Protocol Title: Nonmyeloablative Stem Cell Transplantation with or without Lenalidomide for Chronic Lymphocytic Leukemia (RV-CLL-PI-0294)

STUDY DRUG	**Revlimid®** **(lenalidomide)**
MD Anderson Protocol NUMBER:	**2007-0871**
Celgene Tracking Number:	**RV-PI-CLL-0294**

STUDY PERSONNEL

Supporter: **Celgene Corporation**
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Protocol Synopsis

PROTOCOL TITLE: Non-Myeloablative Transplantation with or without Lenalidomide maintenance for CLL

PROTOCOL NUMBER:	2007-0871
STUDY DRUG SUPPLIES: For study participants, Celgene Corporation will provide lenalidomide at no charge through the RevAssist® program.	Revlimid®, lenalidomide
INDICATION:	CLL/Maintenance
STUDY PHASE:	Phase II

Introduction:

The clinical efficacy of lenalidomide in patients with relapsed or refractory CLL has now been confirmed in two independent clinical trials. Investigators conducted a phase II study at Roswell Park Cancer Institute (Buffalo, NY), in CLL patients progressing, or refractory to at least one prior therapy administering lenalidomide for 21 days of a 28-day cycle. Among the first 29 patients, the starting dose of lenalidomide was 25 mg/d, whereas the subsequent 16 patients started lenalidomide at 10 mg/d and the dose at 5 mg every 2 weeks as tolerated to a maximum of 25 mg/d. Forty-five patients with a median of four (range, one to 10) prior therapies were enrolled, 64% with Rai stage III/IV, 51% were fludarabine refractory, and 29% had Zap-70+ cells. In another phase II study, Ferrajoli et al used a starting dose of 10 mg every day followed by a dose escalation of 5 mg every 28 days to a maximum of 25 mg/d to treat 44 patients with a median of 5 prior therapies, a median β2 microglobulin level of 4.3 mg/dL (range, 1.6 to 10.1 mg/dL), advanced Rai stage in 45%, fludarabine refractory in 27%, and prior alemtuzumab in 51%.

The overall response in the Roswell Park study was 57.5% with a complete response rate of 18%.The median time to best response was 5.9 months (range, 1.6 to 18.3 months) with a median progression-free survival of 19.4 months (range, 1.2 to 38 months). Complete responses observed in this study were associated with undetectable minimal residual disease by flow cytometry and polymerase chain reaction for immunoglobulin heavy chain gene. The overall response in the M.D. Anderson study was 32% with a 7% complete response rate. With a median follow-up of 11 months, the median duration of response was 12 months.

Notably, clinical responses were observed even in patients with high-risk cytogenetics, Zap-70 patients or those were fludarabine refractory. Additionally, patients in the Roswell Park study who developed disease progression while on lenalidomide responded when rituximab was added to lenalidomide (ORR71%), suggesting additive benefit.

Correlative investigations were conducted on pretreatment primary tumor cells to study the effect of lenalidomide on the tumor cell as well as its micro-environment. It was observed that exposure to lenalidomide failed to induce a direct proapoptotic effect on these CLL cells in vitro despite an obvious antileukemic effect in corresponding patients. Nevertheless, treatment with lenalidomide resulted in modulation of the CLL cell phenotype with upregulation of costimulatory mlecules (including CD80, CD86, and CD40). This change in surface expression of costimulatory molecules concurrently with increase in circulatory NK cells may explain the immediate immune recognition phenomenon clinically presenting as the flare reaction that is associated with antileukemic effects in vivo.

The most common toxicity reported in the Roswell Park study was grade 1/2 fatigue (73%). The

incidence of grade 3/4 neutropenia and thrombocytopenia was 70% and 45%, respectively, with only 15% of patients developing neutropenic infections. In the University of Texas M.D. Anderson Cancer Center experience, the incidence of grade 3/4 neutropenia and thrombocytopenia was 39% and 15%, respectively, in 325 courses of treatment. The incidence of fatigue was 1%. Differences in toxicity between studies may reflect the lower starting dose of lenalidomide in the latter study.

Allogeneic stem-cell transplantation after myeloablative conditioning is an effective therapy for relapsed chronic lymphocytic leukemia (CLL). The treatment-related mortality has been significant, however, with a 30-40% risk of death within 100 days of the transplant. Allogeneic transplantation can confer an immune mediated graft-versus-malignancy effect. This has stimulated the development of reduced dose, non-myeloablative conditioning regimens, which support allogeneic donor cell engraftment and allow graft-versus-leukemia effect to occur.

Nonmyeloablative allogeneic transplantation is an effective therapy for patients with CLL who have failed conventional chemotherapy, and or who have high risk features or had Richter's transformation. We have used successfully a conditioning fludarabine, cyclophosphamide, and rituximab (FCR) as conditioning regimen. However, about 50% of patients with refractory disease at study entry require early immunosuppression withdrawal after transplantation and donor lymphocyte infusion, due to either persistent or progressive disease. This is a significant cause of mortality and morbidity. Maintenance with lenalidomide after transplant may decrease both the need for immunomanipultation and the risk of graft-versus-host disease.

Starting with patients enrolled in 2011, a conditioning fludarabine, bendamustine (130 mg/m^2/dayx3), and rituximab (FBR) as conditioning regimen has been developed in our Department (protocol 2008-0246), Bendamustine is proven to be effective in patients with CLL. With the FBR conditioning, 56% of patients did not nadir to an ANC<500 and 81% did not reach a platelet count of <20,000. An important detail that has thus far precluded randomization in 50% of patients after FCR. In addition, the FBR regimen has been well tolerated and is now given as outpatient.

STUDY OBJECTIVES:

Primary:

To compare the need for immunomanipulation within 18 months after non-myeloablative allogeneic transplantation for CLL between the two combination therapies with or without lenalidomide maintenance. For this purpose, "immunomanipulation" is defined as any one of the following events:

1) Cessation of administering tacrolimus treatment within the first 6 months after allotransplant due to persistent disease or progression.

2) Boost of donor lymphocytic infusion (DLI) administered anytime between 3 and 18 months after allotransplant.

Secondary:

To evaluate:

1) time to treatment failure
2) time to molecular remission
3) safety profile of the combination therapies
4) acute and chronic graft-vs-host disease rates and
5) percentage of blood donor cell after transplant in the recipient.

STUDY DESIGN:

This randomized phase II trial compared FCR, and Thymoglobulin plus lenalidomide (FCR+ L) to FCR, and Thymoglobulin (FCR) in patients with CLL undergoing allotransplant on 25 patients enrolled from May 13, 2009 to December 2, 2010.

Starting with patients enrolled in 2011, this randomized phase II trial will compare FBR, (and Thymoglobulin, if unrelated donor) plus lenalidomide (FBR+ L) to FBR, (and Thymoglobulin, if unrelated donor)(FBR) in patients with CLL undergoing allotransplant.

The primary objective is to compare the need for immunomanipulation between the treatment groups. For this trial, immunomanipulation is defined as either the cessation of the administration of immunosuppression treatment within the first six months after allotransplant due to intolerability or the administration of DLI any time between 3 and 18 months after transplant.

Our primary outcome is the need for immunomanipulation by month 18. Our target enrollment is to have a maximum of 60 patients to be randomized, and we expect to enroll 3 patients per month. We will follow all patients for 18 months. We also expect that 20 additional patients may be initially enrolled to receive the transplantation, but later may not meet the criteria for maintenance randomization.

Based upon published data, we expect that 49% of the patients in the FCR arm will need immunomanipulation by 18 months. We do not expect this incidence to be different with FBR. We hope to see a reduction in this proportion in the FBR + L arm to 25%.

Patients who are not in CR following transplant will be randomized in a 1:1 ratio between FBR and FBR + L. Patients will be stratified by the presence or absence of del 17 by FISH by PB at any point in time during their disease history, and the number of prior therapies received (less or equal to 2 vs greater than 2). Prior therapies are defined by 1) combination chemotherapies, 2) chemo-antibodies, 3) biological agents. The trial will be stopped early and a treatment selected as being “better” if the probability is 0.95 or more that the probability of needing immunomanipulation on one treatment arm is greater than for the other arm. However, if all 60 patients are enrolled, then a treatment will be selected as being “better” if the probability is 0.90 or more that the probability of needing immunomanipulation for one treatment is greater than the other. Additional details are provided below in the section labeled “Technical Details”. The operating characteristics of this study design based upon 2000 simulations of this trial are summarized in Table 1 below.

We will report the posterior probability that the need for immunomanipulation in one arm is greater than the need for immunomanipulation in the other arm.

Table 1. Operating Characteristics of Study Design			
	Neither	FCR	FCR + L
True Rate of Need for Immunomanipulation	---	0.49	0.25
Pr(Selected)	19.7%	0	80.3%
True Rate of Need for Immunomanipulation	---	0.49	0.49
Pr(Selected)	81.8%	8.9%	9.3%
True Rate of Need for Immunomanipulation	---	0.25	0.25
Pr(Selected)	75.5%	3.8%	20.7%
True Rate of Need for Immunomanipulation	---	0.49	0.35
Pr(Selected)	53.5%	0.6%	45.9%
True Rate of Need for Immunomanipulation	---	0.60	0.35
Pr(Selected)	26.5%	0.2%	73.3%

Analyses of secondary endpoints include evaluation of:

1) time to treatment failure
2) time to molecular remission
3) safety profile of the combination therapies
4) acute and chronic graft-vs-host disease rates and
5) percentage of blood donor cell after transplant in the recipient.

Technical Details

Starting with patients enrolled in 2011: The two treatment arms will be denoted by **T** (FBR) and **TL** (FBR + L). Denote the probability that a patient needs immunomanipulation in each arm as θ_T and θ_{TL}, respectively. Assume that θ_T and θ_{TL} are independent and that $\theta_T \sim \text{Beta}(a_T,b_T)$ and that $\theta_{TL} \sim \text{Beta}(a_{TL},b_{TL})$. Here, (a_T,b_T) can be interpreted as the number of prior successes and failures, respectively, in arm T, and (a_{TL},b_{TL}) can be interpreted as the number of prior successes and failures in arm TL. The mean values of these distributions are $a_T/(a_T + b_T)$ and $a_{TL}/(a_{TL} + b_{TL})$

In a previous trial of FCR, 19 of 39 patients required immunomanipulation by 18 months. We expect the same incidence with FBR. We discount the information available by 75% and assume that $(a_T,b_T) = (4.9,5.1)$. We further assume that $(a_{TL},b_{TL}) = (0.98, 1.02)$, which has the same mean but a higher variance, reflecting that little information is available regarding the FBR + L arm.

During the trial, the posterior probability that the need for immunomanipulation rate is greater in arm T is represented by $p_T(\text{data}) = \Pr(\theta_T > \theta_{TL})$. Similarly, $p_{TL}(\text{data}) = 1 - p_T(\text{data})$. If at any point during the trial $p_{TL}(\text{data}) > 0.95$ (< 0.05) the trial will be terminated and treatment FBR + L will be selected as superior (inferior). If the maximum number of patients is enrolled in the trial and $p_{TL}(\text{data}) > 0.90$ (< 0.10) treatment T_L will be selected as superior (inferior).

Background and Rationale

Introduction

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.[1]. 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.[2] Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity. [3]

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 [4]. 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 patients resistant to melphalan, doxorubicin and dexamethasone [5].

Clinical experience in solid tumors with lenalidomide

Twenty patients 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 patient dose-escalation design, where patients 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 [6].

Investigators at the NCI have enrolled 20 patients, including 18 patients with recurrent high-grade gliomas and 2 with other refractory CNS malignancies (1 recurrent atypical meningioma and 1 multiple recurrent spinal hemangioblastomas) into a phase I trial of lenalidomide given on Days 1 through 21 every 28 days. Treatment has been well tolerated with 1 grade 2 myelosuppression as the only toxicity > grade 1 [7].

In an ongoing phase I trial in patients with refractory metastatic cancer conducted through the NCI, 12 patients with metastatic androgen independent prostate cancer have been enrolled. Lenalidomide was administered in daily doses of 5mg (3 patients), 10mg (3 patients) and 20mg (6 patients). Dose limiting toxicity was seen at 20mg/day (1 grade 3 thrombosis and 1 grade 3 hypotension). Stable PSA values for at least 8 weeks were observed in 6 patients [8].

In a phase III, multi-center, randomized parallel group study comparing two dose regimens of lenalidomide, 293 patients with malignant melanoma were enrolled. Subjects were randomized to receive treatment with lenalidomide at a dose of 5 mg per day orally for 28 days or to 25 mg per day orally for 21 days with a 7 day rest (28 day cycle). Treatment continued until the patient developed disease progression or intolerable adverse events occurred. Interim analysis failed to show an advantage of one regimen over the other with respect to survival. Analyses of response rates are pending. The toxicity profile was similar in both dose groups and the most frequent adverse events were fatigue, seen in 32% of patients, followed by nausea and diarrhea, seen in 24% and 20% of patients respectively. Neutropenia and thrombocytopenia were seen in 2.4% and 2.0% of patients respectively. Grade 3 and 4 toxicities were seen infrequently (<15%).

A second phase III randomized trial compared a lenalidomide dose of 25 mg daily orally for 21 days with a 7 day rest (28 day cycle) to placebo in patients with metastatic melanoma. Three hundred and five patients enrolled on this study and a preplanned interim analysis failed to demonstrate a survival advantage. Response rates are being analyzed. The toxicity profile was favorable and similar to the previous phase III study. [14]

Clinical experience in multiple myeloma with lenalidomide

In 2 phase I studies in multiple myeloma, a total of 41 patients have been treated with lenalidomide. In one study at the University of Arkansas, 15 patients 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. Patient cohorts were treated at the following daily doses: 5mg, 10mg, 25mg, and 50mg [(9)]. In a similar study at the Dana Farber Cancer Institute, 27 patients with rapidly advancing refractory multiple myeloma were enrolled [(10)].

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 patients 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 [(11)].

A multicenter, randomized, phase II trial compared 2 syncopated dose schedules of lenalidomide used alone or in combination with dexamethasone in the treatment of relapsed or refractory multiple myeloma. All patients were treated on Days 1-21 of a 28-day cycle. Patients treated with 15mg BID experienced more myelosuppression and dose reductions compared with patients treated with 30mg daily. Anti-myeloma activity was observed with each dose and schedule of single agent lenalidomide. The addition of dexamethasone to lenalidomide yielded responses in some patients who had not responded to lenalidomide alone [(12)].

A recent phase II trial utilizing lenalidomide plus dexamethasone for newly diagnosed multiple myeloma patients was recently 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 patients 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 patients not achieving an objective response, two had minor response (MR) and one stable disease. Forty-seven percent of patients experienced grade 3 or higher non-hematologic toxicity, most commonly fatigue (15%), muscle weakness (6%), anxiety (6%), pneumonitis (6%) and rash (6%). Lenalidomide®/dexamethasone is a highly active regimen with manageable side-effects in the treatment of newly diagnosed myeloma.

A phase I/II trial of liposomal doxorubicin (Doxil®), vincristine, dexamethasone (DVd) and lenalidomide in heavily pretreated relapsed/refractory multiple myeloma patients 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 patients 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 [(13)]. 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 patients with relapsed or refractory multiple myeloma [(14)]. More than 350 patients were enrolled into each of these studies.

All patients 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, patients 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 patients that have received at least one prior therapy.

Clinical experience in myelodysplastic syndromes (MDS) with lenalidomide

An exploratory trial in 43 MDS patients with transfusion dependent or symptomatic anemia was conducted at the University of Arizona [(15)]. Patients received lenalidomide at doses of 25mg or 10mg per day, or of 10mg on Days 1-21, repeated every 28 days. All patients 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 patients overall (56%) including 21 patients with a major response and 20 patients with sustained transfusion independence. Patients 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 patients with karyotypic abnormalities, 10 (50%) patients had a complete cytogenetic remission. The response rate was highest in patients 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 patients (58%).

Celgene Corporation sponsored a multicenter trial (MDS-003) of 148 MDS patients 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 patients, and at a dose of 10mg daily to the other 104 patients. Transfusion independence was achieved in 93 patients (64%), with a median hemoglobin increase of 3.9g/dl. Cytogenetic response was achieved in 76% of transfusion independent patients with 55% achieving a cytogenetic complete response. Pathologic complete response was documented in 32 out of 110 (29%) evaluable patients. 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.

Another Celgene sponsored trial (MDS-002) in patients with low to intermediate-1 risk MDS enrolled 215 patients, of whom, 166 were documented to have low to intermediate-1 risk MDS. Among the patients with documented low to intermediate-1 risk MDS, 84 patients (51%) responded to treatment. Transfusion independence was achieved in 54 patients (33%) and 30 patients (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 patients. Among 20 patients evaluable for cytogenetic response, 9 patients (45%) experienced a cytogenetic remission [(14)].

Clinical Experience in Chronic Lymphocytic Leukemia (CLL)

The clinical efficacy of lenalidomide in patients with relapsed or refractory CLL has now been confirmed in two independent clinical trials. Investigators conducted a phase II study at Roswell Park Cancer Institute (Buffalo, NY), in CLL patients progressing, or refractory to at least one prior therapy administering lenalidomide for 21 days of a 28-day cycle[16]. Among the first 29 patients, the starting dose of lenalidomide was 25 mg/d, whereas the subsequent 16 patients started lenalidomide at 10 mg/d and the dose at 5 mg every 2 weeks as tolerated to a maximum of 25 mg/d. Forty-five patients with a median of four (range, one to 10) prior therapies were enrolled,

64% with Rai stage III/IV, 51% were fludarabine refractory, and 29% had Zap-70+ cells. In another phase II study, Ferrajoli et al[17] used a starting dose of 10 mg every day followed by a dose escalation of 5 mg every 28 days to a maximum of 25 mg/d to treat 44 patients with a median of 5 prior therapies, a median β2 microglobulin level of 4.3 mg/dL (range, 1.6 to 10.1 mg/dL), advanced Rai stage in 45%, fludarabine refractory in 27%, and prior alemtuzumab in 51%.

The overall response in the Roswell Park study was 57.5% with a complete response rate of 18%.The median time to best response was 5.9 months (range, 1.6 to 18.3 months) with a median progression-free survival of 19.4 months (range, 1.2 to 38 months). Complete responses observed in this study were associated with undetectable minimal residual disease by flow cytometry and polymerase chain reaction for immunoglobulin heavy chain gene. The overall response in the M.D. Anderson study was 32% with a 7% complete response rate. With a median follow-up of 11 months, the median duration of response was 12 months.

Notably, clinical responses were observed even in patients with high-risk cytogenetics, Zap-70 patients or those were fludarabine refractory. Additionally, patients in the Roswell Park study who developed disease progression while on lenalidomide responded when rituximab was added to lenalidomide(ORR71%), suggesting additive benefit.

Correlative investigations were conducted on pretreatment primary tumor cells to study the effect of lenalidomide on the tumor cell as well as its micro-environment[18]. It was observed that exposure to lenalidomide failed to induce a direct proapoptotic effect on these CLL cells in vitro despite an obvious antileukemic effect in corresponding patients. Nevertheless, treatment with lenalidomide resulted in modulation of the CLL cell phenotype with upregulation of costimulatory mlecules (including CD80, CD86, and CD40). This change in surface expression of costimulatory molecules concurrently with increase in circulatory NK cells may explain the immediate immune recognition phenomenon clinically presenting as the flare reaction that is associated with antileukemic effects in vivo.

The most common toxicity reported in the Roswell Park study was grade 1/2 fatigue (73%). The incidence of grade 3/4 neutropenia and thrombocytopenia was 70% and 45%, respectively, with only 15% of patients developing neutropenic infections. In the University of Texas M.D. Anderson Cancer Center experience, the incidence of grade 3/4 neutropenia and thrombocytopenia was 39% and 15%, respectively, in 325 courses of treatment. The incidence of fatigue was 1%. Differences in toxicity between studies may reflect the lower starting dose of lenalidomide in the latter study.

Tumor flare reaction is an important adverse effect of lenalidomide observed uniquely in patients with CLL. It is characterized by the sudden onset of tender swelling of disease-involved lymph nodes with overlying inflammation of the skin, enlargement of liver and/or spleen, low-grade fever, rash, and, rarely, with a rise in the peripheral-blood white cell count. The median duration of the flare reaction in the Roswell Park study was 14 days, with most patients experiencing the flare only during the first cycle. In neither of the two studies was the flare reaction the cause of termination of therapy.

The incidence of flare reaction was significantly lower in the M.D. Anderson study. The differences between these studies may reflect disparities in patient populations (more heavily pretreated and prior treatment with alemtuzumab) or variation in starting dose (25 *v* 10 mg). In the Roswell Park experience, tumor flare correlated with clinical response; all but one patient who achieved a complete response had grade 3 or worse flare reaction. Ongoing studies will further clarify the importance of flare reaction. Although no deaths were attributed to tumor flare in either trial.

Rationale for Allogeneic Stem Cell Transplantation for CLL and Use of Lenalidomide

Allogeneic stem-cell transplantation after myeloablative conditioning is an effective therapy for relapsed chronic lymphocytic leukemia. The treatment-related mortality has been significant, however, with a 30-40% risk of death within 100 days of the transplant. Allogeneic

transplantation can confer an immune mediated graft-versus-malignancy effect. This has stimulated the development of reduced dose, non-myeloablative conditioning regimens, which support allogeneic donor cell engraftment and allow graft-versus-leukemia effect to occur[19,20].

Nonmyeloablative allogeneic transplantation is an effective therapy for patients with CLL who have failed conventional chemotherapy, and or who have high risk features or had Richter's transformation. We have used successfully a conditioning fludarabine, cyclophosphamide and rituximab as conditioning regimen[20.] However, about 50% of patients with refractory disease at study entry require early immunosuppression withdrawal after transplantation and donor lymphocyte infusion, due to either persistent or progressive disease. This is a significant cause of mortality and morbidity. Maintenance with lenalidomide after transplant may decrease both the need for immunomanipultation and the risk of graft-versus-host disease.

Starting with patients enrolled in 2011, a conditioning fludarabine, bendamustine (130 mg/m^2/dayx3), and rituximab (FBR) as conditioning regimen has been developed in our Department (protocol 2008-0246), Bendamustine is proven to be effective in patients with CLL. With the FBR conditioning, 56% of patients did not nadir to an ANC<500 and 81% did not reach a platelet count of <20,000. An important detail that has thus far precluded randomization in 50% of patients after FCR. In addition, the FBR regimen has been well tolerated and is now given as outpatient.

Indications and Usage:

Lenalidomide® (lenalidomide) is indicated for the treatment of patients 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. Lenalidomide® is also approved in combination with dexamethasone for the treatment of patients 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.

Lenalidomide may cause breakdown products of the cancer cells to enter the blood stream, which may lead to heart rate abnormalities, kidney failure, muscle twitching, and/or muscle cramps. Tumor flare reaction (TFR) has been reported frequently in CLL patients treated with lenalidomide. Tumor lysis syndrome (TLS) has been reported in CLL patients treated with lenalidomide. Precautions must be taken to prevent TLS including proper selection of patients with regard to renal function, correction of electrolyte abnormalities, and TLS prophylaxis and monitoring.

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

Study Objectives and Endpoints

Objectives

Primary objectives

- To compare the need for immunomanipulation within 18 months after non-myeloablative allogeneic transplantation for CLL between the two combination therapies with or without lenalidomide maintenance. For this purpose, “immunomanipulation” is defined as any one of the following events: 1) Cessation of administering tacrolimus treatment with in the first 6 months after allotransplant due to persistent disease or progression. 2) Boost of donor lymphocytic infusion (DLI) administered anytime between 3 and 18 months after allotransplant.

Secondary study objectives

- To evaluate 1) time to treatment failure; 2) time to molecular remission; 3) safety profile of the combination therapies; 4) acute and chronic graft-vs-host disease (GVHD) rates; and 5) percentage of blood donor cell after transplant in the recipient.

Endpoints

Primary Endpoint

- The primary endpoint is the need for immunomanipulation after non-myeloablative stem cell transplantation for CLL. The hypothesis is that lenalidomide will decrease the need for immunomanipulation, compared with the arm without it.

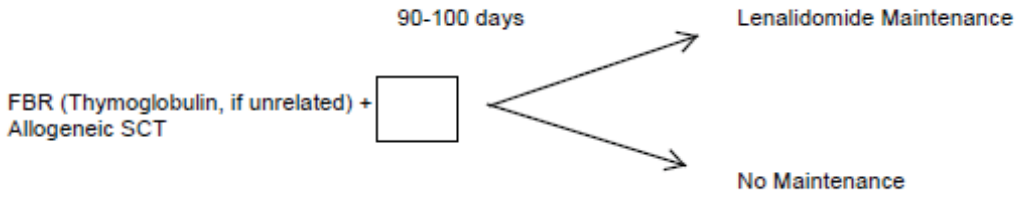
Secondary Endpoints

- To evaluate 1) time to treatment failure; 2) time to molecular remission; 3) safety profile of the combination therapies, and 4) aGVHD and cGVHD rates, 5) percentage of donor cell after transplant in the recipient.
- For each treatment arm, the evidence of toxicity will be monitored closely.
- The stopping boundaries for either arm are (# Grade 3 or 4 non-hematologic toxicity).
- Adverse events will be tabulated by category and grade in each treatment arm. The rate of acute GVHD or chronic GVHD will be estimated.

Investigational Plan

Overall design

Starting with patients enrolled in 2011: Patients with eligible CLL will receive an allogeneic stem cell transplantation after a non-myeloablative conditioning with fludarabine, bendamustine, and rituximab (FBR). Thymoglobulin will be added to enhance the donor engraftment rate of unrelated donors (a standard procedure undertaken in many SCT protocols, and most recently in 2008-0246). Between day 90 and 100 after transplantation, patients who engrafted donor cells (> 20% donor T cells from the blood), who had no severe acute GVHD (defined by no grade III-IV; or grade II but requiring $\leq$ 16 mg -medrol/day), and with no unresolved toxicity of >grade 2, and adequate counts (ANC $\geq$ 1,500; platelets $\geq$ 70,000), and who are not in CR will be randomized to receive lenalidomide maintenance vs observation.



Conditioning Regimen

The regimen is considered as standard of care, and consists of:

Fludarabine (F) at 30mg/im² intravenously (i.v.) will be given daily on days -5, -4, -3. On the same days, Bendamustine (B) 130mg/m²/day will be given i.v . Rituximab (R) of 375 mg/m2 will be given i.v. on day -13; this will be followed by a dose of 1,000mg/ m² on days -6, +1 and +8. Patients receiving an unrelated transplant will be given rabbit anti-thymocyte globulin (Thymoglobulin) 1.0 mg/kg (day -2) and 1.0 mg/kg (day -1). Stem cell will be given on day 0.

Allopurinol 300mg po daily beginning at the start of lenalidomide therapy and continuing for 3 months as TLS prophylaxis is required for all subjects who are randomized to receive lenalidomide.

Lenalidomide Maintenance

Patients who are not in complete remission, including by molecular studies.

Dose:

1. Dose starting at 5 mg every other day; increase to 5 mg/d daily in 4-5 weeks (28-35 days from Dose #1 of Revlimid®), if well tolerated; then to 10mg/d in 4-5 weeks (28-35 days).
2. If the daily dose of 10 mg is not tolerated, the dose will be decreased to 5 mg (and will not be increased again).
3. If the dose of 5 mg is not tolerated, the dose would be decreased to starting level, at 5 mg orally every other day.

Duration of maintenance:

1. Drug will be discontinued after 3 months if CR has been achieved with the lenalidomide maintenance (by CT, bone marrow biopsy and aspiration, PCR, flow cytometry, FISH) is achieved.
2. If CR is not achieved by above criteria at 3 months, patients will then be re-assessed at 6, 9, and 12 months by the same criteria.
3. Maximum duration of maintenance, 12 months

Patients will receive 1 baby aspirin/day while on lenalidomide to prevent deep vein thrombosis.

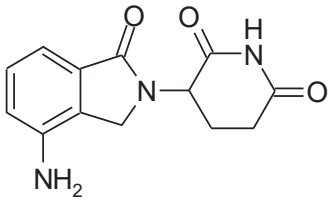
GVHD Prophylaxis

Standard tacrolimus, methotrexate will be used for GVHD prophylaxis, as per our standard practice guidelines. Other supportive care guidelines will be followed as per our standard practice.

Lenalidomide Description

Revlimid® (lenalidomide), a thalidomide analogue, is an immunomodulatory agent with anti-angiogenic properties. The chemical name is 3-(4-amino-1-oxo 1,3-dihydro -2*H*-isoindol-2-yl) piperidine-2,6-dione and it has the following chemical structure:

Chemical Structure of Lenalidomide



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

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 1.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

LENALIDOMIDE® (lenalidomide) is available commercially in 5 mg, 10 mg, 15 mg and 25 mg capsules for oral administration.

CLINICAL PHARMACOLOGY

Mechanism of Action:

The mechanism of action of lenalidomide remains to be fully characterized. Lenalidomide possesses immunomodulatory and antiangiogenic properties. Lenalidomide inhibited the secretion of pro-inflammatory cytokines and increased the secretion of anti-inflammatory cytokines from peripheral blood mononuclear cells. Lenalidomide inhibited cell proliferation with varying effectiveness (IC50s) in some but not all cell lines. Of cell lines tested, lenalidomide was effective in inhibiting growth of Namalwa cells (a human B cell lymphoma cell line with a deletion of one chromosome 5) but was much less effective in inhibiting growth of KG-1 cells (human myeloblastic cell line, also with a deletion of one chromosome 5) and other cell lines without chromosome 5 deletions. Lenalidomide inhibited the expression of cyclooxygenase-2 (COX-2) but not COX-1 in vitro.

Pharmacokinetics and Drug Metabolism:

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) patients was not performed. In multiple myeloma patients 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 patients 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 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's RevAssist® program.

Dosage Form

Lenalidomide will be supplied as 5 mg capsules for oral administration.

Packaging

Lenalidomide will be shipped directly to patients via Biologics, a specialty pharmacy. Bottles will contain a sufficient number of capsules for one cycle of dosing.

Only enough lenalidomide for 1 month of therapy may be provided to the patient at a time.

Storage

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

Prescribing Information

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

Other Non-Investigational Drugs

Fludarabine may cause fever, loss of appetite, fatigue, confusion, numbness, nausea, vomiting, and/or diarrhea. It may cause you to have chills and/or feel tired and/or weak. It may cause vision and/or hearing problems. It may cause paralyzed arms and/or legs, muscle weakness, blindness, and/or coma. It may cause skin rash, mouth ulcers, sore throat, and/or hair loss. It

may cause tingling of the hands and/or feet. It may cause heart failure, lung scarring, bleeding from the bladder, and/or seizures. It may cause kidney, liver, and/or brain damage. It may also cause central nervous system damage, including cortical blindness, and/or permanent sterility (inability to produce children). It may cause your red blood cells to burst.

Cyclophosphamide may cause diarrhea, nausea, vomiting, and/or loss of appetite. It may cause imbalance of salt and fluid status. It may cause irritation of the urinary bladder (where urine is stored). This can cause pain, blood in the urine, and/or scarring of the bladder. You should be able to avoid this by drinking 8-10 glasses of water a day and urinating every 2-3 hours, especially before bedtime. You will be monitored closely and will be given fluids by mouth and vein to "flush out" the bladder, in an attempt to avoid this side effect. Cyclophosphamide may cause a metallic taste right after it is given. It may cause abdominal (stomach area) pain, ulcers in the mouth and/or stomach, and/or hair loss. It may cause headache, dizziness, stuffy nose, and/or shrinkage of the testicles. It may increase the risk of developing a second form of cancer. It may also cause loss of menstrual periods and/or allergic reaction. Cyclophosphamide may also cause damage to heart muscles, leading to severe weakening of the heart muscle (congestive heart failure).

Bendamustine may cause fatigue, fever, headache, nausea, vomiting, diarrhea, constipation, loss of appetite, jaundice (yellowing and/or darkening of the skin), and cough. Bendamustine may likely cause low blood cell counts (white blood cells, red blood cells, and platelets). This means that while you take the drug, there is more of a chance of getting an infection, including pneumonia. You may become anemic and/or have problems with bleeding, bruising, fatigue, and/or shortness of breath. You may need a blood transfusion. Bendamustine may cause arm and/or leg swelling, fast heartbeat, low blood pressure, chest pain, worsening high blood pressure, chills, dizziness, difficulty sleeping, anxiety, depression, pain, skin rash, itching, dry skin, dehydration, low blood levels of potassium (possible weakness), increased blood levels of uric acid (possible gout), high blood sugar (possible diabetes), weight loss, sores in the mouth, abdominal pain, loss of appetite, upset stomach, heartburn, dry mouth, taste changes, fungal mouth infection, abdominal swelling, urinary tract infection, fever and low white blood cell counts, back pain, weakness, abnormal liver tests (possible liver damage), joint, bone, and/or limb pain, difficulty breathing, airway infection, inflammation of the sinuses, throat pain, pneumonia, head cold, wheezing, stuffy nose, infusion/catheter site pain, herpes infection, infection, allergic reaction, sweating, and night sweats. Bendamustine may cause heart failure, drowsiness, blistering skin rash, death of skin tissue, severe skin damage with loss of a large portion of skin, toxic skin reactions, low blood levels of calcium (possible weakness and/or cramping), low blood level of sodium (possible headache, confusion, seizures, and/or coma), inflammation of the mucus membrane, bone marrow disease where not enough blood cells are made, kidney failure, scarring of the lung, severe allergic reaction, severe blood infection, organ failure caused by blood infection, breakdown products of the cancer cells entering the blood stream (possible heart rate abnormalities, kidney failure, muscle twitching, and/or muscle cramps), and new occurrence of cancer.

Rituximab may cause allergic reactions at the site of injection, including fever, chills, nausea, vomiting, headache, muscle aches, dizziness, and/or skin rash. It may cause swelling due to the build-up of fluid in the arms and/or legs. It may cause hives, breathing problems, low blood pressure, and/or sweating. It may cause tenderness and/or swelling at sites of lymphoma in the body. It may cause breathing problems and/or skin reactions. It may cause irregular or slow heartbeat, high blood pressure, and/or arthritis.

Rituximab may cause disorders of blood vessels, lungs, and/or eyes. You will be carefully monitored for these reactions during the rituximab infusions.

Rituximab may cause itching, runny nose, coughing, wheezing, flushing, and/or chest pain. It may cause loss of appetite, anxiety, malaise (sadness), agitation, nervousness, an inability to sleep, and/or abnormal blood tests. It may cause throat irritation, changes in taste, low oxygen levels in the blood, infections, asthma, increased sweating, and/or reactivation of hepatitis.

Rituximab may cause low or high blood sugar and/or rapid death of tumor cells (tumor cell lysis). After tumor cell lysis occurs, high amounts of uric acid will be released into your blood. When uric acid is present in large amounts in your blood, especially after receiving chemotherapy, the ability of your kidneys to filter uric acid can be overwhelmed and uric acid can form crystals within the kidneys. If crystals form in the kidneys, it can lead to kidney damage and possibly acute kidney failure.

Materials taken from humans and animals were used in the making of rituximab. These materials are removed from the final product during the manufacturing process. However, infection from known or unknown substances may occur. In addition, an antibiotic called gentamycin was used in the making of rituximab, and very small amounts may still be present. It may also cause an allergic reaction.

In people who have ever been infected with hepatitis B virus, there is a risk that the virus can flare up during treatment with drugs that affect your immune system, such as rituximab. This could lead to liver failure. The risk of hepatitis B virus flaring up may continue for several months after you stop taking rituximab. If you become jaundiced (yellowing of the skin and eyes) or develop viral hepatitis while taking rituximab or after stopping treatment, you should tell your study doctor immediately. Your study doctor will discuss this risk with you and explain what testing is recommended to check for hepatitis.

Because rituximab is a mouse antibody that has been changed to make it similar to a human antibody, treatment with rituximab may cause the body to make human antibodies to the mouse-based antibody. These antibodies are called HAMA or HACA. The potential response of your body to rituximab may lead to decreasing the effectiveness of mouse-based antibody therapies for you in the future.

Tacrolimus may cause kidney and/or liver damage, high blood pressure, high blood sugar, and/or diabetes. It may cause low levels of potassium, magnesium, and/or phosphate in the blood, which can lead to weakness or other neurological symptoms. Your hands may shake. You may have a burning feeling in the hands and/or feet. The drug may cause nausea, vomiting, constipation, seizures, coma, and/or confusion. An allergic reaction may occur. The drug may cause headache, difficulty sleeping, diarrhea, high blood pressure, blurred vision, chest pain, higher sensitivity to pain, ringing in the ears, sweating, enlarged heart, and/or weakening of the immune system, which may result in the development of infections. It may cause rapid growth of body hair, loss of appetite, weight loss, wheezing, facial flushing, yellowing and/or darkening of the skin due to bile in the blood, and/or abdominal pain. It may cause an increased risk of cancer of the lymph glands. It may also cause rashes, itching, changes in hearing, fluid in the lungs, and/or back pain.

Methotrexate may cause low blood cell counts (white blood cells, red blood cells, and platelets). This means that while you take the drug, there is more of a chance of getting an infection, including pneumonia. You may become anemic and/or have problems with bleeding, bruising, fatigue, and/or shortness of breath. You may need a blood transfusion.

Methotrexate may cause mouth sores, intestinal sores, liver damage, and/or kidney damage. It may cause vision problems, hearing problems, stomach ulcers, nausea, abdominal pain, weakness, chills, fever, and/or dizziness. Damage to the central nervous system may also occur.

Thymoglobulin® may cause low blood cell counts (white blood cells and platelets). This means that while you take the drug, there is more of a chance of getting an infection, including pneumonia. You may become anemic and/or have problems with bleeding, bruising, fatigue, and/or shortness of breath. You may need a blood transfusion.

Thymoglobulin® may cause high blood pressure, buildup of fluid in the feet and legs, fast heartbeat, facial swelling, and/or lymph node swelling. It may cause low blood pressure affecting

liver, kidney, heart, and/or lung functions. It may cause hives, shaking, chills, fever, headache, pain, weakness, dizziness, and/or fainting.

Thymoglobulin® may cause skin rash and/or itching. It may cause kidney damage, liver damage, and/or fluid leakage into tissues such as the lung, causing shortness of breath. It may cause high levels of potassium in the blood, which may mean kidney failure.

Thymoglobulin® may cause abdominal pain, diarrhea, nausea, and/or vomiting. It may cause muscle aches, chest pain, back pain, joint aches, and/or nerve pain. It may cause allergic reactions. The allergic reactions may be severe, and may cause trouble breathing, bone pain, muscle pain, skin rash, and/or changes in blood pressure.

Thymoglobulin® may cause an increased risk of developing new forms of cancer (lymphoma or leukemias). It may increase the risk of graft failure (problems with transplanting new tissue). It may cause the disease to reappear.

Screening and Eligibility

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 2, Schedule of Study Assessments and unless otherwise specified, must take place within 28 days prior to initiation of therapy.

Approximately (80) of subjects with CLL will be screened for enrollment and must meet the eligibility criteria below. It is estimated that 20 patients may not meet the necessary criteria after transplantation, to be randomized for maintenance. These 20 patients will be analyzed separately and followed for toxicity and response at the same frequency that the study patients are followed.

Inclusion Criteria

Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.

Inclusion criteria for the transplant procedure

1. Age 18-75 years at the time of signing the informed consent form.
2. Disease:
   - 2.1 CLL in relapse, after failing conventional chemo-antibody combination therapy.
   - 2.2 CLL patients who failed to achieve CR with frontline conventional chemo-antibody.
   - 2.3 CLL patients with 17p deletion.
   - 2.4 CLL in Richter's.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Donor: HLA compatible related (HLA-A,-B,-DRBI matched or with one-antigen mismatched) or HLA compatible unrelated.
5. ECOG performance status of ≤ 2 at study entry (see Appendix C).
6. FEV1, FVC and DLCO $\geq$ 40%.
7. Left ventricular EF > 40% with no uncontrolled arrhythmias or symptomatic heart disease.
8. Serum creatinine $\leq$ 1.6 mg/dL. Serum bilirubin < 1.6 mg/dL.
9. SGPT < 2x upper limit of normal.
10. Voluntary signed, written IRB-approved informed consent 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.

11. All previous cancer therapy, including radiation, hormonal therapy and surgery, must have been discontinued at least 3 weeks prior to treatment in this study.
12. Disease free of prior malignancies for ≥ 5 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma “insitu” of the cervix or breast.
13. 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 study entry.
14. Disease must be chemosensitive (ie, patients must have PR or better based on CT Scans, PET Scan, and bone marrow biopsy).
15. Patients suspected to have Richter's transformation (such as elevated LDH) and/or who are PET positive, should have a lymph node biopsy to assess histological status of the disease.
16. Patients must be off of alemtuzumab for 6 weeks prior to consenting.

Exclusion criteria

1. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
2. Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking lenalidomide).
3. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
4. Use of any other experimental drug or therapy within 28 days of baseline.
5. Known hypersensitivity to thalidomide, lenalidomide, bendamustine, fludarabine. For patients will unrelated donors: Known hypersensitivity to thymoglobulin.
6. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.
7. Concurrent use of other anti-cancer agents or treatments.
8. Known positive for HIV or infectious hepatitis, type A, B or C.
9. Sinuses should be evaluated by either CT neck or CT sinuses to exclude infections
10. Deep-vein thrombosis or pulmonary embolism with 3 months of study entry.
11. History of serious infection requiring hospitalization within the last 3 months of consenting.

† 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).

Treatment Plan

Conditioning Regimen

Prior to starting the preparative regimen a related or unrelated donor will be identified. Whether the source of hematopoietic stem cells is the bone marrow or the peripheral blood, stem cell procurement will follow Department of Stem Cell Transplantation and Cellular Therapy standard procedures. A minimum of 2 x 10^6 CD 34 + cells/Kg (peripheral blood) or 1 x 10^6 CD34 + cells/Kg recipient body weight (bone marrow) should be available.

The preparative regimen is as follows:

1. Fludarabine 30 mg/m2 will be given intravenously daily on days -5, -4, -3.
2. Bendamustine 130 mg/m^2/day will be given intravenously daily on day -5, -4, -3 (following Fludarabine).
3. Rituximab 375 mg/m2 will be given intravenously on day -13, and 1000 mg/m^2 on days -6, +1 and +8.
4. Patients receiving an unrelated donor will receive rabbit anti-thymocyte globulin (ATG) 1 mg/kg (days -2) and 1mg/kg (day -1).
5. Day zero is the day of stem cell transplant.

ATG may be given as per other IRB approved protocol. Rituximab will be infused following standard procedures for the Department of Stem Cell Transplantation and Cellular Therapy.

Supportive Care

GVHD Prophylaxis

Patients are to receive standard prophylaxis consisting of tacrolimus and mini-dose methotrexate. Methotrexate is given at 5 mg/m^2 on transplant days 1, 3 and 6 for recipients of HLA-identical sibling transplants, and on day 1, 3, 6 and 11 for recipients of unrelated or mismatched related donor transplants. Tacrolimus starts on day -2 (targeting levels at 5-10 ng/mL) with monitoring of blood levels and dose adjustments as clinically indicated.

Administration of blood products, intravenous fluids, allopurinol, G-CSF, antibiotic, antifungal and antiviral medications, will follow institutional and departmental guidelines and should be administered as clinically indicated.

Lenalidomide Maintenance Treatment

Treatment Assignments

Patients who are not in CR will be randomized between days 90-100 after transplantation to receive or not, lenalidomide maintenance.

Criteria to start lenalidomide after transplant in patients initially randomized to receive the drug:

1. Absolute neutrophil count $\geq$ 1,500 mm^3.
2. Platelet count $\geq$ 70,000 mm^3.
3. No Active Bleeding.
4. No clinical evidence of life-threatening infection.
5. No uncontrolled acute GVHD [i.e., no acute grade III – IV; no acute grade II requiring. > 16 mg steroids/day]
6. Adverse events that may have occurred have resolved to < grade 2 toxicity.

7. Engraftment of donor cells (i.e., > 20% donor T-cell from PB/PCR)
8. Creatinine clearance >/= 30
9. 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 A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.
10. All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.

Patients can start lenalidomide when randomized to the maintenance area, between days 90-100 after transplantation.

Duration of maintenance:

1. Drug will be discontinued after 3 months if CR has been achieved with the lenalidomide maintenance (CT, bone marrow biopsy and aspiration, PCR, flow cytometry, FISH) is achieved.
2. If CR is not achieved by above criteria at 3 months, patients will then be re-assessed at 6, 9, and 12 months by the same criteria.
3. Maximum duration of maintenance, 12 months

Patients will receive 1 aspirin of 81 mg/day while on lenalidomide to prevent deep vein thrombosis.

Tumor Lysis Syndrome (TLS) Prophylaxis (allopurinol and hydration)

Tumor lysis syndrome (TLS), characterized by hyperkalemia, hyperuricemia, and hyperphosphatemia resulting from the rapid release of potassium, uric acid, and phosphate, has been reported in CLL patients treated with lenalidomide necessitating TLS prophylaxis including allopurinol and oral hydration. The risk of TLS is highest during the first few weeks of therapy and may be elevated when lenalidomide is re-started after treatment interruptions or when the lenalidomide dose is escalated.

Allopurinol 300mg po daily beginning at the start of lenalidomide therapy and continuing for 3 months as TLS prophylaxis is required for all subjects who are randomized to receive lenalidomide.

Based on a patient's reaction and laboratory parameters, TLS prophylaxis may be continued or restarted as needed at the Investigator's discretion.

Tumor Flare Reaction (TFR):

† 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).

Prophylaxis for (TFR) is not recommended for patients who receive lenalidomide. Grade 1 TFR may be treated with NSAIDs (i.e. ibuprofen 400-600 mg orally every 4-6 hours as needed). TFR ≥ Grade 2 may be treated with corticosteroids. Narcotic analgesics may be added as needed for pain control in subjects experiencing ≥ Grade 2 tumor flare.

Patients who already have a history of deep-vein thrombosis or pulmonary embolism will receive either coumadin or low-molecular weight heparin while on lenalidomide.

If patients develop thrombosis or embolism while they are receiving aspirin prophylaxis, lenalidomide will be held, patients will be anticoagulated, and once a stable anticoagulation is achieved, patients with be restarted on the same dose of lenalidomide. Patients will then continue to receive either coumadin or low-molecular weight heparin as long as they continue to receive lenalidomide.

Visit schedule and assessments

See Appendix B: Schedule of Study Assessments

Pre-Transplant Evaluation

The following tests/procedures will be performed within 30 days prior to signing a consent form for the protocol:

A complete history and physical including the following information: diagnosis, PS, prior therapy and response, pulmonary function tests, MUGA or Echo and EKG.

Staging of diseases: i.e., CT scans of the neck, chest, abdomen, pelvis, bone marrow biopsy and aspiration, CxR, PET scan, cytogenetics, PCR/ fluorescence in situ hybridization (FISH) studies for JH and immunophenotyping.

Laboratory studies shall include:

CBC with differential, platelet count, PT, PTT, creatinine, liver function tests, urinalysis, Beta 2 microglobulin level, Hepatitis serology, HIV, HTLV-1, quantitative serum immunoglobulins, baseline peripheral CD4/CD8 counts and immunodeficiency panel.

Enrollment into the RevAssist® program.

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

Evaluation at 25-35 days and the first 100 days

Staging of diseases: i.e., CT scans of the neck, chest, abdomen, pelvis, bone marrow biopsy and aspiration, CxR, PET scan (if previously positive), cytogenetics, PCR/ fluorescence in situ hybridization (FISH) studies, for JH and immunophenotyping.

Chimeric studies, quantitative serum immunoglobulins, CD4/CD8 counts, serum immunoglobulin, immunodeficiency panel.

Laboratory studies shall include: CBC with differential, platelet count, liver function tests, creatinine, electrolytes, tacrolimus levels and CMV, antigenemia, once a week, or more frequently if needed.

Evaluation after the first 100 days:

Staging with CT scans of the neck, chest, abdomen, pelvis, marrow biopsy and aspiration, PET scan (if previously positive), FISH, PCR for JH, flow cytometry at 6, 9, 12, 15 months, 18 months (+/- 2 weeks for each time point) and then every 6 months x 3 years (+/- 4 weeks for each time point).

Chimeric studies

Immunodeficiency panel with CD4/CD8

CBC with differential, platelets, Cr, liver function tests, electrolytes

Additional evaluation while on lenalidomide:

CBC with differential, Serum chemistry basic metabolic profile, (sodium, potassium, chloride, CO2, BUN, creatinine, uric acid, ALT, AST, alkaline phosphatase, (bilirubin and glucose) platelets weekly until the maximum tolerated dose is reached, then once every two weeks thereafter. At every re-start of lenalidomide following an interruption, the afore mentioned tests should be performed weekly for the first 4 weeks, then once every 2 weeks.

Pregnancy testing per the RevAssist® program.

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

Frequency of pregnancy test to be done:

1. Every week during the first 28 days of starting lenalidomide and a pregnancy test every 28 days during the patient's participation in this study if no menstrual cycle or menstrual cycles are regular or every 14 days if cycles are irregular.

2. If the patient missed a period or has unusual menstrual bleeding.

3. When the patient is discontinued from the study and at day 28 after discontinuation from the study if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after discontinuation from the study.

Optional testing:

Patients will be asked to have 2 x10cc heparin tubes and 1x15 red tube of blood at the time of consent. This will be repeated at 3, 6, 9, 12, and 15 months after transplantation. Cytokine levels and immune cell function (T-cell, B-cell, and NK-cell and dendritic cells) will be measured for correlation studies. Samples will be stored at Dr. James Reuben's Lab; all leftover samples will be discarded.

Dosing Regimen

The drug will be in the morning at approximately the same time each day. Only enough lenalidomide for one month of therapy will be supplied to the patient.

Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.

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

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

Subjects experiencing adverse events may need study treatment modifications (See section 5.5).

Special Handling Instructions

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

Record of administration

Accurate records will be kept of all study drug administration (including prescription dispensing and dosing) will be made in the source documents.

Dose Continuation, Modification and Interruption

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v3.0 (Appendix D: NCI CTCAE v3.0) used as a guide for the grading of severity. Refer to Sections 6.5.1, 6.5.2 and 6.5.3 for full instruction on initiation of a new cycle of therapy and dose modifications during a cycle of therapy.

Dose Reduction Steps

Table 1: LENALIDOMIDE Dose Escalation Steps	
Dose Level 2	10 mg daily
Dose Level 1	5 mg daily
Starting Dose	**5 mg every other day**

Instructions for Dose Modifications or Interruption During a Cycle

Dose Modification Guidelines for Lenalidomide	
NCI CTC Toxicity Grade	**Action**
Grade 3 neutropenia associated with fever (temperature $\geq$38.5° C) or Grade 4 neutropenia (ANC $\leq$500/mm^3, $\leq$75% of baseline)*.	1) Hold (interrupt dose). 2) Follow CBC weekly until resolution or stabilization 3) If neutropenia has resolved to $\leq$ grade 2, implement one dose reduction and continue therapy. 4) If neutropenia is the only toxicity for which a dose reduction is required, GCSF may be used and the lenalidomide dose maintenance.
Thrombocytopenia Grade 4 (platelet count $\leq$25,000/mm^3)*.	1) Hold (interrupt dose). 2) Follow CBC weekly until resolution or stabilization 3) If thrombocytopenia resolves to $\leq$ grade 2, implement one dose reduction and continue therapy.
Non-blistering rash Grade 3	1) If grade 3, hold (interrupt) dose. Follow weekly until resolution or stabilization. 2) If the toxicity resolves to $\leq$grade 1, implement one dose reduction and continue

Grade 4	therapy. 1) Discontinue lenalidomide study drug.
Desquamating (blistering) rash-any Grade	Discontinue lenalidomide study drug.
Erythema multiforme Grade 3	Discontinue lenalidomide study drug.
Neuropathy Grade 3 Grade 4	1) If grade 3, hold (interrupt) dose. Follow weekly until resolution or stabilization. 2) If the toxicity resolves to ≤grade 2, implement one of dose reduction and continue therapy. Discontinue lenalidomide study drug.
Sinus bradycardia/other cardiac arrhythmia Grade 2 ≥ Grade 3	1) Hold (interrupt dose). Follow at least weekly until resolution or stabilization. 2) If the toxicity resolves to ≤grade 1, implement one dose reduction and continue therapy. Discontinue lenalidomide study drug.
Allergic reaction or hypersensitivity Grade 3 Grade 4	1) Hold (interrupt dose). Follow at least weekly until resolution or stabilization 2) If the toxicity resolves to ≤grade 1, implement one dose reduction and continue therapy. Discontinue lenalidomide study drug.
Venous thrombosis/embolism ≥Grade 3	Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion (maintain dose level).
Hepatic or other non-hematologic toxicity assessed as lenalidomide-related ≥ Grade 3	1) Hold (interrupt) dose. Follow at least weekly until resolution or stabilization. 2) If the toxicity resolves to ≤grade 2, implement one dose reduction and continue therapy.
Tumor flare refractory to oral pain meds and/or antihistamines	Hold dose and differentiate tumor flare from progression. Restart therapy at the investigator's discretion.

Treatment and Dose Modification for Tumor Lysis Syndrome for Patients receiving Lenalidomide

All subjects meeting criteria of laboratory TLS or ≥ Grade 1 TLS according to the Cairo-Bishop Definition of Tumor Lysis Syndrome (see Appendix R) should receive vigorous intravenous hydration and should be considered for rasburicase therapy as needed to reduce hyperuricemia, until correction of electrolyte abnormalities.

- In cases of laboratory TLS and Grade 1 TLS (see Appendix R: Cairo-Bishop Definition of Tumor Lysis Syndrome), lenalidomide will be continued at the same dose without interruption or dose reduction. TLS prophylaxis measures outlined in Lenalidomide Maintenance should be continued or re-instituted.

- Subjects with ≥ Grade 2 TLS (see Appendix R: Cairo-Bishop Definition of Tumor Lysis Syndrome) will be managed as follows in addition to intravenous hydration and consideration for rasburicase therapy (above).
    - Hold (interrupt) treatment.
    - First episode: restart lenalidomide at the current dose with appropriate TLS prophylaxis after resolution of electrolyte abnormalities to Grade 0.
    - Subsequent episodes: restart lenalidomide with appropriate TLS prophylaxis after resolution of electrolyte abnormalities to Grade 0. At physician discretion, the lenalidomide dose may be restarted at the current dose or lenalidomide may be reduced by 1 dose level.
    - First or subsequent episodes: subjects should be closely monitored for signs of TLS after resuming treatment. To monitor for TLS, serum chemistry and uric acid tests should be performed at least every week following initiation of lenalidomide for 4 consecutive weeks and on Day 3 or 4 following initiation of lenalidomide.

Treatment compliance

At all times, when dispensing study drug, research center personnel will review the instructions, printed on the packaging, with subjects. Subjects will be asked to maintain a diary to record the drug administration. Subjects will be asked to bring any unused study drug and empty study drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules at each visit and reconcile with the patient diary.

Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the RevAssist® program.

Concomitant Therapy

Recommended Concomitant Therapy

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, antiemetics, antihistamines, and allopurinol when appropriate.

Anticoagulation Consideration

Lenalidomide increases the risk of thrombotic events in patients who are at high risk or with a history a 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.

For this study, patients will receive one aspirin (81 mg) a day while on lenalidomide. Low molecular weight heparin may be utilized in patients that are intolerant to aspirin. Coumadin should be used with caution and close monitoring of INR.

Patients who already have a history of deep-vein thrombosis or pulmonary embolism will receive either coumadin or low-molecular weight heparin while on lenalidomide.

If patients develop thrombosis or embolism while they are receiving aspirin prophylaxis, lenalidomide will be held, patients will be anticoagulated, and once a stable anticoagulation is achieved, patients with be restarted on the same dose of lenalidomide. Patients will then continue to receive either coumadin or low-molecular weight heparin as long as they continue to receive lenalidomide.

Prohibited Concomitant Therapy

Concomitant use of sargramostim (GM-CSF), other anti-cancer therapies, including radiation, thalidomide, or other investigational agents is not permitted while subjects are receiving study drug during the treatment phase of the study.

Discontinuation of Lenalidomide

Treatment will continue for one year or the occurrence of any of the following events:

1. Disease progression.
2. Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
3. Discontinuation of lenalidomide for any reason.
4. Major violation of the study protocol.
5. Withdrawal of consent.
6. Lost to follow up.
7. Death.
8. Pregnancy or suspected pregnancy.
9. Immobility or unwillingness to have follow-up visit and/or laboratory test required by this protocol.

Follow-Up

At treatment discontinuation, subjects will undergo a safety assessment approximately 30 days post the last dose of study drug. Additional off study evaluations, per the Schedule of Assessments.

Adverse Events

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.

MD Anderson (Sponsor) Reporting Requirements for Serious Adverse Events and Dose Limiting Toxicities:

Serious Adverse Event (SAE) Definition

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

1. Results in death

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

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

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

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

Adverse Drug Reaction Reporting

Toxicity will be scored using CTCAE Version 3.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (Appendix D). All appropriate treatment areas should have access to a copy of the CTCAE Version 3.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient'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 patient's outcome.

Serious Adverse Events Reporting: The principle investigator has the obligation to report all serious adverse events to the University of Texas M. D. Anderson Cancer Center (MDACC) IRB via the Office of Protocol Research and to Celgene within 24 hours.

In IND studies, all serious adverse events must be reported to the FDA by the investigator through the Office of Research Education & Regulatory Management (ORERM) as required by 21 CFR 312.32. These reports are to be filed utilizing the University of Texas M. D. Anderson Cancer Center Adverse Event Reporting Form. This includes serious, related, labeled (expected) and serious, related, unlabeled (unexpected) adverse experiences. All other serious adverse events not requiring expedited reporting should be reported to MDACC IRB and ORERM within 5 business days.

All deaths during treatment or within 30 days following completion of active protocol therapy must be reported within 24 hours of knowledge regardless of the attribution. SAEs beyond 4 weeks after the end of study drug administration will be reported if thought to be drug related.

NOTE: Instructions concerning procedures and reporting for pregnancies below.

Pregnancies

Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered expedited 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. The pregnancy must be reported by the investigator to MDACC IRB and ORERM AND to Celgene Corporation Drug Safety within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

The Investigator will follow the pregnant female until completion of the pregnancy, and must notify Celgene Corporation Drug Safety of the outcome as specified below. The Investigator will provide this information as a follow-up to the initial SAE.

If the outcome of the pregnancy meets the criteria for immediate classification as a SAE (i.e., spontaneous abortion [any congenital anomaly detected in an aborted fetus is to be documented], stillbirth, neonatal death, or congenital anomaly), the Investigator should follow the procedures for reporting SAEs (i.e., report the event to Celgene Corporation Drug Safety by facsimile within 24 hours of the Investigator's knowledge of the event) and report the event to MDACC IRB and ORERM.

Any suspected fetal exposure to lenalidomide must be reported to Celgene, MDACC IRB AND ORERM within 24 hours of being made aware of the event. The pregnant female should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to lenalidomide should also be reported.

In the case of a live "normal" birth, Celgene Corporation Drug Safety MDACC IRB AND ORERM should be advised as soon as the information is available.

Celgene Drug Safety Contact Information:

Celgene Corporation
Drug Safety
86 Morris Avenue
Summit, N.J. 07901

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

Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements. Serious Adverse Events Reporting: The principle investigator has the obligation to report all serious adverse events to the University of Texas M. D. Anderson Cancer Center (MDACC) IRB via the Office of Protocol Research and also to Celgene within 24 hours.

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 with MD Anderson's ORERM, who will then forward to FDA. An additional copy should be placed in the study's Regulatory Binder and a copy must be sent to Celgene Corporation as a supporter of this study as follows:

Celgene Corporation
Attn: Medical Development
86 Morris Avenue
Summit, NJ 07901
Tel: (908) 673-9000

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

Expedited reporting by Principal Investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator should inform Celgene of any SAE within 24 hours of being aware of the event. This must be documented on an MD Anderson SAE form. This form must be completed and supplied to MDACC IRB, ORERM and Celgene within 24 hours/1 business day. The initial report must be as complete as possible including an assessment of the causal relationship between the event and the investigational product(s) 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 MD Anderson SAE form. A final report to document resolution of the SAE is required. The MD Anderson Protocol Number (2007-0871) and the Celgene protocol number (RV-CLL-PI-0294) should be included on SAE reports to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

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.

Sponsor Reporting to the FDA

Adverse drug reactions that are **Serious, 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) in writing by each investigator/physician engaged in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The sponsor shall notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug. As soon as possible, but no later than 7 calendar days after the sponsors initial receipt of the information. Each phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND if applicable.

Adverse event updates/IND safety reports

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

1. Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.

2. 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 and the IRB/EC, on file.

Response Criteria

Response criteria will be defined by the NCIWG. In addition, patients will undergo CT Scans. PET and marrow aspiration and biopsy, flow cytometry, PCR and FISH to evaluate response.

Instructions for interpreting response criteria for lesion evaluation and best overall response may be found in Appendix F.

Neutrophil engraftment is defined as a sustained ANC $\geq$ 0.5 x 10^9/L for at least 3 consecutive days. Platelet engraftment is defined as a sustained transfusion-independent platelet count.$\geq$ 20 x10^9/L for seven consecutive days without transfusion support.

Definition of success/efficacy

Patient alive, engrafted, in remission 18 months, without requiring immunomanipulation.

Definition of toxicity

Not able to tolerate the lowest dose of 5 mg every other day, because of toxicity.

Primary graft failure is defined as failure to achieve an ANC $\geq$ 0.5 x 10^9/L for 3 consecutive days by day 28, with <10% cellularity on bone marrow biopsy and no evidence of donor chimerism and no evidence of persistent disease.

Secondary graft failure is defined as a sustained decline of ANC below 0.5 X 10^9/L of for 3 consecutive days after initial documented engraftment with no evidence of disease progression.

Protocol Amendments/Deviations

Protocol amendments

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by Celgene. Amendments should only be submitted to IRB/EC after consideration of Celgene 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.

Data Management

Analyses and Reporting

Data will be analyzed and reported as per the statistical design in the Biostatistical Analysis section.

Study monitoring and auditing

Investigator responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

The Investigator will permit study-related monitoring visits and audits by MDACC's ORERM, Celgene, or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

The Investigator, or a designated member of the Investigator's staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to MDACC ORERM and the Celgene representative so that the accuracy and completeness may be checked.

Biostatistical Analysis

This randomized phase II trial compared FCR, and Thymoglobulin plus lenalidomide (FCR+ L) to FCR, and Thymoglobulin (FCR) in patients with CLL undergoing allotransplant on 25 patients enrolled from May 13, 2009 to December 2, 2010.

Starting with patients enrolled in 2011, this randomized phase II trial will compare FBR, (and Thymoglobulin if unrelated) plus lenalidomide (FBR+ L) to FBR, (and Thymoglobulin if unrelated donor) (FBR) in patients with CLL undergoing allotransplant.

The primary objective is to compare the need for immunomanipulation between the treatment groups. For this trial, immunomanipulation is defined as either the cessation of the administration of immunosuppression treatment within the first six months after allotransplant due to intolerability or the administration of DLI any time between 3 and 18 months after transplant.

Our primary outcome is the need for immunomanipulation by month 18. Our target enrollment is to have a maximum of 60 patients to be randomized, and we expect to enroll 3 patients per month. We will follow all patients for 18 months. We also expect that 20 additional patients may be initially enrolled to receive the transplantation, but later may not meet the criteria for maintenance randomization.

Based upon pilot data, we expect that 49% of the patients in the FCR arm will need immunomanipulation by 18 months, and we hope to see a reduction in this proportion in the FCR + L arm to 25%. We expect the same incidence to occur with FBR.

Patients will be randomized in a 1:1 ratio between FCR (now FBR) and FCR (now FBR)+ L. Patients will be stratified by the presence or absence of del 17 by FISH by PB at any point in time during their disease history, and the number of prior therapies received (less or equal to 2 vs

greater than 2). Prior therapies are defined by 1) combination chemotherapies, 2) chemo-antibodies, 3) biological agents. The trial will be stopped early and a treatment selected as being "better" if the probability is 0.95 or more that the probability of needing immunomanipulation on one treatment arm is greater than for the other arm. However, if all 60 patients are enrolled, then a treatment will be selected as being "better" if the probability is 0.90 or more that the probability of needing immunomanipulation for one treatment is greater than the other. Additional details are provided below in the section labeled "Technical Details". The operating characteristics of this study design based upon 2000 simulations of this trial are summarized in Table 1 below.

We will report the posterior probability that the need for immunomanipulation in one arm is greater than the need for immunomanipulation in the other arm.

Table 1. Operating Characteristics of Study Design

	Neither	FCR	FCR + L
True Rate of Need for Immunomanipulation	---	0.49	0.25
Pr(Selected)	19.7%	0	80.3%
True Rate of Need for Immunomanipulation	---	0.49	0.49
Pr(Selected)	81.8%	8.9%	9.3%
True Rate of Need for Immunomanipulation	---	0.25	0.25
Pr(Selected)	75.5%	3.8%	20.7%
True Rate of Need for Immunomanipulation	---	0.49	0.35
Pr(Selected)	53.5%	0.6%	45.9%
True Rate of Need for Immunomanipulation	---	0.60	0.35
Pr(Selected)	26.5%	0.2%	73.3%

Analyses of secondary endpoints include evaluation of:

1) time to treatment failure
2) time to molecular remission
3) safety profile of the combination therapies
4) acute and chronic graft-vs-host disease rates and
5) percentage of blood donor cell after transplant in the recipient.

Technical Details

Starting with patients enrolled in 2011: The two treatment arms will be denoted by **T** (FBR) and **TL** (FBR + L). Denote the probability that a patient needs immunomanipulation in each arm as θ_T and θ_{TL}, respectively. Assume that θ_T and θ_{TL} are independent and that $\theta_T \sim \text{Beta}(a_T,b_T)$ and that $\theta_{TL} \sim \text{Beta}(a_{TL},b_{TL})$. Here, (a_T,b_T) can be interpreted as the number of prior successes and failures, respectively, in arm T, and (a_{TL},b_{TL}) can be interpreted as the number of prior successes and failures in arm TL. The mean values of these distributions are $a_T/(a_T + b_T)$ and $a_{TL}/(a_{TL} + b_{TL})$

In a previous trial of FCR, 19 of 39 patients required immunomanipulation by 18 months. Since we expect the same incidence with FBR, we will use the same statistical guidelines thus far adopted with FCR. Patients who have been treated with FCR will be included within the final analysis and the total number patients randomized will not change. We discount the information

available by 75% and assume that $(a_T,b_T) = (4.9,5.1)$. We further assume that $(a_{TL},b_{TL}) = (0.98, 1.02)$, which has the same mean but a higher variance, reflecting that little information is available regarding the FBR + L arm.

During the trial, the posterior probability that the need for immunomanipulation rate is greater in arm T is represented by $p_T(data) = Pr(\theta_T > \theta_{TL})$. Similarly, $p_{TL}(data) = 1 - p_T(data)$. If at any point during the trial $p_{TL}(data) > 0.95$ (< 0.05) the trial will be terminated and treatment FBR + L will be selected as superior (inferior). If the maximum number of patients is enrolled in the trial and $p_{TL}(data) > 0.90$ (< 0.10) treatment T_L will be selected as superior (inferior).

Data Confidentiality Plan

Data will be collected in the SCT&CT departmental database (BMTWeb). This database is password-protected, contains audit tracking, and follows all federal guidelines. Your personal identifying information will be removed for this analysis; no sensitive information will be shared.

Data from this clinical trial will be shared with PA17-0588 which is a retrospective data analysis study. No new testing will be undertaken on any specimen. (See Waiver of Informed Consent.)

Safety evaluation

Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drug(s) and had this confirmed, will not be evaluated for safety.

The severity of the toxicities will be graded according to the NCI CTCAE v3.0 whenever possible.

Regulatory Considerations

Institutional Review Board/Ethics Committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

The Investigator will be responsible for preparing documents for submission to the relevant IRB/EC and obtaining written approval for this study. The approval will be obtained prior to the initiation of the study.

The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

Any amendments to the protocol after receipt of IRB/EC approval must be submitted by the Investigator to the IRB/EC for approval. The Investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

Any advertisements used to recruit subjects for the study must be reviewed and approved by the IRB/EC prior to use.

Informed consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

Study records 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; 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.

Premature discontinuation of study

Single center

The responsible local clinical Investigator as well as Celgene have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Possible reasons for termination of the study could be but are not limited to:

1. Unsatisfactory enrollment with respect to quantity or quality.
2. Inaccurate or incomplete data collection.
3. Falsification of records.
4. Failure to adhere to the study protocol.

Study as a whole

Celgene reserves the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).

References

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Appendices

Appendix A: 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. The risks to a fetus are not known. However, because lenalidomide is related to thalidomide, and thalidomide is known to cause severe birth defects, the following requirements must be observed.

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

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 study drug; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

Before starting study drug:

Female Subjects:

- FCBP must have two 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 (prescriptions must be filled within 7 days). The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

Male Subjects:

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

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

All Subjects:

- If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

Female Subjects:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at 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).

discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study.

- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.
- Pregnancy testing and counseling must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.

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.

Appendix B: Schedule of Study Assessments *

Nonmyeloablative Stem Cell Transplantation with or without Lenalidomide for Chronic Lymphocytic Leukemia (RV-CLL-PI-0294) Protocol 2007-0871														
Issa F. Khouri, MD	**Evaluation**													
SCT&CT	**Pretreatment**		**During Study (post transplant)**											
	Within 30 days		25-35 days		3 months		6 months (+/- 2 weeks)		9 months (+/- 2 weeks)		12 months (+/- 2 weeks)		15 months (+/- 2 weeks)	
Assessment	R	Date	R	Date	R	Date	R	Date	R	Date	R	Date	R	Date
History & Physical														
Physical Examination	X		X		X		X		X		X		X	
PS	X													
Stage	X													
MUGA/Echo, EKG, Pulmonary Function Tests	X													
Prior Therapies	X													
GVHD & Toxicity			X		X		X		X		X		X	
Staging of Disease			X		X		X		X		X		X	
CT Neck	X		X		X		X		X		X		X	
CT Chest	X		X		X		X		X		X		X	
CT Abdomen & Pelvis	X		X		X		X		X		X		X	
BM Biopsy & Aspiration	X		X		X		X		X		X		X	
CxR	X		X		X									
PET Scan	X		X	if previously positive	X	if previously positive	X	if previously positive	X	if previously positive	X	if previously positive	X	if previously positive
Cytogenetics	X		X		X		X		X		X		X	
PCR/FISH	X		X		X		X		X		X		X	
Laboratory Studies														
CBC	X		X		X		X		X		X		X	
Platelet Counts	X		X		X		X		X		X		X	
PT	X													
PTT	X													
Creatinine	X		X		X		X		X		X		X	
2 Microglobulin Level	X													
Hepatitis Serology	X													
HIV	X													
HTLV-1	X													
Tacrolimus levels			X		X									
CD4/CD8 (PB)	X		X		X		X		X		X		X	
Liver Function Test	X		X		X		X		X		X		X	
Immunodeficiency Panel (PB)	X		X		X		X		X		X		X	
Chimeric Studies (PB, T Cells, Myeloid)			X		X		X		X		X		X	
Quantitative Immunoglobulins	X		X		X		X		X		X		X	
Optional Blood Work					X		X		X		X		X	
Pregnancy Test	X†‡													
Urinalysis	X													

Nonmyeloablative Stem Cell Transplantation with or without Lenalidomide for Chronic Lymphocytic Leukemia (RV-CLL-PI-0294) Protocol 2007-0871								
Issa F. Khouri, MD	**Evaluation**							
SCT&CT	**During Study (post transplant)**							
	18 months (+/- 2 weeks)		24 months (+/- 4 weeks)		30 months (+/- 4 weeks)		36 months (+/- 4 weeks)	
Assessment	R	Date	R	Date	R	Date	R	Date
History & Physical								
Physical Examination	X		X		X		X	
PS								
Stage								
MUGA/Echo, EKG, Pulmonary Function Tests								
Prior Therapies								
GVHD & Toxicity	X		X		X		X	
Staging of Disease	X		X		X		X	
CT Neck	X		X		X		X	
CT Chest	X		X		X		X	
CT Abdomen & Pelvis	X		X		X		X	
B M Biopsies & Aspiration	X		X		X		X	
CxR								
PET Scan	X	if previously positive	X	if previously positive	X	if previously positive	X	if previously positive
Cytogenetics	X		X		X		X	
PCR/FISH	X		X		X		X	
Laboratory Studies								
CBC	X		X		X		X	
Platelet Counts	X		X		X		X	
PT								
PTT								
Creatinine	X		X		X		X	
2 Microglobulin Level								
Hepatitis Serology								
HIV								
HTLV-1								
Tacrolimus levels								
CD4/CD8 (PB)	X		X		X		X	
Liver Function Test	X		X		X		X	
Immunodeficiency Panel (PB)	X		X		X		X	
Chimeric Studies (PB, T Cells, Myeloid)	X		X		X		X	
Quantitative Immunoglobulins	X		X		X		X	
Optional Blood Work								
Pregnancy Test								
Urinalysis								

Nonmyeloablative Stem Cell Transplantation with or without Lenalidomide for Chronic Lymphocytic Leukemia (RV-CLL-PI-0294) Protocol 2007-0871								
Issa F. Khouri, MD SCT&CT	**Additional Tests for Patients Receiving Lenalidomide**							
	Week 1	Week 2	Week 3	Week 4	Every 2 Weeks	Every 28 Days	Study Discontinued	28 days after Study Discontinued
CBC with differential, sodium, potassium, chloride, CO2, BUN, creatinine, uric acid , ALT, AST, alkaline phosphatase, bilirubin, glucose, platelets	X^	X^	X^	X^	X^			
Register patient in RevAssist® Program	≤ **28 days from Screening**							
Pregnancy Test	X†‡	X†‡	X†‡	X†‡		X†‡	X†‡	X†‡
Prescribe Revlimid®	X☼					X☼		
Assess Revlimid® toxicity (if applicable)	X	X	X	X	X	X	X	X

- *Variations of ± 3 days of the scheduled visit are permitted.
- ^ At every re-start of lenalidomide following an interruption: Weekly until the maximum dose is reached, then once every 2 weeks.
- †Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
- ‡Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide (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 A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
- ☼Lenalidomide must be prescribed through and in compliance with Celgene's RevAssist® program. Prescriptions must be filled within 7 days. Any unused Revlimid® (lenalidomide) should be returned to Celgene for disposition in accordance with the RevAssist® program.

Appendix C: ECOG Performance Status Scale

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

Appendix D: NCI CTC Version 3.0

TOXICITY WILL BE SCORED USING NCI CTC VERSION 3.0 FOR TOXICITY AND ADVERSE EVENT REPORTING. A COPY OF THE NCI CTC VERSION 3.0 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**

Appendix E: CLL Staging – NCIWG Criteria

Table 1. NCI-Working Group Response Guidelines for CLL

Response Criteria	
CR	
Physical exam	Normal
Symptoms	None
Lymphocytes (x 10^9/L)	≤4
Neutrophilis (x 10^9/L)	≥1.5
Platelets (x 10^9/L)	≥100
Hb (g/dL)	>11 (untransfused)
Bone Marrow lymphs (%)	<30; no nodules
PR	
Physical exam (nodes, and/or liver, spleen)	≥50% decrease
Plus ≥ 1 of:	
Neutrophilis (x 10^9/L)	≥1.5
Platelets (x 10^9/L)	>100
Hemoglobin (g/dL)	>11 or 50% improvement
Duration of CR or PR	≥2 mo
Progressive disease	
Physical exam (nodes, liver, spleen)	≥50% increase or new
Circulating lymphocytes	≥50% increase
Other	Richter's syndrome
Stable disease	All others