eligible, he/she will then be offered the option to participate. An informed consent will be signed by the subject after thorough review of the study is completed with the physician and his/her designee. All study participants must be registered into the mandatory Revlimid REMS™ program.

Some insurance carrier's may decline to cover the costs of usual medical care if the subject is participating in a clinical trial. The subject will be provided assistance by the research nurse coordinator in determining if the insurance carrier will decline coverage. Insurance carriers may or may not pay for study related expenses. The subject can then decide if they wish to participate.

4.1 Eligibility Verification/Registration:

Before subjects are enrolled into the study, an eligibility checklist (Appendix H) must be completed to verify the subject meets the eligibility criteria. Date of enrollment is defined as the date of the start of study treatment / first protocol related intervention.

Subjects will be registered through 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).

Study personnel from non-UNMC IRB approved sites will contact the UNMC Fred & Pamela Buffett Cancer Center Research Project Coordinator if a non-UNMC subject appears to meet the eligibility criteria. They will fax the completed eligibility checklist (Appendix H) and accompanying applicable de-identified source documents (i.e. laboratory, pathology, and radiology records) to the UNMC research study

coordinator, at FAX: 402-559-8895 (ph:402-559-5582 or 402-559-5286) to verify the subject meets the eligibility criteria. The eligibility check list and source documents will be maintained in the study file. If the UNMC research study coordinator confirms that the non-UNMC subject meets criteria, and target accrual has not been met, approval for the non-UNMC subject will be given. A confirmation of registration will be forwarded by the UNMC research study coordinator.

UNMC:
Study personnel will provide the UNMC Fred & Pamela Buffett Cancer Center PRMS office (ZIP 6805) a copy of the signed and dated consent form for each UNMC subject registered to the protocol within one (1) week that includes the following information:

- Protocol Number
- Subject Identification: Subject's name UNMC/NMC medical record number
- Subject demographics: gender, birth date (mm/dd/yyyy), race, ethnicity
- New CTRP reporting requirements: Subject zip code/country (if not USA) and primary method of payment information

Collaborating Sites:
Collaborating sites must have both local *and* UNMC IRB approval, and have met all other UNMC criteria to enroll. Study personnel from non-UNMC IRB approved sites will provide the UNMC Research Project Coordinator with:

- Study Manual demographics fax/scan cover
- Copy of the signed (subject signature obliterated with signature line and subject initials visible) and dated consent form
- Signed eligibility checklist
- De-identified source documents (with study assigned subject I.D. if known on each page) to support eligibility (i.e., H&P, Medical/Surgical Hx, lab, pathology, scans, etc.).

UNMC Research Project Coordinator will register collaborating site subjects to the National Cancer Institute (NCI) Clinical Trials Reporting Program (CTRP) Accrual Registry. Collaborating sites will utilize the Fax/Scan Cover provided in the Study Manual which includes demographics required for CTRP accrual reporting compliance.

The information listed below for subjects enrolled at collaborating sites will be provided to the PRMS office by the UNMC Research Project Coordinator within one (1) week of enrollment as applicable:

- UNMC and Collaborating Site Protocol Numbers
- Investigator/Collaborating Site Identifier (ID)
- Subject ID: Assigned by UNMC [Site ID followed by subject number (##-###)]

- Consent Date: Date subject signed consent
- Re-consent Date: (If applicable)
- Ineligibility Status: (If known)
- Off Study Date: (If applicable)
- CTRP Status (Entered/Not entered)

University of Nebraska Medical Center
Fred & Pamela Buffett Cancer Center PRMS Office
Attn: Anna Grant, RRT, PRMS Administrator
986805 Nebraska Medical Center
Omaha, NE 68198-6805
Ph: (402)-559-4232
FAX: (402)-559-4970

4.2 Requirements for Non-UNMC Sites/ Collaborating Institutions:

Submitting Regulatory Documents
Before a collaborating institution may enter subjects, protocol specific regulatory documents must be submitted to the UNMC Fred & Pamela Buffett Cancer Center study Project Coordinator.

4.3 Required Protocol Specific Regulatory Documents

1. Confirmation that UNMC PI and Research Study Coordinator conducted an initial Site Visit/Teleconference prior to opening a protocol to accrual at collaborating sites.
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

Subjects will receive the suggested transplant regimen of R/BEAM treatment and AHSCT (Standard of Care) followed by lenalidomide maintenance. For the

lenalidomide maintenance portion of the study, a Phase I study design was needed to determine the maximum tolerated dose (MTD) of lenalidomide in this setting. The dose of lenalidomide used for the Phase II maintenance portion will be 10 mg.

5.1 Administration of Lenalidomide Maintenance Regimen

Visits in between day of dismissal from transplant, as close as feasible to day 100 and 1 year can be done at the subjects referring or home physician. Disease re-evaluation at day 100 (+/- 7 days), and 1 year is preferred to be done at UNMC but if not possible can be done referring or home physician office.

Phase II maintenance therapy (the first cycle should be started day 100, or as close as possible by treating physician's discretion and dependent on the subject's travel conditions, etc., post-transplant, when the ANC is $\geq$ 1000 and the plts are $\geq$ 60K) with Lenalidomide (see Lenalidomide dosing cohorts section 5.8.1) administered orally on days 1-21 followed by 7 days of rest (28 day cycle) for 12 cycles. Prescriptions must be filled within 7 days.

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

Lenalidomide will be supplied as capsules for oral administration.

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

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

Subjects are required to take a daily dosing of aspirin (81 or 325 mg) beginning Day 1 of Lenalidamide. Low molecular weight heparin may be utilized in subjects that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

Subjects experiencing adverse events may need study treatment modifications (See section 5.8.4).

5.1.1 Lenalidomide dosing

Based in Phase I data, the MTD was determined to be 15 mg but, the MTD for the study was based on cycle 1 of the Lenalidomide maintenance. However, there is

cumulative toxicity of Lenalidomide, especially in the post-transplant setting which led to a need to lower the dose to 10 mg for the Phase II study. At the 10 mg dose, a much higher percentage of subjects were able to complete > 6 months of maintenance therapy. **Therefore the dose for continued Phase II will be 10 mg.**
Lenalidomide capsules will be taken orally daily days 1-21 of a 28 day cycle for 12 cycles post-transplant.

5.1.2 Instructions for Initiation of a New Cycle of Lenalidomide

A new course of treatment may begin on the scheduled Day 1 of a new cycle if lab work is obtained prior to Day 1:

- The ANC is ≥1000mm³;
- The platelet count is ≥ 60K;
- Any drug-related rash or neuropathy that may have occurred has resolved to ≤ grade 1 severity;
- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If lenalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. **If lenalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1**, then the new cycle will be started with a one-level dose reduction of lenalidomide.

5.1.3 Instructions for Dose Modifications or Interruption During a Cycle of Lenalidomide

(See the following Table.)

NCI CTC Toxicity Grade	Dose Modification Instructions	

NCI CTC Toxicity Grade	Dose Modification Instructions	
Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained. If G-CSF is needed in more than one consecutive cycle then that should be a DLT	
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Hold (interrupt) lenalidomide dose. • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up.	
Platelet count < 50K	• Hold prophylactic anti-coagulation/ASA for platelet <50K • Restart prophylactic anti-coagulation when platelet count is ≥60K	
Non-blistering rash **1** **Grade 3** **2** **3** **4** **5** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove subject from study.	
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide. Remove subject from study.	
Neuropathy when Lenalidomide is <3% **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 of the current cycle, restart lenalidomide at next lower dose level and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle and reduce the dose of lenalidomide by 1 dose level at the start of the next cycle. Omitted doses are not made up. • If Grade 4, discontinue lenalidomide. Remove subject from study.	
Venous thrombosis/embolism **≥ Grade 3**	• Hold (interrupt) lenalidomide and start therapeutic anticoagulation, if appropriate • Restart lenalidomide at investigator's discretion (maintain dose level). • See Anticoagulation Section	

NCI CTC Toxicity Grade	Dose Modification Instructions	
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level.	
other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) lenalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21 of the current cycle, restart lenalidomide and continue through the scheduled Day 21 of the current cycle. Otherwise, omit for remainder of cycle. Omitted doses are not made up. For toxicity attributed to lenalidomide, reduce the lenalidomide dose by 1 dose level when restarting lenalidomide.	•

5.1.4 Treatment compliance for Lenalidomide Dosing

Research center personnel will review the dosing instructions with subjects. Subjects will not receive study medication until they speak with the Revlimid REMS ™ certified pharmacist. To provide a means of ensuring oral route of medication adherence to subject while participating in this clinical trial, standard procedure for "Oral, Sublingual, and/or Buccal Route Medication Adherence Standard Procedure (V 1.0 11-25-2013)" will be followed. See Appendix I. All unused Revlimid® (lenalidomide) capsules should be returned as instructed through Revlimid REMS ™ program. If any study drug is lost or damaged, its disposition should be documented in the source documents.

5.2 Duration of Therapy

Subjects may be withdrawn from the study by the investigator or supporter for the following reasons: any adverse event or toxicity which compromises the subject's ability to participate, disease progression, and discontinuation of lenalidomide for any reason, major violation of the study protocol, suspected pregnancy, any intercurrent illness or condition which in the opinion of the investigator would necessitate withdrawal from the study. Additionally, the subject may decide to withdraw from the study and will be offered consultation with the investigator to discuss consequences and benefits of such withdrawal.

Subjects, who discontinue treatment for any reason, will be followed for toxicity, relapse, and death as per any standard transplant subject.

Subjects with stable disease will remain on study until disease progression. Lenalidomide will be discontinued after 12 cycles after initiation of the therapy. All subjects will continue to be followed for survival following treatment on the study.

5.3 Supportive Care/Additional Therapy

The subjects will be cared for as standard bone marrow transplant subjects. Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate.

Subjects will be discharged from the hospital and followed on an outpatient basis as clinically indicated.

Females of childbearing potential (FCBP)† 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, pre or day 1 of transplant and 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 B Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

† 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).

External beam radiation therapy will not be administered during the transplant course. External beam radiation may, however be given following the transplant as felt to be clinically indicated for areas of bulky tumor prior to transplant. External beam radiation given post –transplant should be given prior to start of lenalidomide.

The use of hematopoietic growth factors (GCSF or GMCSF) to stimulate blood cell production will be initiated post stem cell transplant as per existing institutional policy (ANC < 500 associated with neutropenic fever).

Treatment with corticosteroids, other than transient administration to control or prevent nausea or vomiting, asthma, or allergic reactions, will not be permitted and may result in withdrawal of a subject from the study. Non-steroidal hormones administered for non-lymphoma-related conditions, e.g., insulin for diabetes, are acceptable.

Anticoagulation

Lenalidomide increases the risk of thrombotic events in subjects who are at high risk of thrombosis or with a history of thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide is

combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased.

The use of daily dosing of aspirin (81 or 325 mg) will be required to start with Day 1 of Lenalidamide. Low molecular weight heparin may be utilized in subjects that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

5.4 Staging Re-Evaluations

Subjects will be restaged and evaluated by radiographic tests that are disease appropriate, such as: CT scans, PET scans, MRI. A bone marrow biopsy (only if previously positive) and evaluated with labs (CBC, diff, plt, CMET, LDH, TSH) at Day 100 as close as feasible and one year post-transplant evaluation. If <CR at Day 100 (+/- 7 days) repeat staging evaluations at the treating physicians discretion.

At yearly intervals for 5 years minimum after the first annual visit post-transplant, the subjects will be clinically evaluated. Yearly labs, chest x-ray, scans and other tests will be performed as clinically appropriate and more frequently for symptoms or problems.

5.5 Biospecimens for Research Purposes

1. Diagnostic Tissue Block:
   For DLBCL -- immunostaining to distinguish between GBC and non-GBC, Ki67
   For FL -- CD20, 3, 68, 10, BCL2, Fox P3, PD-1
   For MCL -- CD20, 3, 5, Ki67, cyclin D1
   For all tumors – CD34 for vascular density

Shipping: Send frozen tissue overnight on dry ice Monday through Thursday only. Do not send the day before a holiday. Tissue should be frozen in an OCT block, or a sample of tissue frozen (not embedded) and wrapped in foil and sent overnight on dry ice. It is critical that the frozen tissue remains frozen, is well-packed and surrounded by dry ice.

Please contact Chengfeng Bi or Xuan Zhang, Dept. of Pathology/ Microbiology at (402) 559-7753 AND the UNMC Research Project Coordinator to advise of planned shipments and to discuss appropriate procedures in the event a tissue sample must be sent on a Friday or before a holiday.

If alternative methods require consideration, please contact Kai Fu M.D., Ph.D. for guidance on acceptable specifications.

2. Post PSCT:
   2- 10ml Na Heparin tubes, baseline before Lenalidomide, 6 months and 1 year post-transplant on Lenalidomide (or end of study drug if off Lenalidomide before this time point) if the subject returns to site.

   1- 10ml Serum tubes, baseline before Lenalidomide, 6 months and 1 year post-transplant on Lenalidomide (or end of study drug if off Lenalidomide before this time point) if the subject returns to site.

   Serum to assay for VEGF, sIL2R, IL12, TNFa
   Flow analysis for total T-cells (Th1, Th2, Th17), B-cells, NK-cells, monocytes (subsets)

Shipping: Send blood sample overnight at room temp Monday through Thursday only; do not send the day before a holiday.

Please contact Michelle Varney, Dept. of Pathology/ Microbiology at (402) 559-5580 AND the UNMC Research Project Coordinator 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.

If alternative methods require consideration, please contact Rakesh Singh, PhD for guidance on acceptable specifications.

6.0 Measurement of Effect

Response to therapy will be classified as complete response (CR), complete response, partial response (PR), no response (NR), progressive disease (PD), early death, or not evaluable. Response to therapy will be determined at Day 100. For specific definitions of the International Harmonization Project's update to the International Working Group guidelines, see Appendix D.

Subjects will be analyzed with respect to overall survival and event-free survival. Overall survival is defined as time from the first chemotherapy administered on the transplant trial until death from any cause. Event-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.

7.0 Study Parameters

Schedule of Study Assessments for Lenalidomide

Procedure	**Transplant Related Procedures (Standard of Care)**	Cycle 1 of Revlimid® (lenalidomide) Day 100				**Subsequent Cycles**	28 days after therapy completed 12 cycles	**Follow-Up Phase**[3]
		Day **1**	Day **8**	Day **15**	Day **22**	Day **1**		
Record prior medications, treatments		X						
Record prior anti-cancer therapies		X						
Physical exam, vital signs, weight, height[9,] as medically indicated[9a]		X[9]				X[9a]	X	x
KS performance status		X[9]					X	x
CT , or PET or MRI	Pre-transplant					X[7 11]	X [11]	
Chest x-ray [1]								
Bone Marrow Bx [2, 11]	Pre-transplant if positive previously					X[2, 11]	X[2, 11]	
ECG, PFTs, Echocardiogram	Pre-transplant							
HIV testing pre-transplant	Pre-transplant							
Hematology CBC diff, PLT		X[9, 12]	X	X	X	X	X	
C MET LDH		X[9,12]		X		X	X	
TSH[4]		X[4, 12]				X[4,]		
Pregnancy testing[5]		X[6]	X	X	X	X[6]	X[6]	
Research blood specimen Dr. Singh's lab VEGF and cytokines (2-10ml NA Heparin green top tubes and 1-ml no additive red top at baseline, 6 months and 1 year post-transplant)		X				X 1yr post-transplant		
Request Research tissue block for immunostaining Dr. Fu's lab (see Appendix J)		X						
Register subject into Revlimid REMS ™ program		X						

Prescribe lenalidomide via Revlimid REMS™ [10]		X[10]				X[10]		
Response assessment						X[7]	X	
Record adverse events[8]			X	X	X	X	X[8]	
Record concomitant therapies/procedures			X		X	X	X	
Obtain Follow-Up anti-cancer treatments								X
Obtain Follow-Up survival information								X

* Variations of ± 3 days of the scheduled visit are permitted.

If Physical examination, vital signs, weight, height and KS performance status were done within 7 days of Day 1, they do not need to be repeated at Study Day 1.

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

[1] Not needed if Chest CT scan has been obtained.

[2] If subject had previously positive bone marrow bx.scan or if symptoms suggest metastases.

[3] Follow-up day 100, and yearly at UNMC or Collaborating Site preferably. Otherwise for the first year every 3 months by local MD's per SOC with CBC, B-met, exams. Then once every 6 months for the second year then yearly.

[4] To include Thyroid Stimulating Hormone (TSH) at Screening and at treatment discontinuation. T3 and T4 levels may be assessed as clinically indicated.

[5] 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).

[6] Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods). See Revlimid REMS™ program requirements for FCBP and birth control

[7] As clinically indicated.

[8] An additional safety assessment will be done 30 days (+/- 2 days) following the last dose of study drug.

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

[9a] Physical exam, vital signs, weight, height only as medically indicated.

[10] Lenalidomide must be prescribed through and in compliance with Celgene Corporation's Revlimid REMS™ program. Prescriptions must be filled within 7 days. Any unused Revlimid® (lenalidomide) 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.

[11] Subjects will be restaged and evaluated by radiographic tests that are disease appropriate, such as: CT scans, PET scans, MRI. A bone

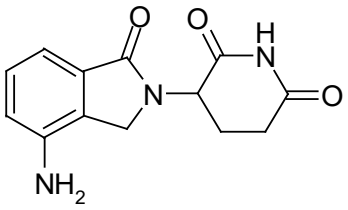
marrow biopsy (only if previously positive) and evaluated with labs (CBC, diff, plt, CMET, LDH, TSH) at Day 100 and yearly unless clinical suspicion of progression. If <CR at Day 100 repeat staging evaluations at the treating physicians discretion.
[12] Day 1 reference Day 1 of treatment. Lab work to be obtained as close to Day 1 or within Day 1.

8.0 Drug Formulation and Procurement:

8.1 Lenalidomide

REVLIMID® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The Chemical Abstract Service (CAS) registry number and name for lenalidomide are 191732-72-6 and 3-(4-amino-1-oxo 1, 3-dihydro-2H-isoindol-2-yl) piperidine-2, 6-dione, respectively. Lenalidomide is also known by the earlier clinical code names, CC-5013 and CDC-501.

The chemical structure of lenalidomide is as follows:



Lenalidomide has an empirical formula of $C_{13}H_{13}N_3O_3$ and a molecular weight of 259.3. It is an off-white to pale-yellow solid powder, with a melting point between 265ºC to 270ºC.

Lenalidomide has 1 chiral center and is prepared as a 50:50 racemic mixture of the R (+) and S (-) isomers.

Mechanism of Action: The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Experiments have demonstrated that lenalidomide inhibits the growth of cells derived from subjects with multiple myeloma and del (5q) myelodysplastic syndromes in vitro. Lenalidomide causes a delay in tumor growth in some in vivo nonclinical hematopoietic tumor models, including multiple myeloma. Lenalidomide inhibits the secretion of pro-inflammatory cytokines such as tumor necrosis factor alpha (TNF-α), from peripheral blood mononuclear cells. Lenalidomide also inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

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

Pharmacokinetic sampling in myelodysplastic syndrome (MDS) subjects was not performed. In multiple myeloma subjects treated in the Phase I studies, maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single

and multiple doses. Exposure (AUC) in multiple myeloma subjects is 57% higher than in healthy male volunteers.

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

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

Supplier(s)

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the **Revlimid Risk Evaluation and Mitigation Strategy™ (REMS) program (**formerly known as RevAssist® Program). 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 **Celgene Corporation's Revlimid REMS™ program**.

Dosage Form:

For clinical study, lenalidomide is provided as 1.25-, 2.5-, 5-, 10-, 15-, 20-, and 25-mg capsules for oral administration. Each capsule of lenalidomide contains 1.25, 2.5, 5, 10, 15, 20 or 25 mg of lenalidomide and the following inactive ingredients: anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate. The 1.25-, and 2.5-mg dose of lenalidomide is contained in a size 4 hard gelatin capsule. The 5-mg dose of lenalidomide is contained in a size 2 hard gelatin capsule. The 10-, 15-, 20-, and 25-mg doses of lenalidomide are contained in a size 0 hard gelatin capsules. The lenalidomide capsules are supplied in push-through blister foil or tamperevident, child-resistant, opaque, high-density polyethylene (HDPE) containers with HDPE caps.

Packaging: Lenalidomide will be shipped directly to subjects. Bottles will contain a sufficient number of capsules for one cycle of dosing.

Labeling

Lenalidomide supplies are dispensed in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: "Caution: New drug - Limited by Federal law to investigational use." Lenalidomide should not be handled by FCBP unless wearing gloves.

The study drug label must be clearly visible. Additional labels must not cover the Celgene label.

Storage:

Subjects should store Lenalidomide in a locked, safe area, and out of the reach of children to prevent unauthorized access.

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

Care should be exercised in the handling of REVLIMID ® (lenalidomide). REVLIMID capsules should not be opened or crushed. If a powder from REVLIMID contacts the skin, wash the skin immediately and thoroughly with soap and water. If REVLIMID contacts the mucous membranes, flush thoroughly with water.

Procedures for the proper handling and disposal of anticancer drugs should be considered. Several guidelines on the subject have been published.

White opaque capsules imprinted “REV” on one half and “5 mg” on the other half in black ink:

- 5 mg bottles of 28 (NDC 59572-405-28)
- 5 mg bottles of 100 (NDC 59572-405-00)
- Blue/green and pale yellow opaque capsules imprinted “REV” on one half and “10 mg” on the other half in black ink:
- 10 mg bottles of 28 (NDC 59572-410-28)
- 10 mg bottles of 100 (NDC 59572-410-00)

Powder blue and white opaque capsules imprinted “REV” on one half and “15 mg”on the other half in black ink:

- 15 mg bottles of 21 (NDC 59572-415-21)
- 15 mg bottles of 100 (NDC 59572-415-00)

White opaque capsules imprinted “REV” on one half and “25 mg” on the other half in black ink:

- 25 mg bottles of 21 (NDC 59572-425-21)
- 25 mg bottles of 100 (NDC 59572-425-00)
- Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [See USP Controlled Room Temperature].
- Dispense no more than a 28-day supply.

Prescribing Information: Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial (12 cycles) at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the Celgene Corporation Revlimid REMS™ program. Per standard Revlimid REMS™ program requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the Revlimid REMS™ program. Prescriptions must be filled within 7 days for females of childbearing potential and 14 days for all other risk categories. **Only enough lenalidomide for one cycle of therapy will be supplied to the subject each cycle**.

Adverse Events of Medical or Regulatory Interest:

Blood and Lymphatic System Disorders
Hematologic Toxicity
Lenalidomide is associated with anemia, neutropenia, febrile neutropenia, thrombocytopenia, and pancytopenia. Grade 3/4 neutropenia and thrombocytopenia are the most common, doselimiting AEs associated with the administration of lenalidomide.

Vascular Disorders
Thromboembolic Events
Lenalidomide, in combination with dexamethasone, has been associated with an increased incidence in thrombotic or thromboembolic events, including deep vein thrombosis (DVT), pulmonary embolism, thrombosis, and thromboembolism, particularly among MM subjects receiving concomitant therapy with an erythropoietic agent. DVT has been reported with both indications but is more frequent in MM than in MDS.

Gastrointestinal Disorders
Constipation, diarrhea, nausea, and vomiting were the most commonly reported gastrointestinal AEs during treatment with lenalidomide.

Hepatic Disorders
Cases of transient liver laboratory abnormalities (predominantly in transaminases) were reported in subjects treated with lenalomide. Successful rechallenge without recurrence of liver laboratory elevation was reported in some subjects.

Cardiac Disorders
Occasional TEAEs such as atrial fibrillation, myocardial infarction, and congestive heart failure have been reported with the use of lenalidomide from clinical studies and post-marketing.

Infections and Infestations
Treatment-emergent adverse events of infections specifically pneumonia (including MedDRA preferred terms of pneumonia NOS, bronchopneumonia NOS, lobar pneumonia, pneumocystis carinii pneumonia, pneumonia bacterial NOS, pneumonia cytomegaloviral, pneumonia legionella, pneumococcal pneumonia, pneumonia primary atypical, and pneumonia staphylococcal) are commonly seen with lenalidomide.

Neoplasms Benign, Malignant and Unspecified (Including Cysts and Polyps)
Cases of AML have been reported in some MDS and MM studies. In addition, cases of MDS have been reported in some MM trials. It is thought that AML and MDS may be part of the natural course of MM. Furthermore, certain treatments for MM, such as alkylating agents (eg, melphalan) are known to be associated with the increased incidence of AML. It is unknown at this time if the use of lenalidomide increases the risk of AML or MDS; any potential causal relationship is under investigation.

Tumor Lysis Syndrome and Tumor Flare Reaction
Tumor lysis syndrome (TLS) and tumor flare reaction (TFR) have commonly been observed in subjects with CLL, and uncommonly in subjects with other lymphomas, who were treated with lenalidomide. Subjects at risk for TLS and TFR are those with high tumor burden prior to treatment. Fatal instances of TLS have been reported during treatment with lenalidomide. Caution should be practiced when introducing these subjects to lenalidomide. There have been rare reports of TLS in subjects with MM treated with lenalidomide, and no reports in subjects with MDS treated with lenalidomide.

Musculoskeletal and Connective Tissue Disorders
The rare TEAE of rhabdomyolysis has been observed with lenalidomide.

Allergic Reactions
Rare TEAEs of angioedema, pneumonitis, and serious dermatologic reactions including Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) have been reported with lenalidomide during commercial use. These events have the potential to be fatal.

Mortality and Morbidity
The results from Study E4A03 provide supportive data that the combination of lenalidomide and dexamethasone is safe and effective for the treatment of newly diagnosed MM. Study E4A03 further demonstrates that reducing the dose of dexamethasone in this combination results in an overall early survival advantage and has less toxicity with an improved safety profile than the standard examethasone regimen in subjects with newly diagnosed MM. A greater clinical benefit was observed in the older subject population (> 65 years). In addition, the treatment difference in improved mortality was maintained with continued observation (> 30 days after the last dose of protocol therapy). In this trial the

combination of lenalidomide plus low dose dexamethasone demonstrated an improved safety profile and reduced mortality resulting in a clinically significant survival advantage. Both the reduced mortality and morbidity are considered meaningful improvements in subject benefit as well as a significant reduction in risk when compared with the standard dose dexamethasone combination for subjects with newly diagnosed MM.

Review of current post marketing data, which consists of thousands of subject exposure, did not identify any additional significant safety signal. Cross-sensitivity with thalidomide has been reported in the literature.

The safety of Lenolidomide will be assessed through collection and analyses of adverse events (AEs), baseline medical conditions, laboratory tests, and vital sign data.

9.0 Toxicity Reporting Guidelines

This protocol will comply with monitoring and adverse event reporting requirements of the UNMC/Fred & Pamela Buffett Cancer Center Data Monitoring plan Celgene Corporation guidelines will also be adhered to for toxicity reporting. The protocol will adhere to the institutional, FDA, and Celgene Corporation guidelines for the toxicity reporting.
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 100 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 for all subjects at all collaborating sites will be reported to the University of Nebraska Medical Center, Institutional Review Board (IRB) and Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC), FDA, and Celgene Corporation Drug Safety.

9.1 Adverse Experiences 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 (e.g. Lenalidomide 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 subject 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 subject 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.

9.2 Adverse Event Reporting

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

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the subject's outcome

Pregnancies and 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.

Pregnancies and suspected pregnancies (including a positive pregnancy test

regardless of age or disease state) of a female subject or the female partner of a male subject occurring while the subject is on lenalidomide or within 4 weeks (28 days) after the subject's last dose of lenalidomide are considered immediately reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator or designee. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Corporation Drug Safety immediately following the Investigator's knowledge of the pregnancy,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 pregnant female until completion of the pregnancy, and must notify Celgene Corporation Drug Safety immediately of the outcome of the pregnancy (either normal or abnormal outcome). The Investigator will provide this information 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 Corporation Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922

Toll Free: **(800)-640-7854**
Phone: **(908) 673-9667**
Fax: **(908) 673-9115**
e-mail: **drugsafety@celgene.com**

Adverse Event Causality
The investigator will use the following definitions to assess the relationship of the adverse event to the use of study drug:

Related An adverse event has a strong temporal relationship to study drug, recurs on re-challenge or is known to be an effect of the study drug. Another reasonable etiology either doesn't exist or is unlikely.

Possibly Related An adverse event has a strong temporal relationship to the study drug and an alternative etiology is either equally or less likely when compared to the potential relationship to study drug.

Not Related An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (*e.g.*, has little or no temporal relationship to study drug or has a much more likely alternative etiology).

If an investigator's opinion of not related to study drug is given, an alternate etiology (underlying disease, co morbid condition, other drug) must be provided for the adverse event.

All subjects will be followed for adverse experiences (AEs) (serious and nonserious), regardless of relationship to study drug starting first day of study treatment (day 100 (+/- 7 days) post-transplant when the ANC is $\geq$ 1000 and the plts are $\geq$ 60K) and will be followed for determination of DLTs. See Section 5.8.2 for determination of DLT and MTD for this trial**.**

All grade 3 or greater toxicities (expected and unexpected, regardless of attribution) will be reported to the UNMC/Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC).

Transplant related Adverse Experiences (AE's) or Serious Adverse Experiences (SAE's) will NOT be collected. However, all AE's and SAE's irrespective of attribution, when occurring after the start of Lenalidomide maintenance therapy. Will need to be reported to the UNMC/Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC).

Any subject withdrawn prior to completion of the planned therapy on this protocol will be followed at a minimum for 30 days following the last dose of the conditioning chemotherapy or Lenalidomide maintenance regardless of

disease progression or discontinuation of planned therapy. Adverse experiences will no longer be followed for this protocol if other disease related treatment is initiated within this 30 day timeframe.

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
Tel: (908) 673-9000

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

Expedited Reporting by Investigator to Celgene Corporation

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 and collaborating site investigator must inform Celgene Corporation in writing using a Celgene SAE Form or MEDWATCH 3500A Form (Appendix F) of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene Corporation by facsmile within 24 hours/1 business day. The initial report must be as complete as possible, including

details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s) if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene Corporation tracking number (RV-LYM-PI-0328) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene Corporation. A copy of the fax transmission confirmation of the SAE report sent to Celgene Corporation should be attached to the SAE and retained with the subject records.

It is the responsibility of the collaborating site investigator to submit the Celgene SAE Form or MEDWATCH 3500A Form to UNMC within 24 hours of his/her knowledge of the SAE: Attn –Research Project/Data Coordinator: FAX 402-559-5669, or email the UNMC Research Project/Data coordinator . The SAE information will be routed to the UNMC Principal Investigator who will further evaluate the SAE.

Report of Adverse Events to the Institutional Review Board

The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

Protocol amendments

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

Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. A decision will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol.

Non-emergency minor deviations from the protocol will be permitted with approval of the Principal Investigator.

Study Record Requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g.,

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

Investigator Reporting to the FDA

Serious adverse events (SAEs) that are **unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) by telephone or by fax. Fatal or life threatening SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 7 calendar days after awareness of the event. All other SAEs that meet the criteria for reporting to the FDA must be reported to the FDA within 15 calendar days after awareness of the event. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

Collaborating study sites should NOT report SAEs to the FDA. The SAEs will be submitted to FDA if the ***UNMC sponsor-investigator, Julie Vose, M.D.,*** determines 21CRF312.32 criteria are met.

Adverse event updates/IND safety reports

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

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

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Celgene Corporation and the IRB/EC, on file.

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

All internal serious adverse events (AE) must be reported to the IRB promptly through the electronic RSS system 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 IRB, no later than *24 hours* through the electronic RSS system 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 through the electronic RSS system no later than ten (10) business days following PI notification that the event occurred.

The RSS system is accessed through a link on the UNMC IRB website (http://unmc.edu/irb).

Data and Safety Monitoring Plan

All grade 3 or greater toxicities (expected and unexpected, regardless of attribution) will be reported to the UNMC/Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC) in accordance with DSMC guidelines. Transplant related Adverse Experiences (AE's) or Serious Adverse Experiences (SAE's) will NOT be collected. However, all AE's and SAE's irrespective of attribution, when occurring after the start of Lenalidomide maintenance therapy, will need to be reported to the UNMC/Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC).

The investigator will assign a causal relationship for all reportable AE's, using the terminology of probably related (AE has strong temporal relationship to study drug or recurs on re-challenge, another etiology is unlikely or significantly less likely), possibly related (AE has strong temporal relationship to study drug, alternative etiology is equally or less likely), probably not related (AE has little or no temporal relationship to study drug and/or a more likely etiology exists), or not related (AE related to underlying or concurrent illness).

AEs will be collected from the time the subject starts Lenalidomide maintenance therapy and ending 4 weeks following the final Lenalidomide maintenance therapy. 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 4 weeks after the final chemotherapy.

Severity 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.

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

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

Unlikely 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.

Copies of the AE report will be submitted to the IRB (when required), the Fred & Pamela Buffett Cancer Center's Data Safety and Monitoring Committee and the Fred & Pamela Buffett Cancer Center Clinical Trials Office.

It is the responsibility of the sponsor-investigator to submit to the FDA IND Safety Reports in accordance with 21 CFR 312.32. In addition the sponsor-investigator must notify the Ethics Review Committee/Institutional Review Board (EC/IRB) of a serious adverse event in writing in accordance with international and local laws and regulations. SAEs not meeting expedited criteria will be made available to FDA by the sponsor-investigator via the annual report.

Monitoring: 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 all collaborating sites.

All adverse events and toxicity reporting for all subjects at all collaborating sites will be reported to the UNMC Fred & Pamela Buffett Cancer Center Data and Safety Monitoring Committee (DSMC). The DSMC will also monitor the protocol according to their evaluation of level of risk to subjects during regularly scheduled DSMC review processing and by request; the DSMC will be notified whenever a change in protocol dose is made (e.g., no DLT's experienced at level 1; dose increased to dose level 2). Approved/applicable UNMC multi-site policies will be adhered to.

The Principal Investigator will inform the DSMC when a dose escalation takes place or when the maximum tolerated dose level has been reached using the DSMC approved form. Celgene Corporation will simultaneously be provided a copy of the DSMC notification.

10.0 Statistical Considerations

10.1 Primary Objective

To establish the MTD of lenalidomide given in the post-transplant setting for a 12 month maintenance period.

10.2 Secondary Objectives

To obtain preliminary estimates of the 1-year response rate, event-free and overall survival using this regimen.

10.3 Sample Size

Phase I 3 +3 Sample Size Design

The number of subjects enrolled in this study will vary depending on the dose escalation results. The Maximum Tolerated Dose (MTD) is defined to be the dose cohort below which 3 out of 6 subjects experience dose limiting toxicities or the highest dose cohort of 25 mg, if 2 dose limiting toxicities are not observed at any dose cohort. The maximum number of subjects for the Phase I portion is 24. Three subjects will be enrolled at the initial dose level. If two of three subjects in Dose Cohort #1 have a dose-limiting toxicity, three additional subjects will be added to that dose level. If 3 of these 6 subjects experience a dose limiting toxicity as defined as grade $\geq$ 4 Hematologic or $\geq$ grade 3 non-hematologic toxicity on the NCI Common Toxicity Criteria (version 4.0, see http://evs.nci.nih.gov/ftp1/CTCAE/About.html or APPENDIX E) no further dose escalation will take place. If two of three subjects in Dose Cohort #2-#4 have a dose-limiting toxicity, three additional subjects will be added to that dose cohort. If 2 of these 6 subjects experience a dose limiting toxicity as defined as grade $\geq$ 4 Hematologic or $\geq$ grade 3 non-hematologic toxicity on the NCI Common Toxicity Criteria (version 4.0, see

http://evs.nci.nih.gov/ftp1/CTCAE/About.html or APPENDIX E) no further dose escalation will occur.

Phase II Sample Size Design
Due to the high dropout rate of subjects and the counting of consented never treated subjects, up to 114 subjects will be enrolled to achieve the 16 evaluable at the 10 mg dose level to estimate the 1 year event-free and overall survival. We will also estimate the response rate at one year. Time point of 1 year is chosen since the regimen to be evaluated is one that is designed for maintenance treatment. A sample of n=16 will provide a maximum width estimate of the 95% confidence interval at ±0.225. The 1-y event-free survival estimate will be used to calculate sample requirements in future studies

10.4 Stopping Rules
During the Phase I portion of the protocol, the safety stopping rules are defined by the dose escalation plan. An interim report for excessive toxicity after 3 subjects have completed 1 **month** of maintenance therapy at the dose level that is determined to be the MTD during the Phase I part of the trial will be performed. Enrollment will continue during that time as Lenalidomide has been used extensively in subjects with multiple myeloma as maintenance in the post-transplant setting and has been found to be safe.

Analysis of treatment-related mortality (TRM) at 90 days post initiation of treatment after accrual of 10 additional subjects will be performed. If 1 of the first 10 (e.g. 5%) subjects experiences mortality due to the addition of the lenalidomide, the protocol will close. If the death is related to other transplant related causes or progressive disease, accrual to the study will continue.

10.5 Evaluable Subject
Subjects are considered evaluable for DLT after they receive the first dose of chemotherapy. Subjects evaluable for the secondary endpoints (Phase II) are those who complete 12 cycles of treatment or have developed disease progression during time of study.

10.6 Analysis of Secondary Endpoints
The complete response rate at 1 year will be estimated as the proportion of subjects who achieve a CR divided by the number of evaluable subjects. The overall response rate will be estimated as the proportions of subjects who achieve a CR or PR divided by the number of evaluable subjects. Each will be reported with their associated 95% confidence interval.

The Kaplan-Meier method will be used to estimate the event-free and overall survival distributions. Disease progression or death will be considered events of interest for event-free survival. We will also describe the gene expression

profile of the different tissues, as well as studies on the microenvironment and immunomodulatory effects or changes over time post-lenalidomide using descriptive statistics. When sample distribution allows, we will explore the correlation between biomarkers tested and response to Lenalidomide in able to assess if there are biomarkers that can predict subjects with better outcome of likely to stay in remission using Chi-square test.

11.0 Records to be Kept

The research data will be stored in the data managers work area and files. The data will be secured behind locked doors during non-business hours. The subjects' data information will be kept confidential and only number identifiers will be used. Only the principal investigator, the subjects' primary physician, the research study coordinator, Celgene Corporation or their designee, UNMC/Fred & Pamela Buffett Cancer Center Scientific Review Committee, the UNMC/NHS IRB, and the Food and Drug Administration will have access to this information.

Information regarding the actual treatments, adverse effects, radiographic and laboratory information, and pathology are to be recorded on appropriate forms. See attached Data forms. 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 subject 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 subject 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).

12.0 Subject Consent

The subject and their family will be placed in a consult room in the outpatient cancer center for their discussion of the protocol. The study, risk/benefit ratio, side effects and possible outcomes are discussed with the subject by the primary investigator or the subject's primary oncologist. The consent form is reviewed in detail by the physician with the subject. The subject and family are given the opportunity to ask questions at this time. In addition, the subject is given the informed consent form to take with them and read in detail at their leisure. They are seen back in a day or so to once again ask questions and to sign the informed consent form.

When the process of informed consent has been completed, the subject will be asked to state in his/her own words all elements of the consent and protocol including, but not limited to, the purpose of the study, the procedures which will be carried out, the potential risks, the potential benefits to him/her, the alternatives and the right to withdraw from the study. If there is any indication that a given subjects' comprehension of the study is anything less than accurate, the points of confusion will be discussed and clarified. The subject will then be asked to explain these same points in his/her own words.

No information will be purposely withheld from the subjects. The consent form used in this study will include the adult consent form.

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Data Forms
See 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 necessary. Active supportive treatment necessary
10	Moribund
0	Dead

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

Appendix B:

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

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the 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.

† 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).

Prophylactic antibiotics should be considered particularly in subjects with neutropenia.

Pregnancy testing

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.

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 lenalidomideuntil 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.

Appendix C:

NEW YORK HEART ASSOCIATION HEART DISEASE CLASSIFICATION

Class	Definition
I.	No limitation of physical activity. Ordinary physical activity does not cause undue fatigue, or dyspnea.
II.	Slight limitation of physical activity. Comfortable at rest, but ordinary physical activity results in fatigue, or dyspnea.
III.	Marked limitation of physical activity. Comfortable at rest, but less than ordinary activity causes fatigue, or dyspnea.
IV.	Unable to carry on any physical activity without symptoms. Symptoms are present even at rest. If any physical activity is undertaken, symptoms are increased.

Appendix D: RESPONSE CRITERIA

Response criteria (listed below) are the recommendations of the International Harmonization Project's update to the International Working Group guidelines.

PET using [18F]fluorodeoxyglucose (FDG), has emerged as a powerful functional imaging tool for staging, restaging, and response assessment of lymphomas. The advantage of PET over conventional imaging techniques such as computed tomography (CT) or magnetic resonance imaging is its ability to distinguish between viable tumor and necrosis or fibrosis in residual mass (es) often present after treatment.

Complete Response (CR) The designation of CR requires the following (Table 1):
1. Complete disappearance of all detectable clinical evidence of disease and disease-related symptoms if present before therapy.
2a. Typically FDG-avid lymphoma: in subjects with no pretreatment PET scan or when the PET scan was positive before therapy, a post-treatment residual mass of any size is permitted as long as it is PET negative.
2b. Variably FDG-avid lymphomas/FDG avidity unknown: in subjects without a pretreatment PET scan, or if a pretreatment PET scan was negative, all lymph nodes and nodal masses must have regressed on CT to normal size ($\leq$1.5 cm in their greatest transverse diameter for nodes > 1.5 cm before therapy). Previously involved nodes that were 1.1 to 1.5 cm in their long axis and more than 1.0 cm in their short axis before treatment must have decreased to$\leq$1.0cm in their short axis after treatment.
3. The spleen and/or liver, if considered enlarged before therapy on the basis of a physical examination or CT scan, should not be palpable on physical examination and should be considered normal size by imaging studies, and nodules related to lymphoma should disappear. However, determination of splenic involvement is not always reliable because a spleen considered normal in size may still contain lymphoma, whereas an enlarged spleen may reflect variations in anatomy, blood volume, the use of hematopoietic growth factors, or causes other than lymphoma.
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 subject outcome.

Partial Response (PR) The designation of PR requires all of the following:
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; and they should include mediastinal and retroperitoneal areas of disease whenever these sites are involved.
2. No increase should be observed in the size of other nodes, liver, or spleen.
3. Splenic and hepatic nodules must regress by $\geq$50% in their SPD or, for single nodules, in the greatest transverse diameter.
4. With the exception of splenic and hepatic nodules, involvement of other organs is usually assessable and no measurable disease should be present.
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 (e.g., large-cell lymphoma or small neoplastic B cells). Subjects 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, subjects should be considered partial responders.
6. No new sites of disease should be observed.
7. Typically FDG-avid lymphoma: for subjects with no pretreatment PET scan or if the PET scan was positive before therapy, the post-treatment PET should be positive in at least one previously involved site.
8. Variably FDG-avid lymphomas/FDG-avidity unknown: for subjects without a pretreatment PET scan, or if a pretreatment PET scan was negative, CT criteria should be used. In subjects with follicular lymphoma or mantle-cell lymphoma, a PET scan is only indicated with one or at most two residual masses that have regressed by more than 50% on CT; those with more than two residual lesions are unlikely to be PET negative and should be considered partial responders.

Stable Disease (SD) Stable disease is defined as the following:
1. A subject is considered to have SD when he or she fails to attain the criteria needed for a CR or PR, but does not fulfill those for progressive disease (see Relapsed Disease [after CR]/Progressive Disease [after PR, SD]).
2. Typically FGD-avid lymphomas: the PET should be positive at prior sites of disease with no new areas of involvement on the post treatment CT or PET.
3. Variably FDG-avid lymphomas/FDG-avidity unknown: for subjects without a pretreatment PET scan or if the pretreatment PET was negative, there must be no change in the size of the previous lesions on the post-treatment CT scan.

Relapsed Disease (RD) ***(after CR)/Progressive Disease (after PR, SD)***
1. 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 $\leq$1.0 x$\leq$ 1.0 cm will not be considered as abnormal for relapse or progressive disease.
2. 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 subjects with no prior history of pulmonary lymphoma, new lung nodules identified by CT are mostly benign. Thus, a therapeutic decision should not be made solely on the basis of the PET without histologic confirmation.
3.. 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 (e.g., splenic or hepatic nodules). To be considered progressive disease, a lymph node with a diameter of the short axis of less than 1.0cm must increase by $\geq$ 50% and to a size of 1.5 x 1.5 cm or more than 1.5 cm in the long axis.
4. At least a 50% increase in the longest diameter of any single previously identified node more than 1 cm in its short axis.
5. Lesions should be PET positive if observed in a typical FDG avid lymphoma or the lesion was PET positive before therapy unless the lesion is too small to be detected with current PET systems (< 1.5 cm in its long axis by CT). 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 (e.g., pleural effusions,

bone lesions) will be recorded as present or absent only, unless, while an abnormality is still noted by imaging studies or physical examination, it is found to be histologically negative. In clinical trials where PET is unavailable to the vast majority of participants, or where PET is not deemed necessary or appropriate for use (eg, a trial in subjects with MALT lymphoma), response should be assessed as above, but only using CT scans. However, residual masses should not be assigned CRu status, but should be considered partial responses.

Table 1. Response Definitions for Clinical Trials

Response	Definition	Nodal Masses	Spleen, Liver	Bone Marrow
CR	Disappearance of all evidence of disease	(a) FDG-avid or PET positive prior to therapy; mass of any size permitted if PET negative (b) Variably FDG-avid or PET negative; regression to normal size on CT	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 (a) FDG-avid or PET positive prior to therapy; one or more PET positive at previously involved site (b) Variably FDG-avid or PET negative; regression on CT	≥ 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	(a) FDG-avid or PET positive prior to therapy; PET positive at prior sites of disease and no new sites on CT or PET (b) Variably FDG-avid or PET negative; no change in size of previous lesions on CT		

Relapsed disease or PD	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 in SPD of more than one node, or ≥50% increase in longest diameter of a previously identified node > 1 cm in short axis Lesions PET positive if FDG-avid lymphoma or PET positive prior to therapy	≥ 50% increase from nadir in the SPD of any previous lesions	New or recurrent involvement
Abbreviations: CR, complete remission; FDG, [18F] 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.				

Cheson BD, Pfistner B, Juweid ME, Gascoyne RD,Specht L, Horning SJ, et al. Revised Resonse Criteria for Malignant Lymphoma. J Clin Oncol 2007; 25: 579-586.

Appendix E: NCI Common Toxicity Criteria Version 4.0 (CTCAE)
Active Date: October 1, 2009

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage: (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version 4.0.

Appendix F: FDA 3500A MEDWATCH Form

Available on-line at http://www.fda.gov/medwatch/SAFETY/3500.pdf

Appendix G: 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):

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

Cockcroft-Gault estimation of creatinine clearance (CrCl): (Cockcroft, 1976; Luke 1990)

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

$$\text{CrCl (ml/min)} = \frac{(140\text{-age}) \times (\text{actual wt in kg}) \times 0.85}{72 \times (\text{serum creatinine, mg/dL})} \quad (\textbf{Females})$$

Note: In markedly obese subjects, the Cockroft-Gault formula will tend to overestimate the creatinine clearance. (Adipose tissue tends to contribute little creatinine requiring renal clearance.)

Appendix H – ELIGIBILITY CHECKLIST
NCI/DCTC/CTMS CASE REPORT FORM

Phase I/II Study of Lenalidomide Maintenance Following BEAM (+/- Rituximab) for Chemo-Resistant or High Risk Non-Hodgkin's Lymphoma

Date Completed: (dy/mth/yr)	Protocol #: 446-08	Institution:	Subject ID:
Checklist #: v4.7	Effective Date		Waiver #:

Eligibility Checklist	Yes	No	N/A
1. Persistent, or relapsed non-Hodgkin's lymphoma (NHL) (any histology) that is chemo-resistant (< a PR), subjects who have received ≥3 prior chemotherapy regimens, or subjects with lymphomas that have a high relapse rate following autologous or syngeneic stem cell transplantation (transformed NHL, peripheral T-cell lymphoma (PTCL), mantle cell lymphoma, ALK-negative anaplastic large cell lymphoma (ALCL, alk neg), intermediate IPI or high risk IPI or subjects with a positive PET scan prior to transplant, and otherwise eligible for transplantation with adequate end-organ function.	[ ]	[ ]	1.
2. Subjects that relapse within one year of diagnosis.	[ ]	[ ]	2.
3. Able to collect ≥ 1.5 X 10^6 CD34+/kg cell for transplantation.	[ ]	[ ]	3.
4. ANC ≥ 1000 cells/mm^3 and Platelet Count ≥ 60K when maintenance Lenalidomide is started; as close as feasible to day 100 post-transplant.	[ ]	[ ]	4.
5. Age ≥19 years.	[ ]	[ ]	5.
6. Subjects 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, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care.	[ ]	[ ]	6.
7. Able to adhere to the study visit schedule and other protocol requirements.	[ ]	[ ]	7.
8. Expected survival duration of ≥ six months.	[ ]	[ ]	8.
9. Karnofsky Performance Status ≥ 70. (Appendix A)	[ ]	[ ]	9.
10. Subjects > age 60 or with clinical signs of heart disease must have ejection fraction ≥ 45% LVEF pre-transplant.	[ ]	[ ]	10.
11. Subjects with clinical signs of pulmonary insufficiency must have DLCO to be measured at ≥ 50% of predicted value prior to transplant.	[ ]	[ ]	11.
			.

Appendix H ELIGIBILITY CHECKLIST

NCI/DCTC/CTMS CASE REPORT FORM

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Date Completed: (dy/mth/yr)	Protocol #: 446-08	Institution:	Subject ID:
Checklist #: v4.7	Effective Date		Waiver #:

12 No serious disease or condition that, in the opinion of the investigator, would compromise the subject's ability to participate in the study.	[ ] [ ]12.
13 Disease free of prior malignancies for ≥ 2 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "insitu" of the cervix or breast or low risk prostate cancer after curative therapy.	[ ] [ ]13.
14 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.	[ ] [ ]14.
15 Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of prescribing lenalidomide (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix B Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.	[ ] [ ]15.
16 Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (subjects intolerant to ASA may use warfarin or low molecular weight heparin).	[ ] [ ]16.
17 Male subject agrees to use an acceptable method for contraception for the duration of the study.	[ ] [ ]17.
† 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).	

Appendix H- ELIGIBILITY CHECKLIST

NCI/DCTC/CTMS CASE REPORT FORM

Phase I/II Study of Lenalidomide Maintenance Following BEAM (+/- Rituximab) for Chemo-Resistant or High Risk Non-Hodgkin's Lymphoma

Date Completed: (dy/mth/yr)	Protocol #: 446-08	Institution:	Subject ID:
Checklist #: v4.7	Effective Date		Waiver #:

*All of the above must be **yes** to be eligible.*	
1. Chemosensitive NHL, except subjects receiving ≥ 3 prior chemotherapy regimens, or subjects having transformed NHL, PTCL, MCL, or ALCL, alk neg.	[ ] [ ]1.
2. End-organ function not appropriate for transplantation.	[ ] [ ]2.
3. Inability to collect adequate stem cells.	[ ] [ ]3.
4. Known positive for HIV or infectious hepatitis, type A, B or C or active Hepatitis.	[ ] [ ]4.
5. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.	[ ] [ ]5.
6. Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking lenalidomide).	[ ] [ ]6.
7. Known hypersensitivity to thalidomide.	[ ] [ ]7.
8. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.	[ ] [ ]8.
9. Any prior use of lenalidomide.	[ ] [ ]9
10. Concurrent use of other anti-cancer agents or treatments.	[ ] [ ]10.
11. Serum creatinine >2.0mg/dL or calculated creatinine clearance <_30ml/min.	[ ] [ ]11.
12. Active infection at the start of Lenalidomide.	[ ] [ ]12.
13. Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. (Appendix C) Prior to study entry, any ECG abnormality at Screening has to be documented by the investigator as not medically relevant.	[ ] [ ]13.
14. History of life threatening or recurrent thrombosis/embolism. Subjects may participate if they are adequately anticoagulated during the treatment.	[ ] [ ]14.
15. Subject has >Grade 2 peripheral neuropathy within 14 days before enrollment.	[ ] [ ]15.
*All of the above must be **no** to be eligible.*	

Appendix H- ELIGIBILITY CHECKLIST

NCI/DCTC/CTMS CASE REPORT FORM

Phase I/II Study of Lenalidomide Maintenance Following BEAM (+/- Rituximab) for Chemo-Resistant or High Risk Non-Hodgkin's Lymphoma

Date Completed: (dy/mth/yr)	Protocol #: 446-08	Institution:	Subject ID:
Checklist #: v4.7	Effective Date		Waiver #:

Eligibility: [ ] Subject satisfies all criteria.
[ ] Subject not formally eligible, but admitted to study because (state reason);

Subject Initials: _____MR or Study ID#_____DOB _____

ELIGIBILITY reviewed and confirmed
Site Investigator Signature _____Date_____

Date Completed: (dy/mth/yr)	Protocol #: **VOSE 446-08**	Institution:	Subject ID:

Appendix I:
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. Subjectss 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) *EXAMPLE Month*

~ September 2013 ~						
Sun	**Mon**	**Tue**	**Wed**	**Thu**	**Fri**	**Sat**
1	**2** Revlimid® at: _____AM / PM	**3** Revlimid® at: _____AM / PM	**4** Revlimid® at: _____AM / PM	**5** Revlimid® at: _____AM / PM	**6** Revlimid® at: _____AM / PM	**7** Revlimid® at: _____AM / PM
8 Revlimid® at: _____AM / PM	**9** Revlimid® at: _____AM / PM	**10** Revlimid® at: _____AM / PM	**11** Revlimid® at: _____AM / PM	**12** Revlimid® at: _____AM / PM	**13** Revlimid® at: _____AM / PM	**14** Revlimid® at: _____AM / PM
15 Revlimid® at: _____AM / PM	**16** Revlimid® at: _____AM / PM	**17** Revlimid® at: _____AM / PM	**18** Revlimid® at: _____AM / PM	**19** Revlimid® at: _____AM / PM	**20** Revlimid® at: _____AM / PM	**21** Revlimid® at: _____AM / PM
22 Revlimid® at: _____AM / PM						
		Notes:				

Appendix J:

Blood and Tissue Sample Processing and Shipping for Cytokine Level Studies

(For research purposes only, to study factors that influences a subject's response to a particular drug.)

Description of Sample Collection: The proposed **Cytokine Levels** will be tested in the subject's existing lymphoma specimen. Tissue samples for immunostaining from either a baseline diagnostic or relapsed biopsy in either frozen or paraffin embedded tissue will be retrieved from all subjects and sent to the laboratory of Kai Fu, MD, PhD (a.k.a. Dr. Chan's lab) at UNMC.

Research blood specimens VEGF and cytokines will be obtained at baseline, 6 months and 1 year post transplant (or at the end of taking lenalidomide if before these time points) and sent to the laboratory of Rakesh Singh, PhD at UNMC.

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
Laboratory of Kai Fu, MD, PhD, Professor, Pathology/Microbiology, Director, Hematology Fellowship Program, Co-Director, Center for Lymphoma and Leukemia Research University of Nebraska Medical Center	Tissue samples from either a baseline diagnostic or relapsed biopsy in either frozen or paraffin embedded tissue	**Xuan Zhan and Chengfeng Bi** Dr. Kai Fu's Lab Lied Bldg 11th Floor, Rm 11711 Phone# 402-559-7753 **Shipping Address:** Department of Pathology UMA Bldg, Rm 3528, Zip 3135 University of Nebraska Medical Center 668 S. 41st Street Omaha, NE 68105 Phone# 402-559-7689 Fax# 402-559-6018	Baseline Tissue date: ___/___/____ Check one: ☐ Diagnostic or ☐ Relapsed biopsy Check one: ☐ Frozen or ☐ Paraffin embedded
Laboratory of Rakesh Singh, PhD, Professor, Department of Pathology/ Microbiology University of Nebraska Medical Center	Research blood specimen for VEGF and cytokines. Two (2) -10ml NA Heparin green top tubes and one (1) 10 ml no additive red top at baseline, 6 months and 1 year post transplant(or at the	**Michelle Varney** Dr. Rakesh Singh's Lab DRC2 Bldg, Rm 7072 phone 402-559-5580 **Shipping Address:** Michelle Varney DRC2 Bldg, Rm 70, Zip 5900	Samples will need immediate handling in a research laboratory to evaluate the changes in the levels of various cytokines. Ship all specimens the day of collection. Please contact Michelle Varney to

	end of taking lenalidomide if before these time points).	University of Nebraska Medical Center 668 S. 41st Street Omaha, NE 68105 ATTENTION: Dr. Rakesh Singh's Phone# 402-559-5580	advise of planned shipments. Whole blood tubes should be shipped with cold packs that are cold, but not frozen. Check one: ☐ Baseline Sample: Date: _____ Time: _____ ☐ Other Time Point: Date: _____ Time: _____

Research Nurse: Mary Mailliard, RN, BSN, OCN Office (402) 559-5582 pager (402) 888-2123 Fax (402) 559-8895

Appendix K:
International Prognostic Index

PURPOSE

The **International Prognostic Index (IPI)** is a clinical tool developed by oncologists to aid in predicting the prognosis of subjects with aggressive non-Hodgkin's lymphoma.

CATEGORIES

International Prognostic Index

One point is assigned for each of the following risk factors:

- Age greater than 60 years
- Stage III or IV disease
- Elevated serum LDH (Lactic Acid Dehydrogenase)
- ECOG/Zubrod performance status of 2, 3, or 4
- More than 1 extranodal site

The sum of the points allotted correlates with the following risk groups:

- Low risk (0-1 points) - 5-year survival of 73%
- Low-intermediate risk (2 points) - 5-year survival of 51%
- High-intermediate risk (3 points) - 5-year survival of 43%
- High risk (4-5 points) - 5-year survival of 26%

Age-Adjusted IPI

A simplified index can be used when comparing subjects within an age group (i.e. 60 or younger, or over 60) and includes only 3 of the above factors:

- Stage
- LDH (Lactic Acid Dehydrogenase)
- Performance status

The sum of the points allotted correlates with the following risk groups:

- Low risk (0 points) - 5-year survival of 83%
- Low-intermediate risk (1 point) - 5-year survival of 69%
- High-intermediate risk (2 points) - 5-year survival of 46%
- High risk (3 points) - 5-year survival of 32%

Although the IPI has shown itself to be a useful clinical tool, widely used by oncologists and a mainstay of risk stratification in clinical trials for lymphoma, it should be kept in mind that it was developed prior to the use of rituximab, which is now included with anthracycline-based combination chemotherapy as of the standard of care in B-cell lymphomas (the majority of non-Hodgkin's lymphomas). Rituximab has dramatically improved the outcomes of lymphoma subjects, and its effect on the prognostic value of the IPI is uncertain.