Protocol Update #18
02/15/2013

CANCER AND LEUKEMIA GROUP B

PROTOCOL UPDATE TO CALGB 100104/ECOG 100104

A PHASE III RANDOMIZED, DOUBLE-BLIND STUDY OF MAINTENANCE THERAPY WITH CC-5013 (NSC # 703813, IND # 70116) OR PLACEBO FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION FOR MULTIPLE MYELOMA

Investigational agent, CC-5013, will be supplied by the National Cancer Institute

Limited Access Study: Member Institutions of an NCI Cooperative Group Approved for Autologous Transplantation or Member of the Bone Marrow Transplant Clinical Trials Network Meeting the Protocol Requirements for Autologous Transplantation, or FACT-credentialed CICRS Sites Meeting the Protocol Requirements

[X] **Update:**	[ ] **Status Change:**
[ ] Eligibility changes	[ ] Activation
[X] Therapy / Dose Modifications / Study Calendar changes	[ ] Closure
[ ] Informed Consent changes	[ ] Suspension / temporary closure
[ ] Scientific / Statistical Considerations changes	[ ] Reactivation
[ ] Data Submission / Forms changes	
[X] Editorial / Administrative changes	
[ ] Other :	

IRB review of this update is required within 90 days. Expedited review is allowed. Please follow your local IRB guidelines.

UPDATES:

The changes in this update reflect the new CTEP PIO/FDA requirements for protocol formatting. The entire protocol document has been reformatted. The table of contents has been updated. The consent document has been separated out, with a separate update cover page summarizing the changes to the consent.

Section 5.1.1 (Registration Requirements, page 12):

The last sentence of the last paragraph of the section has been revised to remove reference to Appendix IX, which was included in error. The language referring to Appendix IX has been replaced with the following: "the RevAssist Overview on the CALGB 100104 study web page for further information."

Section 6.0 (Required Data, page 20):

- In footnote ‡, the follow-up time points have been revised to match those changed with the previous protocol update #16: "Q 3 months for four years, then q 6 months year five. If patient continues on study maintenance therapy after year 5, then follow-up will continue every 6 months until disease progression."
- In Footnote G, the last sentence has been revised to remove reference to Appendix IX, which was included in error. The language referring to Appendix IX has been replaced with the following: "the RevAssist Overview on the CALGB 100104 study web page for further information."

UPDATES TO THE MODEL CONSENT:

No changes have been made to the model consent document.

This study remains closed to patient accrual.

A replacement protocol document has been issued.

ATTACH TO THE FRONT OF EVERY COPY OF THIS PROTOCOL

CC: CTSU, ECOG, SWOG

Activation Date: 12/15/04
Includes Update #18

CANCER AND LEUKEMIA GROUP B

CALGB 100104/ECOG 100104

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CAEPR for lenalidomide appears in Section 14.3

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This study is supported by the NCI Cancer Trials Support Unit (CTSU). Institutions not aligned with CALGB or ECOG will participate through the CTSU mechanism as outlined below and detailed in the CTSU logistical appendix.

- The **study protocol and all related forms and documents** must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org
- Send completed **site registration documents** to the CTSU Regulatory Office. Refer to the CTSU **logistical** appendix for specific instructions and documents to be submitted.
- **Patient enrollments** will be conducted by the CTSU. Refer to the CTSU logistical appendix for specific instructions and forms to be submitted.
- Data management will be performed by the CALGB. **Case report forms** (with the exception of patient enrollment forms), **clinical reports, and transmittals** must be sent to CALGB unless otherwise directed by the protocol. Do not send study data or case report forms to the CTSU Data Operations.
- **Data query and delinquency reports** will be sent directly to the enrolling site by CALGB. (generally via email but may be sent via fax or postal mail). Please send query responses and delinquent data to CALGB and do not copy the CTSU Data Operations. Query responses should be sent to CALGB via postal mail (no transmittal form needs to accompany response). Each site should have a designated CTSU Administrator and Data Administrator and must keep their CTEP AMS account contact information current. This will ensure timely communication between the clinical site and the CALGB Statistical Center.

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A PHASE III RANDOMIZED, DOUBLE-BLIND STUDY OF MAINTENANCE THERAPY WITH CC-5013 (NSC # 703813, IND # 70116) OR PLACEBO FOLLOWING AUTOLOGOUS STEM CELL TRANSPLANTATION FOR MULTIPLE MYELOMA

Schema Page 1 of 2

Eligibility Criteria:

Patients must have active multiple myeloma requiring treatment (Durie-Salmon stage ≥ 1) and have stable disease or be responsive to at least 2 months of any induction therapy.

Prior Therapy:

- No more than 12 months of any prior therapy (see Section 4.2.1).
- Within 12 months of initiation of induction therapy.
- No prior progression after initial therapy. For example, patients whose therapy is changed due to suboptimal response, intolerance, etc. remain eligible provided they do not meet criteria for progression in Section 11.2.5. No more than two regimens (not including dexamethasone alone).
- No prior peripheral blood, bone marrow or solid organ transplant.

Peripheral blood stem cell collection ≥ 2 x 10^6 CD34+ cells/kg (patient body weight) and preferably 5 x 10^6 cells/kg (patient body weight). Stem cells may be collected at any time prior to transplant. Peripheral blood stem cell collection may occur before or after registration.

Age ≥ 18 to ≤ 70 years.

ECOG Performance Status 0-1

DLCO > 50% predicted with no symptomatic pulmonary disease.

LVEF ≥ 40% by MUGA or echo.

No uncontrolled diabetes mellitus or active serious infection.

No HIV, HBSag, or Hep C positive patients.

Non-pregnant and non-nursing.

Initial Required Laboratory Values:

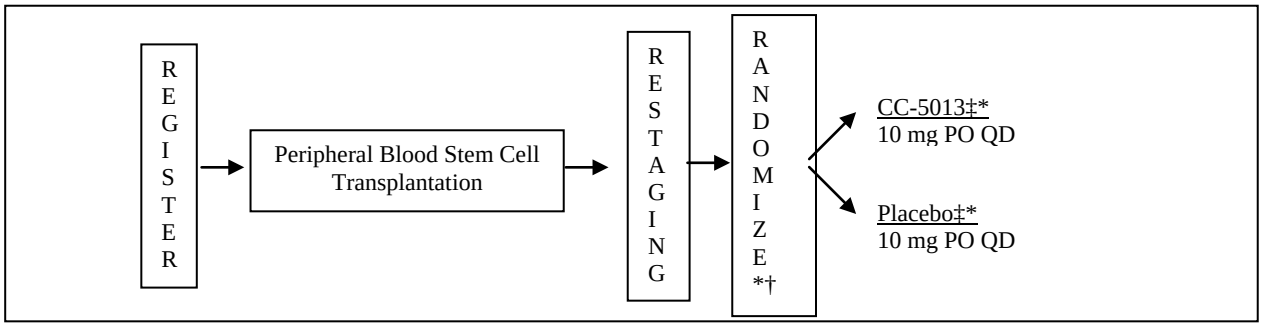
ANC	≥ 1000/μL
Platelets	≥ 100,000/μL
Creatinine Clearance*	≥ 40 cc/min
Creatinine	≤ 2 mg/dL
Total Bilirubin	≤ 2 mg/dL
AST, Alk. Phos.	≤ 3 x ULN
U-HCG or serum HCG	Negative

**To be calculated by method of Cockcroft-Gault (see Appendix I) or after 24 hour urine collection.*

Treatment assignments were unblinded on 12/17/09. As of 12/17/09, no more patients will be randomized between CC-5013 and placebo. See Section 7.3.

SCHEMA OVERVIEW

Patients will be registered prior to stem cell transplantation. Stem cell transplant must begin within 4-6 weeks of registration.



* **Collect 5-7 mL bone marrow aspirate at time of original diagnosis or after a maximum of no more than 2 cycles of induction therapy (if possible), prior to transplant, prior to randomization, at time of progression or relapse.**

** Re-staging will occur between Day +90 and +100 after transplant and prior to randomization.

† Prior to randomization, patients must have adequate organ function (ANC ≥ 1000/μL, platelet count ≥ 75,000/μL, creatinine ≤ 2 mg/dL, bilirubin ≤ 2 mg/dL, AST ≤ 3 x ULN, and Alk. Phos. ≤ 3 x ULN) and must have no evidence of progressive disease. Randomization to study drug (CC-5013 or placebo) will occur between Day +90 to +100. Initiation of maintenance therapy will begin between Day +100 to +110.

‡ Study drug (CC-5013 or placebo) will begin at a dose of 10 mg PO daily (2 capsules per day). After three months, the dose

will be increased, provided ANC ≥ 1,000/μL, platelet count ≥ 75,000/μL, and all non-hematologic toxicity is ≤ grade 1, to 15 mg PO daily (3 capsules per day).

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TREATMENT SCHEMA
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SCHEMA

All therapy & growth factor doses are based on corrected weight (see Section 7.0, 8.2).

I. AUTOLOGOUS PERIPHERAL BLOOD STEM CELL TRANSPLANT - Autologous Stem Cell Product

Mobilization of autologous peripheral blood stem cells will be performed according to institutional guidelines. Peripheral blood stem cell collection should target an optimal CD34+ cell dose > 5 x 10^6 cells/kg (actual weight) with a minimum of ≥ 2 x 10^6 CD34+ cells/kg. Collection may be performed at any time prior to registration.

Autologous Peripheral Blood Stem Cell (PBSC) Transplantation

Peripheral blood stem cell transplant must begin within 4-6 weeks of registration.

	ACV/VCV — *through Day + 100 for pts. with a history of herpes simplex infection or seropositivity* →									
	Melphalan (see below)									
				PBSCT						
				G-CSF ***(To Begin After Day 0 and on or Before Day +5)*** ⟶						
						F ⟶				
						Levo ⟶				
	TMP/SMX to be initiated on Day + 30 or at time ANC > 1000/µL until Day +100 (see below)									
Day	**-3**	**-2**	**-1**	**0**	**+1**	**+2**	**+3**	**+4**	**+5**	**+6…**

ACV/VCV Patients with a history of herpes simplex infection or seropositivity will receive acyclovir 200-400 mg PO TID Days -3 through Day +100 (or institutional standard). Valacyclovir or another antiviral, according to institutional practices, may be substituted for acyclovir.

Mel Melphalan may be given **EITHER AS A SINGLE DOSE** of 200 mg/m^2 IV over 30-60 minutes on Day -2 **OR Day -1**, **OR AS A DIVIDED DOSE** of 100 mg/m^2/day IV over two days on **EITHER** Days -3 and -2 **OR** Days -2 and -1 (**200 mg/m^2 total dose**).

PBSCT Peripheral blood stem cell infusion on Day 0.

F Fluconazole 200 mg/day PO **recommended** beginning Day +2 until ANC > 500/µL, or as clinically indicated.

Levo Levofloxacin 500 mg/day PO (or equivalent) **recommended** beginning Day +2 until ANC > 500/µL, or as clinically indicated.

G-CSF G-CSF 5 µg/kg/day SubQ after Day 0 and on or before Day +5 and continuing until ANC ≥ 1500/µL for 2 days or ≥ 5000/µL for one day. G-CSF then should be stopped but should be resumed if the ANC < 500/µL. If resumed it should be continued until ANC > 5000/µL for 2 days.

TMP/SMX Cotrimoxazole (Bactrim®) will be administered as one double strength (DS) tablet BID three times weekly beginning on Day +30 or when ANC > 1000/µL through Day +100 (or institutional standard). Patients allergic to cotrimoxazole should receive dapsone 100 PO 3x/week or inhaled pentamidine (300 mg monthly). Other PCP prophylaxis regimens, according to institutional procedures, may be substituted.

II. MAINTENANCE THERAPY: CC-5013 VERSUS PLACEBO TREATMENT

Treatment assignments were unblinded on 12/17/09. As of 12/17/09, no more patients will be randomized between CC-5013 and placebo. See Section 7.3.

Randomization to study drug (CC-5013 or placebo) will be undertaken between Day +90 to +100 post-transplantation. Initiation of maintenance therapy with study drug will begin between Day +100 and Day +110. Prior to randomization, patients must undergo disease re-staging between Day +90 and +100, must have adequate organ function (ANC ≥ 1000/µL, platelet count ≥ 75,000/µL, creatinine clearance ≥ 30 mL/min, bilirubin ≤ 2 mg/dL, AST ≤ 3 x ULN, and Alk. Phos. ≤ 3 x ULN), and must have no evidence of progressive disease.

The initial dosage of CC-5013 will be 10 mg (2 capsules of 5 mg each) PO daily. The study drug will be administered until disease progression.

After 3 months of study drug, the dose will be increased to 15 mg daily (3 capsules) if the ANC > 1000/µL and platelets > 75,000/µL. If for any reason, a patient is not able to be dose escalated, dose escalation should be attempted by the time of the next re-staging. If at next restaging, the patient has not recurred or progressed, and the patient is not able to be dose escalated, patient may continue on treatment at current dose level. See Section 8.1 for study drug dose modifications.

TABLE OF CONTENTS

1.0 INTRODUCTION

1.1 Autologous Hematopoietic Stem Cell Transplantation

Autologous stem cell transplantation (ASCT) has become an important form of therapy for patients with multiple myeloma [1-5]. The use of stem cell support allows intensive therapies such as high-dose melphalan to be given with acceptable morbidity and a low treatment-related mortality (TRM) rate of < 3%. The French IFM 90 phase III study of newly diagnosed myeloma patients comparing ASCT to standard chemotherapy demonstrated improved responses, prolongation of median event-free survival (EFS) from 18 to 27 months ($p = 0.01$), and extension of median overall survival (OS) from 37 months to not-reached ($p = 0.03$). Based on this important study, ASCT became the treatment of choice for most young patients with aggressive myeloma. A recent Medical Research Council (MRC) study has confirmed the benefit of ASCT when compared to standard therapy [6]. OS and progression-free survival (PFS) were superior in the transplant arm. Median survival was increased in the transplant arm by almost 1 year (54.1 versus 42.3 months) (6). In the IFM 95 study of ASCT for myeloma, the preparative regimen of melphalan 200 mg/m^2 was shown to be equally effective (median EFS of 21 months in both arms) and considerably less toxic (TRM 0% vs 3.6%) than the regimen of melphalan 140 mg/m^2 plus total body irradiation (TBI) [7]. Based on this finding, the ASCT regimen of melphalan 200 mg/m^2 has become the standard of care.

Despite improvements in the outcome of myeloma with the use of ASCT, the treatment is not curative, and most patients will have progression of disease within 2-3 years. There is no standard approach to treatment after a single autologous transplant. Some centers have advocated performing tandem autologous transplants with the goal of further extending remission duration and survival. This strategy was tested in the French IFM 94 study, which has recently been presented with median follow-up of 75 months [8]. The outcome for EFS and OS appeared identical during the first 4 years of observation, but later diverged. Median EFS was 25 months for single transplant versus 30 months for tandem. However, 7-year EFS was improved in the tandem arm (20% versus 10%, $p = 0.03$) and 7-year OS was improved from 21% to 42% ($p = 0.01$). One problem with extrapolating the results of the IFM 94 study is that the preparative regimens used are no longer considered standard. Thus, the outcome of single versus double transplant using the regimen of melphalan 200 mg/m^2 is unknown. Also, a second trial of tandem transplant has yet to show an advantage to the tandem approach [9]. Another approach to treatment after a single autologous transplant is non-myeloablative allogeneic transplant. A pilot trial of this strategy has been reported, with encouraging results [10]. Based on this study, CALGB has activated protocol 100001 to confirm the safety and efficacy of autologous followed by non-myeloablative allogeneic transplantation in patients under age 65 with matched sibling donors (CALGB 100001). However, the majority of patients with myeloma treated initially with ASCT will not be good candidates for immediate allogeneic transplant or have a suitable allogeneic donor. ASCT after vincristine, adriamycin, and dexamethasone (VAD) or other dexamethasone-based induction is the primary therapy for the majority of patients under 70 years of age. This trial is important because it has the potential to define a new approach to remission extension following initial ASCT for multiple myeloma.

1.2 Standard Chemotherapy for Multiple Myeloma

Standard therapy for multiple myeloma has consisted of single agent melphalan or combination chemotherapy [11, 12]. Several regimens have been developed for induction therapy of myeloma although standard therapy remains controversial [Reviewed in [13]). VAD

is a standard induction regimen for multiple myeloma, although there is data to suggest that dexamethasone is the most active agent in the regimen [14, 15]. Recently thalidomide plus dexamethasone has been utilized as induction therapy for primary myeloma [16, 17]. Response rates have ranged from 64% to 72% with many patients going on to ASCT. With the publication of these results, thalidomide will become more widely used for primary therapy for multiple myeloma; thus it will be allowed as part of induction therapy in this study. However, it is a toxic agent and is not tolerated at high doses for extended time periods. In addition, it is a much less active agent than CC-5013 against multiple myeloma. CC-5013 appears to be an ideal choice to test as a maintenance agent following standard induction therapy and ASCT. It is highly active against relapsed and refractory multiple myeloma (see preliminary data below). It is an oral agent and very well-tolerated, with minimal non-hematologic toxicity, even in heavily pre-treated patients. With appropriate dosing, hematologic toxicity following initial ASCT should be modest.

1.3 Immunomodulatory Therapy for Multiple Myeloma Following Autotransplant

Previously, immunomodulatory therapy to reduce disease progression has been attempted following ASCT for multiple myeloma with no clear benefit. The most studied agent is interferon-α. The results of several randomized trials demonstrated either a modest or no benefit for the use of interferon-α following ASCT in an attempt to prevent disease progression and increase survival [18-23].

Immunomodulatory drugs (IMiDs) have been utilized for the treatment of a variety of malignant and nonmalignant disorders. In particular, thalidomide has been investigated because of its diverse pharmacologic and immunologic effects [24]. CC-5013 3-(4'aminoisoindoline-1'-one)-1-piperidine-2,6-dione, is an IMiD analog of thalidomide that is under clinical development for use in the treatment of multiple myeloma. Thalidomide's pleiotrophic effects are mediated, at least in part, through its ability to modulate the immune system. Thalidomide inhibits tumor necrosis factor-alpha (TNF-α) production, IL-1®, IL-6 secretion by activated peripheral blood mononuclear cells. CC-5013 has the same effects but is 50 to 2000 times more potent than thalidomide. CC-5013 increases the anti-inflammatory cytokine IL-10 and upregulates T helper 2 (Th2) type immunity [25]. Thalidomide has proven to be a useful agent for the treatment of patients with *de novo*, recurrent or progressive multiple myeloma [16, 17, 26-28]. The exact mechanism by which thalidomide and other IMiDs exert anti-tumor effects is not clear. In addition to their immune modulatory effects, both thalidomide and CC-5013 induce apoptosis in multiple myeloma cell lines and overcome drug resistance of multiple myeloma cells to conventional therapy [Investigator's Brochure, Celgene Corporation, Version 6, 2002].

The major hypothesis of this study is that CC-5013 maintenance therapy after ASCT for multiple myeloma will prolong the time to disease progression. CC-5013 has a superior side-effect profile when compared to thalidomide, which can cause peripheral neuropathy, somnolence, bradycardia, skin rash and edema even in doses as low as 50 to 100 mg per day. CC-5013 has been well tolerated in normal human volunteers as a single dose up to 400 mg or in weekly 100 mg twice a day dosing [Investigator's Brochure, Celgene Corporation, Version 6, 2002]. The most common adverse events were rash and pruritis. Elevated serum transaminases were observed, but at less than 2 times the normal range. Mean lymphocyte counts were decreased. There was no evidence of electrocardiogram abnormalities. The CC-5013 phase I-II studies have been completed [29]. The maximum tolerated dose (MTD) as a daily dose is 25 mg with dose-limiting toxicity (DLT) being grade 3/4 myelosuppression. A second randomized phase II study has been reported that examined two higher dose schedules of CC-5013 (15 mg twice daily versus 30 mg daily) on a 3 weeks on/1 week off schedule [30]. This study examined 70 patients randomized to the two schedules. Fifty-seven patients were

analyzed for toxicity, and 46 were analyzed for response. In a heavily pre-treated group of patients, 24% of patients responded with a complete response (CR) or partial response (PR), and only 16% had progressive disease. One patient developed grade 3 neuropathy. The most common grade 1 and 2 toxicities were fatigue, self-limited rash, muscle cramps and diarrhea. Grade 3 or 4 myelosuppression was seen in 26% (n=15) of patients. Eleven of these 15 patients had undergone a prior stem cell transplant, and the majority of patients (n=11) were in the 15 mg twice a day dose. The dose and schedule were selected as most appropriate for long-term maintenance therapy. This dose has activity in relapsed and refractory patients. The daily dosing schedule is the simplest and will provide the best opportunity for compliance. There is no evidence that an interrupted schedule will enhance long-term tolerability or response. The starting dose of 10 mg was selected based on a high probability of hematologic tolerability following ASCT. For those patients who do not show cumulative myelosuppression, after 3 months there will be an opportunity to escalate the dose to 15 mg daily. We believe that this it is very unlikely that a higher dose than 15 mg will be tolerable on a long-term basis. Conversely, the study is designed so that the dose can be de-escalated to 5 mg daily or to 5 mg for 3 weeks out of 4 weeks. This treatment design will allow for an adequate evaluation of the drug at a high dose level if tolerated and for continued therapy at a lower dose if myelosuppression occurs.

New treatment strategies must be developed for maintaining remissions in patients with myeloma following ASCT. This trial consists of standard induction therapy, stem cell mobilization and collection and autotransplant to cytoreduce multiple myeloma patients followed by a randomized placebo-controlled trial that will examine the utility of CC-5013 for the prevention of disease progression.

1.4 Inclusion of Women & Minorities

Multiple myeloma, a relatively uncommon malignancy in the United States, is more prevalent among men than women (6:1 male to female ratio), and its incidence in African Americans is higher than in Caucasians (1:2 Caucasian to African American ratio).

Patients who meet the eligibility criteria of this study will be included without regard to gender, race, or ethnicity. Although there is no evidence to suggest that the outcome will differ by gender or ethnicity and there is insufficient power to detect small or moderate effects, we will, in a secondary analysis, report the results by gender and ethnicity. In addition, multiple myeloma is rarely seen under the age of 30 and is reportable under the age of 20.

2.0 OBJECTIVES

2.1 Primary Objective

To determine the efficacy of CC-5013 in prolonging time to disease progression in patients with multiple myeloma after ASCT

2.2 Secondary Objectives

2.2.1 To determine if CC-5013 will increase the CR rate in patients with multiple myeloma following ASCT

2.2.2 To compare the progression-free survival (PFS) and overall survival (OS) in patients with multiple myeloma who have undergone ASCT and who then are randomized to either CC-5013 or placebo

2.2.3 To determine the feasibility of long-term administration of CC-5013 to multiple myeloma patients who have undergone ASCT

3.0 ON-STUDY GUIDELINES

This clinical trial can fulfill its objectives only if patients appropriate for the trial are enrolled. All relevant medical and other considerations should be taken into account when deciding whether this protocol is appropriate for a particular patient. To maximize patient safety, patients will be treated on this protocol only at Cooperative Group-approved autologous transplant centers. Physicians should consider the risks and benefits of any therapy and, therefore, only enroll patients for which the agents administered are appropriate. Although they will not be considered as formal eligibility criteria, as part of this decision-making process, physicians should recognize that the following may increase the risk to the patient entering this protocol:

- Other serious illnesses which would limit survival to less than two years, or psychiatric conditions which would prevent compliance with treatment or informed consent. In particular, non-compliance would preclude long-term management during the maintenance portion of this study.
- Patients with a "currently active" second malignancy other than non-melanoma skin cancers. Patients are not considered to have a "currently active" malignancy if they have completed therapy and are considered by their physician to be at less than 30% risk of relapse.
- Patients considered to be at high risk of developing DVT/PE or arterial thromboses during maintenance therapy are to receive prophylactic aspirin or low molecular weight heparin unless contraindicated. Warfarin also may be used. High risk will be defined as a history of DVT/PE, significant family history, performance status ≥ 2, smoking history, use of oral contraceptives, and concurrent use of epoetin. Patients with diabetes mellitus or coronary artery disease also are considered to be at high risk.

4.0 ELIGIBILITY CRITERIA

4.1 Active Multiple Myeloma

Patients must have active multiple myeloma requiring treatment (Durie-Salmon stage ≥ 1) and have stable disease or be responsive to at least 2 months of any induction therapy. Patients with smoldering myeloma are not eligible unless the disease has progressed to ≥ stage 1.

4.2 Prior Therapy

4.2.1 No more than 12 months of any prior therapy, including CC-5013 and thalidomide

4.2.2 Within 12 months of initiation of induction therapy

4.2.3 **No prior progression after initial therapy.** For example, patients whose therapy is changed due to suboptimal response, intolerance, etc., remain eligible, provided they do not meet criteria for progression in Section 11.2.5. In addition, no more than two regimens will be allowed excluding dexamethasone alone.

4.2.4 **No prior peripheral blood, bone marrow, or solid organ transplant.** CC-5013 is associated with upregulation of T-cell function, as well as other pleiotrophic immunomodulatory effects. Patients receiving solid organ transplants who receive immunosuppressive agents could be at risk for graft rejection while receiving study drug on this protocol. Because it is not known how CC-5013 could affect solid organ transplant function, patients who have received a solid organ transplant will be excluded from study.

4.3 Peripheral Blood Stem Cell Collection

Patients must have peripheral blood stem cell collection of $\geq 2 \times 10^6$ CD34+ cells/kg (patient body weight) and preferably 5×10^6 cells/kg (patient body weight). Stem cells may be collected at any time prior to transplant. Peripheral blood stem cell collection may occur before or after registration.

4.4 Age Requirement

Patients must be ≥ 18 and ≤ 70 years of age.

4.5 ECOG Performance Status

Patients must have ECOG performance status of 0-1.

4.6 DLCO

Patients must have DLCO > 50% predicted with no symptomatic pulmonary disease.

4.7 LVEF

Patients must have LVEF $\geq 40\%$ by MUGA or echocardiogram.

4.8 Diabetes

Patients must not have ncontrolled diabetes mellitus.

4.9 Infection

Patients must not have an active serious infection.

4.10 HIV, HBSag, or Hep C

Patients must not be HIV, HBSag, or Hep C positive. Patients with immune dysfunction may be at a significantly higher risk of toxicity from intensive immunosuppressive therapies.

4.11 Pregnancy and Nursing Status

Patients must be non-pregnant and non-nursing. Due to the unknown teratogenic potential of lenalidomide, pregnant or nursing patients may not be enrolled. Women of childbearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL 10-14 days prior to registration and repeated within 24 hours prior to the first dose of lenalidomide. In addition, women of childbearing potential taking lenalidomide must have a pregnancy test performed by the doctor weekly during the first 4 weeks of treatment, and then every 4 weeks if menses are regular and every 2 weeks if menses are irregular, and then 30 days following the last dose of lenalidomide. Women of childbearing potential must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control - one highly effective method (IUD, hormonal, tubal ligation, or partner's vasectomy), and one additional effective method (latex condom, diaphragm, or cervical cap) - AT THE SAME TIME, at least 4 weeks before she begins lenalidomide therapy. "Women of childbearing" potential is defined as a sexually mature woman who has not undergone a hysterectomy or who has had menses at any time in the preceding 24 consecutive months. Men must agree not to father a child and must use a latex condom during

any sexual contact with women of childbearing potential while taking lenalidomide and for 4 weeks after therapy is stopped, even if they have undergone a successful vasectomy.

4.12 Initial Required Laboratory Values

ANC	≥ 1000/μL
Platelets	≥ 100,000/μL
Creatinine Clearance*	≥ 40 cc/min
Creatinine	≤ 2 mg/dL
Total Bilirubin	≤ 2 mg/dL
AST, Alk. Phos.	≤ 3 x upper limits of normal
U-HCG or serum HCG	negative (if patient of childbearing potential)

* To be calculated by method of Cockcroft-Gault (see Appendix I) or after 24-hour urine collection.

5.0 REGISTRATION, RANDOMIZATION, STRATIFICATION, DATA SUBMISSION, AND SAMPLE SUBMISSION

5.1 Registration

5.1.1 Registration Requirements

Informed Consent: the patient must be aware of the neoplastic nature of his/her disease and willingly consent after being informed of the procedures to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts. Human protection committee approval of this protocol and of its consent form are required.

Lenalidomide Counseling Program (LCP): Each site must have two trained counselors available for counseling all patients receiving lenalidomide supplied by the Division of Cancer Treatment and Diagnosis. Two healthcare professionals (including, but not limited to, nurses, pharmacists, and non-investigator physicians) must complete training using the online program provided free by Celgene, the Lenalidomide Counseling Program (LCP). (See Section 9.3 for information regarding the requirements of the LCP.)

Starting on September 15, 2012, the LCP will transition to the RevAssist® for Study Participants (RASP) program. As of December 15, 2012, the RASP program will completely replace the LCP. Please see Section 9.3 and the RevAssist Overview on the CALGB 100104 study web page for further information.

5.1.2 CALGB Registration Procedures

This study uses the CALGB on-line Patient Registration system. Registration will be accepted only through CALGB Main Member institutions, selected affiliate institutions, and CCOPs using the on-line Patient Registration system.
Confirm eligibility criteria (see Section 4.0). Complete the Registration Worksheet. Access the on-line Patient Registration system via the patient registration icon on
the CALGB Information Systems (IS) Application main menu. If the registering CRA requires assistance, he/she may consult the on-line help file located under the Help menu of the CALGB IS Application. If further assistance is required, the registering CRA may call the CALGB Registrar (919-668-9396, Monday-Friday, 9 AM – 5 PM, Eastern Time; Registration fax 919-668-9397). Enter the following information:
Study
Name of group (CALGB)
Name of institution where patient is being treated
Name of treating physician
Name of treating physician or responsible CRA
Other group patient ID #, if applicable

CALGB patient ID #, if applicable
Patient's initials (Last Initial, First Initial, Middle Initial)
Patient's Social Security #, date of birth, and hospital ID #
Patient's gender
Patient's race
Type of insurance (Method of Payment)
Disease, type and stage, if applicable
Patient's Postal Code, if applicable
Treatment start date
Date of signed consent
Date of HIPAA authorization
Patient demographics, if applicable
Eligibility criteria met (no, yes)

When the patient is registered, a patient identification number will be generated. Please write the number in your records.

The Main Member Institution and registering institution will receive a Confirmation of Registration. Please check for errors. Submit corrections in writing to CALGB Statistical Center, Hock Plaza, 2424 Erwin Road, Suite 802, Durham, NC 27705.

5.1.3 ECOG Registration Procedures

NOTE: Participation in this study is limited to ECOG approved autologous transplant centers. A list of ECOG-approved autologous transplant centers is located on the ECOG web at: http://www.ecog.org/ecoginst/transplant.hmtl - autologous.

Submitting Regulatory Documents

Before an ECOG institution may enter patients, protocol specific regulatory documents must be submitted to the CTSU Regulatory Office at the following address:

CTSU
Coalition of National Cancer Cooperative Oncology Groups
1818 Market Street, Suite 1100
Philadelphia, PA 19102
Fax: (215) 569-0206

Required Protocol Specific Regulatory Documents

1. CTSU Regulatory Transmittal Form.

2. Copy of IRB Informed Consent Document.

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

3. A. CTSU IRB Certification Form, or

   B. HHS 310 Form, or

   C. IRB Approval Letter

Note: The above submissions must include the following details:

- indicate all sites approved for the protocol under an assurance number.
- OHRP assurance number of reviewing IRB.
- Full protocol title and number.

- Version Date.
- Type of review (full board vs. expedited).
- Date of review.
- Signature of IRB official.

The CTSU encourages you to link to the following RSS2.0 webpage so that more information on RSS2.0 as well as the submission forms can be accessed: http://www.ctsu.org/rss2_page.asp.

If you have questions regarding regulatory document submission, please telephone the CTSU Help Desk at 1-888-823-5923 or e-mail CTSUContact@westat.com Monday through Friday, 9:00 am - 6:00 pm.

Patients must not start protocol treatment prior to registration.

ECOG Registration Procedures

Institutions may begin to register eligible patients to this study by completing the Registration Worksheet via the ECOG webpage using the Web-based Patient Registration Program (http://webreg.ecog.org). If you need assistance or have questions please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022. Please note that a password is required to use this program. The following information will be requested: Protocol Number; Investigator Identification (including institution and/or affiliate name and investigator's name); Patient Identification (including patient's initials, chart number, social security number and demographics [sex, birth date, race, nine-digit zip code and method of payment]); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 4.0. After completing the Registration Worksheet on the web, the institution will call the Central Randomization Desk at the ECOG Coordinating Center to provide the Transaction ID# at (617) 632-2022, Monday-Friday, between the hours of 9:00 am and 4:30 pm ET. ECOG members should not call the CALGB directly.

The ECOG Randomization Desk will complete the registration process and call the institution back with confirmation of registration for the patient.

5.2 Randomization

Treatment assignments were unblinded on 12/17/09. As of 12/17/09, no more patients will be randomized between CC-5013 and placebo. See Section 7.3.

5.2.1 Randomization Requirements

Randomization will be undertaken between Day + 90 - +100 post-transplantation. Prior to randomization, patients must undergo disease re-staging between Day +90 - +100, must have adequate organ function (ANC $\geq$ 1000/µL, platelet count $\geq$ 75,000/µL, creatinine $\leq$ 2 mg/dL, bilirubin $\leq$ 2 mg/dL, AST $\leq$ 3 x ULN, and Alk. Phos. $\leq$ 3 x ULN), and must have no evidence of progressive disease.

5.2.2 CALGB Randomization Procedures

Randomization occurs as a separate event from registration and must occur between Day +90 - +100 post-transplantation. Randomization through CALGB Main Member, selected affiliates, and CCOP institutions is to be performed by an approved institutional contact using the on-line registration system. Patients must begin maintenance therapy between Day +100 – Day +110. Confirm eligibility criteria. Complete the Confirmation of Randomization Worksheet. Access the on-line Patient Registration system via the Patient Registration icon on the CALGB IS Application main menu. If the registering CRA

requires assistance, he/she may consult the on-line help file located under the help menu of the CALGB IS Application. If further assistance is required, the registering CRA may call the CALGB Registrar (919-668-9396, Monday-Friday, 9 AM – 5 PM, Eastern Time). Enter the following information:

Study
Name of group (CALGB)
Name of institution where patient is being treated
Name of treating physician
NCI Investigator ID number
Express courier account number (if desired to guarantee expedited arrival of CC-5013 at clinical site)
Name of treating physician or responsible CRA
Other group patient ID #, if applicable
CALGB patient ID #

The patient is randomized according to the stratification factors in Section 5.3, which must be entered before the treatment is assigned. For example, if age is a stratification factor, the actual age is collected. If the stratification question is a "no, yes" question, please enter the value “1” for no and “2” for yes. Once the randomization is complete, note the patient's treatment assignment in your records.

The Main Member Institution and registering institution will receive a Confirmation of Randomization. Please check for errors. Submit corrections in writing to CALGB Statistical Center, Hock Plaza, 2424 Erwin Road, Suite 802, Durham, NC 27705.

Blinded, patient specific clinical supplies of CC-5013/Placebo will be requested from the Pharmaceutical Management Branch, CTEP, NCI by the CALGB at the time of randomization and should arrive at the clinical site within 7 to 10 days of randomization (see Section 9.3).

5.2.3 ECOG Randomization Procedures

Randomization occurs as a separate event from registration and must occur between Days +90 - +100 post-transplantation.

Please refer to Section 5.2.1 for specific study requirements. Patients must begin maintenance therapy between Day +100 - +110 post-transplantation.

Institutions may begin to randomize eligible patients to this study by completing the Randomization Worksheet via the ECOG webpage using the Web-based Patient Registration Program (http://webreg.ecog.org). If you need assistance or have questions please telephone the Central Randomization Desk at the ECOG Coordinating Center at (617) 632-2022. Please note that a password is required to use this program. The following information will be requested: Protocol Number; Investigator Identification (including institution and/or affiliate name and investigator’s name); Patient Identification (including patient’s initials, chart number, social security number and demographics [sex, birth date, race, nine-digit zip code and method of payment]); Eligibility Verification. Patients must meet all of the eligibility requirements listed in Section 7.2. After completing the Randomization Worksheet on the web, the institution will call the Central Randomization Desk at the ECOG Coordinating Center to provide the Transaction ID# at (617) 632-2022, Monday-Friday, between the hours of 9:00 am and 4:30 pm ET. ECOG members should not call the CALGB directly.

The ECOG Randomization Desk will complete the randomization process and call the institution back with confirmation of randomization for the patient.

Blinded patient specific clinical supplies of CC-5013/Placebo will be requested from the Pharmaceutical Management Branch, CTEP, NCI by the CALGB at the time of randomization and should arrive at the clinical site within 7 to 10 days of randomization (see Section 9.3).

5.3 Stratification Factors

(at time of randomization)

- β2 Microglobulin (baseline): elevated (≥ 2.5 mg/dL) [1] vs normal [2].
- Prior therapy with thalidomide: yes [1] vs no [2].
- Prior therapy with CC-5013: yes [1] vs no [2].

5.4 Data Submission

Forms should be submitted to the CALGB Statistical Center in compliance with the data submission schedule below. This study will use NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 for routine toxicity reporting on study forms. There are two options for submitting forms that use the Teleform barcode and cornerstones:

- the forms may be faxed to the DOC at 919-416-4990. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.
- the forms may be mailed to the CALGB Statistical Center, Hock Plaza, 2424 Erwin Road, Suite 802, Durham, NC 27705. Please note that the four cornerstones and the form id ("bitmap") must appear on the form. Copies must be 100% of the original form size.

Supporting documentation for studies using Teleform can be faxed or mailed along with the Teleform forms.

ECOG Institution Data Submission: the original data forms listed below should be submitted at the required intervals to the CALGB Statistical Center, Data Operations Center. Include the CALGB and ECOG study number and patient ID number.

Form		Submission Schedule
C-1223	100104 On-Study Form	
C-1274	100104 Pre-Study Lab Values Form	Within one week of registration.
	Copies of baseline laboratory and pathology reports (including baseline monoclonal paraprotein information, bone marrow aspirate), skeletal survey, and cytogenetic reports*	
C-1337	100104 Sample Submission Form	*Send original to CALGB Statistical Center. Send copy along with sample*
	Autologous Stem Cell Transplant	
C-1224	100104 Follow-up Form	
C-1225	100104 Adverse Event Form	Submit from day of stem cell infusion to Day +100.
C-1284	100104 Multiple Myeloma Response Assessment Form	* If patient does not randomize to the maintenance therapy, submit C-1224, C-1225, and C-664 every 6 months until relapse or initiation of non-protocol therapy, whichever comes first.
C-664	Infectious Complications Form	
	Maintenance Therapy	
C-1224	100104 Follow-up Form	
C-1225	100104 Adverse Event Form	Every 3 months until 1 year post-transplant, then every 6 months until 5 years post-transplant.
C-1284	100104 Multiple Myeloma Response Assessment Form	
C-664	Infectious Complications Form	*If patient continues on study/on drug, proceed as above until progression/non-protocol treatment, or death. Do not stop at ten years if patient continues on study/on treatment. If patient is off study/off treatment before 5 years post-transplant, continue data submission as below.*
C-1273	Dosage and Blood Count Form	
	Copies of laboratory and pathology reports (including monoclonal paraprotein information, bone marrow aspirate), skeletal survey, and cytogenetic reports documenting response, relapse and/or progression.	
C-300	Off-Treatment Notice	At conclusion of treatment.
C-400	Long-Term Follow-up Form	Every 6 months beginning 5 years post-transplant.
C-1001	New Primary Cancer Form	At occurrence of new primary.
C-2090	100104 Cancer Screening Form	Every 6 months, beginning 6 months after randomization, until death.

C-113	Notification of Death	At time of death.
C-1970	**CALGB: 100104 Continuation of Therapy Form (Unblinding)**	For all patients who have not met a study endpoint as of 12/17/09, submit no later than 3/15/10. (See Sections 7.3 and 9.3)

* Legible copies of all institutional laboratory, cytogenetic reports (when available) and baseline CT scan/skeletal survey reports used for patient registration must be submitted with the prestudy forms to the CALGB Statistical Center.

** Legible copies of all institutional laboratory, cytogenetic reports (when available) and baseline CT scan/skeletal survey reports documenting response, relapse, or progression must be submitted to the CALGB Statistical Center.

Please refer to the CALGB web site to obtain up-to-date data forms for this study.

5.5 Sample Submission

5.5.1 Sample Procurement

Collect 5-7 mL of bone marrow aspirate in one heparinized (green top) tube at the following timepoints:

- At time of diagnosis or after a maximum of no more than 2 cycles of induction therapy (if possible);
- Prior to transplant;
- Prior to randomization to either CC-5013 or placebo;
- At time of relapse and/or time of progression.

Label each tube with the CALGB patient ID #, CALGB study number (CALGB 100104), the sample collection timepoint (i.e., at time of diagnosis or after a maximum of no more than 2 cycles of therapy, prior to randomization, etc.), the date of sample collection.

5.5.2 Sample Submission

Samples must be sent on the same day they are obtained. Send the samples at ambient temperature, any day of the week, via overnight carrier for next day (check AM) delivery to:

Michael A. Caligiuri, M.D.
Attn.: CALGB 100104 Sample
CALGB Leukemia Tissue Bank
The Arthur G. James Cancer Hospital
and Research Institute
300 W. 10th Avenue, Lobby
Columbus, OH 43210
Phone: 614-688-4754 Fax: 614-688-4755

Note: If specimen is sent on Friday, CHECK SATURDAY DELIVERY on the overnight carrier invoice. Send a copy of the completed Form C-1337 (100104 Sample Submission Form) to the CALGB Statistical Center at the time of shipment.

5.5.3 ECOG Institution Sample Submission

Samples are to be submitted only from patients who have given written signed consent to allow samples to be banked for future research.

Submit samples as described in Sections 5.5.1 and 5.5.2. Include the CALGB and ECOG study number and patient ID number.

6.0 REQUIRED DATA

Guidelines For Pre-Study Testing

To be completed within 16 DAYS before registration:

- All blood work, history & physical.

To be completed within 42 DAYS before registration:

- Any baseline exams used for screening, e.g., PFTs, bone marrow aspirate and biopsy
- Any x-ray, scan of any type or ultrasound of uninvolved organs which is not used for tumor measurement.

Tests & Observations	Prior to Study	During Autotransplant (Day 0 to 30)	Prior to Randomization†	Maintenance Therapy and Post-Treatment Follow-up‡
History and Progress Notes	X	PRN	X	X
Physical Examination	X	PRN	X	X
Pulse, Blood Pressure	X	PRN	X	X
Height/Weight/BSA	X			
Performance Status	X	PRN	X	X
Tumor Measurements			X	X
Drug Toxicity Assessment			X	X
Education and Counseling				G
Laboratory Studies				
CBC, Differential, Platelets	X	PRN	X	A,X
Creatinine	X	PRN	X	X
Creatinine Clearance	X		F	F
Ca^{++}	X			X
Mg^{++}, AST, Alk. Phos., Bili., Albumin	X	PRN	X	X
Electrolytes	X	PRN	X	
TSH, T4	X			X
β2 Microglobulin	X		X	X
PFTs, MUGA or echocardiogram	X			
U-HCG or serum HCG	X		E	E
EKG	X			
Serum PEP	X		X	X
Serum IEP	X		X	X
Urine PEP (24 hour)	X		X	X
Urine IEP (24 hour)	X		X	X
Serum Free Light Chains	X		X	X
Quantitative Immunoglobulins	X		X	
HBSag, Hep C, HIV	X			
Staging				
Chest x-ray, PA & Lateral	X		X	
Bone Marrow Asp & Bx	X		X,B	B
Cytogenetics	X			C
Skeletal Survey for Myeloma	X		X	D

† Restage between Days +90 to +100 post-transplantation. If a patient does not undergo randomization, follow every 6 months until relapse or initiation of non-protocol therapy, whichever comes first (see Section 5.4).

‡ Q 3 months for four years, then q 6 months year five. If patient continues on study maintenance therapy after year 5, then follow-up will continue every 6 months until disease progression.

A Weekly during the first month of maintenance therapy at 10 mg dose, then q 2 weeks during the second month, then monthly while on study drug. After study drug dose escalation, obtain weekly x 4.

B At 3 and 12 months after Day 0 of autotransplant then yearly until 5 years post autotransplant, and at time of progression.

C Annually if initially abnormal.

D Yearly for five years.

E Women of childbearing potential must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL 10-14 days prior to registration and repeated within 24 hours prior to the first dose of CC-5013. In addition, women of childbearing potential taking CC-5013 must have a pregnancy test performed by the doctor weekly during the first 4 weeks of treatment, and then every 4 weeks if menses are regular and every 2 weeks if menses are irregular, and then 2 and 4 weeks following the last dose of CC-5013. (See Appendix VI, Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines, and Acceptable Birth Control Methods.)

F Perform estimated creatinine clearance (to be calculated by method of modified Cockcroft Gault formula, see Appendix I). See dose modifications in Section 8.1.4.6.

G The Lenalidomide Education and Counseling Guidance Document (Appendix VII) must be completed and signed by a trained counselor at the participating site prior to each dispensing of CC-5013 treatment. A copy of this document must be maintained in the patient records. The Lenalidomide Information Sheet (Appendix VIII) will be given to each patient receiving CC-5013 treatment. The patient must read this document prior to starting CC-5013 study treatment and each time they receive a new supply of study drug. Beginning on September 15, 2012, the LCP will transition to the RevAssist® for Study Participants (RASP) program. As of December 15, 2012, the RASP program will completely replace the LCP. Please see Section 9.3 and the RevAssist Overview on the CALGB 100104 study web page for further information.

7.0 TREATMENT PLAN

All therapy and growth factor drug doses will be based on a corrected body weight as follows: Ideal + 25% of the difference between actual and ideal weight (see Appendix II for ideal body weight). For patients whose actual weight is >150% of ideal, their "actual" weight will be capped at 150% of ideal (i.e., their corrected weight will be 112.5% of ideal). For patients whose actual weight is less than ideal, use their actual weight as the corrected weight.

7.1 Autologous Peripheral Blood Stem Cell (PBSC) Transplant

7.1.1 PBSC Mobilization

Mobilization of autologous peripheral blood stem cells will be performed according to institutional guidelines. Peripheral blood stem cell collection should target an optimal CD34+ cell dose > 5 x 10^6 cells/kg (actual weight) with a minimum of 2 x 10^6 CD34+ cells/kg. Stem cells may be collected at any time prior to transplant.

7.1.2 PBSC Transplant

Peripheral blood stem cell transplant must begin within 4-6 weeks of registration.

- **Melphalan** may be administered **EITHER AS A SINGLE DOSE** of 200 mg/m^2 IV over 30 to 60 minutes on Day -2 **OR** Day -1, **OR AS A DIVIDED DOSE** of 100 mg/m^2/day IV over two days on **EITHER** Days -3 and -2 **OR** Days -2 and -1 (**200 mg/m^2 total dose)**.
- **PBSC infusion** on Day 0.
- **G-CSF** 5 mcg/kg/day SubQ after Day 0 and on or before Day +5 and continuing until ANC ≥ 1500/µL for 2 days or ≥ 5000/µL for one day. G-CSF should then be stopped, but should be resumed if the ANC < 500/µL. If resumed, it should be continued until ANC > 5000/µL for 2 days.

- **Prophylactic antibacterial and antifungal antibiotic therapy are recommended.** Antibacterial and antifungal agents may be started on Day +2. A commonly used regimen is levofloxacin (or equivalent) 500 mg/day PO, fluconazole (or equivalent) 200 mg/day PO. Such therapy may be discontinued once the ANC is > 500/µL, unless otherwise clinically indicated.
- **Prophylactic antiviral therapy is required for patients with a history of herpes simplex infection or seropositivity.** Patients with a history of herpes simplex infection or seropositivity will receive acyclovir 200-400 mg PO TID Days -3 through Day +100 (or institutional standard). Valacyclovir or another antiviral, according to institutional practices, may be substituted for acyclovir.

- **Pneumocystis Carinii Pneumonia (PCP) Prophylaxis**

  In an attempt to prevent PCP, cotrimoxazole will be administered as one double strength (DS) tablet BID three times weekly beginning on Day + 30 or when ANC > 1000/µL through Day +100 (or institutional standard). Patients allergic to cotrimoxazole should receive dapsone 100 mg PO three times weekly or inhaled pentamidine instead (300 mg monthly). Other PCP prophylaxis regimens, according to institutional procedures, may be substituted.

7.2 Restaging

Restaging will be performed between Day +90 and +100 according to Section 6.0. Sample submission must occur prior to randomization (see Section 5.5).

7.3 Maintenance Therapy

(to begin between Days +100 and +110)

Treatment assignments were unblinded on 12/17/09. As of 12/17/09, no more patients will be randomized between CC-5013 and placebo.
Patients who have not been randomized as of 12/17/09 will be assigned to CC-5013.
The following is recommended for those patients already randomized who have not met a study endpoint as of 12/17/09:

- **Patients already receiving CC-5013 maintenance therapy continue CC-5013 until disease progression.**
- **Patients receiving placebo stop placebo therapy. Initiation of CC-5013 maintenance therapy for patients who have not yet met a study endpoint will be at the discretion of the patient and their treatment physician.**

CC-5013 will continue to be provided through the Pharmaceutical Management Branch, CTEP, NCI.
See Section 7.3.2 for information regarding the provision of CC-5013. See Section 9.3 for instructions on requesting drug and documentation of the choice of patient and physicians regarding continuation of therapy.

Patients completing autologous peripheral blood stem cell transplantation who meet the requirements in Section 7.3.1 will be randomized to proceed to maintenance therapy with study drug (i.e., either CC-5013 or placebo). Randomization to study drug will occur between Days +90 to +100. Patients will begin maintenance therapy between Days +100 to +110.
Prophylactic aspirin or low molecular weight heparin are to be given for patients with a high risk of developing DVT/PE or arterial thromboses during maintenance therapy unless contraindicated. Warfarin also may be used. High risk will be defined as a history of DVT/PE, significant family history, performance status ≥ 2, smoking history, use of oral contraceptives, and concurrent use of epoetin. Patients with diabetes mellitus or coronary artery disease also are considered to be at high risk.

7.3.1 Maintenance Therapy Randomization Requirements

Patients must meet all of the following criteria to proceed to maintenance therapy:

- Completion of ASCT as per Section 7.1;
- No evidence of disease progression as determined in Section 7.2;
- Performance Status 0-1 (see Appendix III);
- No uncontrolled diabetes mellitus;
- No active serious infection;
- Required Maintenance Therapy Randomization Laboratory Values:

ANC	≥ 1000/µL

Platelets	≥ 75,000/μL
Creatinine Clearence	≥ 30 mL/min**
Total Bilirubin	≤ 2 mg/dL
AST, Alk. Phos.	≤ 3 x upper limits of normal
U-HCG or serum HCG	negative (if patient of childbearing potential)*

* Required within 24 hours prior to first dose of maintenance therapy.

** To be calculated by method of Modified Cockcroft-Gault (see Appendix I).

- **Sample Submission:** Sample submission is required prior to maintenance therapy randomization (see Section 5.5).

7.3.2 Maintenance Therapy

Treatment assignments were unblinded on 12/17/09. As of 12/17/09, no more patients will be randomized between CC-5013 and placebo. See Section 9.3 for instructions on requesting drug and documentation of the choice of patient and physicians regarding continuation of therapy.

Blinded, patient specific clinical supplies of CC-5013/Placebo will be requested from the Pharmaceutical Management Branch, CTEP, NCI, by the CALGB at the time of randomization and should arrive at the clinical site within 7 to 10 days of randomization (see Section 9.3).

Patients will begin maintenance therapy with study drug between Days +100 and +110. Study drug will begin at 2 capsules per day (10 mg/day). After three months, provided the ANC is ≥ 1000/μL, platelet count ≥ 75,000/μL, and all non-hematologic toxicity is ≤ grade 1, then the dose will be increased to 3 capsules per day (15 mg/day). If for any reason, a patient is not able to be dose escalated, dose escalation should be attempted by the time of the next re-staging. If at next restaging, the patient has not recurred or progressed, and the patient is not able to be dose escalated, patient may continue on treatment at current dose level.

The patient will continue study drug until disease progression.

8.0 DOSE MODIFICATIONS AND MANAGEMENT OF TOXICITY

8.1 CC-5013 Dose Modifications

In the instance of more than one observed toxicity, the greatest dose reduction should be applied.

8.1.1 Hematologic Dose Modification Months 1-3

- **If on 2 capsules per day**, the ANC is < 500/μL or the platelet count is < 30,000/μL, then the study drug may be held for up to 8 weeks. Study drug may be re-instituted at 1 capsule per day if ANC is ≥ 500/μL or the platelet count is ≥ 30,000/μL. If, however, after an 8 week treatment delay, the ANC remains < 500/μL or the platelet count < 30,000/μL, the patient will be removed from protocol therapy.
- **If on 1 capsule per day,** the ANC is < 500/μL or the platelet count is < 30,000/μL, then the study drug may be held for up to 8 weeks. If ANC ≥ 500/μL or the platelet count is ≥ 30,000/μL, then study drug may be re-instituted at 1 capsule per day for 21 of 28 days. If, however, after an 8 week treatment delay, the ANC remains < 500/μL or the platelet count < 30,000/μL, the patient will be removed from protocol therapy.
- **If on 1 capsule per day for 21 of 28 days,** the ANC is < 500/μL or the platelet count is < 30,000/μL, then the patient will be removed from protocol therapy.

8.1.2 Hematologic Dose Modification Beyond Month 3

- **If on 3 capsules per day,** the ANC is < 500/μL or the platelet count is < 30,000/μL, then the study drug may be held for up to 8 weeks. Study drug may be re-instituted at 2 capsules per day if ANC is ≥ 500/μL or platelet count is ≥ 30,000/μL. If, however, after an 8 week treatment delay, the ANC remains < 500/μL or platelet count < 30,000/μL, the patient will be removed from protocol therapy.
- **If on 2 capsules per day,** the ANC is < 500/μL or the platelet count is < 30,000/μL, then the study drug may be held for up to 8 weeks. If ANC is ≥500/μL or the platelet count is ≥ 30,000/μL, then study drug may be re-instituted at 1 capsule per day. If, however, after an 8 week treatment delay, the ANC remains < 500/μL or the platelet count < 30,000/μL, the patient will be removed from protocol therapy.
- **If on 1 capsule per day,** the ANC is < 500/μL or the platelet count is < 30,000/μL, then the study drug may be held for up to 8 weeks. If ANC ≥ 500/μL or the platelet count is ≥ 30,000/μL, then study drug may be re-instituted at 1 capsule per day for 21 of 28 days. If, however, after an 8 week treatment delay, the ANC remains < 500/μL or the platelet count < 30,000/μL, the patient will be removed from protocol therapy.
- **If on 1 capsule per day for 21 of 28 days,** the ANC is < 500/μL or the platelet count is < 30,000/μL, then the patient will be removed from protocol therapy.

8.1.3 Dose Escalation Beyond Month 3

If a dose reduction has occurred and ANC ≥ 1000/μL and platelet count is ≥ 75,000/μL, the study drug dose may be re-escalated by one level (i.e., one capsule every day to two capsules every day, etc.). Hematologic parameters must remain at these threshold values for one month before another dose escalation may occur. Maximum study drug dose will be 3 capsules per day.

If for any reason, a patient is not able to be dose escalated, dose escalation should be attempted by the time of the next re-staging. If at next restaging, the patient has not recurred or progressed, and the patient is not able to be dose escalated, patient may continue on treatment at current dose level.

If for any reason the drug is held for a non-grade 3 hematologic toxicity, the drug will be held until the toxicity resolves and the drug started at one dose level lower. The drug should be re-escalated to the original dose within 4 weeks. The drug should be escalated as per the criteria listed above

8.1.4 Non-Hematologic Toxicity Dose Modifications

8.1.4.1 Neurologic Toxicity

- **If on 3 capsules per day,** a patient experiences ≥ grade 3 neurologic toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 2 capsules per day. If, however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.
- **If on 2 capsules per day,** a patient experiences ≥ grade 3 neurologic toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 1 capsule per day. If, however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.
- **If on 1 capsule per day,** a patient experiences ≥ grade 3 neurologic toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 1 capsule per day for 21 of 28 days. If,

however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.

- **If on 1 capsule per day for 21 of 28 days,** a patient experiences ≥ grade 3 neurologic toxicity, then the patient will be removed from protocol therapy.

8.1.4.2 Cardiac Toxicity

- **If on 3 capsules per day,** a patient experiences ≥ grade 2 cardiac toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 2 capsules per day. If, however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.
- **If on 2 capsules per day,** a patient experiences ≥ grade 2 cardiac toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 1 capsule per day. If, however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.
- **If on 1 capsule per day,** a patient experiences ≥ grade 2 cardiac toxicity, then the study drug may be held for as many as 8 weeks. If toxicity resolves to ≤ grade 1, then study drug may be re-instituted at 1 capsule per day for 21 of 28 days. If, however, after an 8 week treatment delay, the toxicity does not resolve to ≤ grade 1, the patient will be removed from protocol therapy.
- **If on 1 capsule per day for 21 of 28 days,** a patient experiences ≥ grade 2 cardiac toxicity, then the patient will be removed from protocol therapy.

8.1.4.3 Other Non-Hematologic Toxicity

- For other grade 3 non-hematologic toxicity, hold CC-5013 until toxicity resolves to ≤ grade 2, then the study drug should be resumed at the next lower dose level.
- For patients who develop grade ≤ 2 non-hematologic toxicity, an attempt will be made to maintain the patient at that dose level. If the patient cannot tolerate this dose level, the treating physician should decrease the dose to the next lower dose level.
- For other grade 4 non-hematologic toxicity, discontinue study drug and contact the Study Chair or Co-Chair.

8.1.4.4 In the event of any grade 1 or 2 toxicity that the patient finds intolerable, the study drug may be held until the toxicity resolves and the study drug resumed at the next lower dose level. Alternatively, the study drug may be continued at the next lower dose level without cessation of study drug. However, study drug should be held for the occurrence of a rash consistent with evolving Stevens-Johnson syndrome or toxic epidermal necrolysis (bullous, blistering that is purpuric in nature) until appropriate evaluation is made. Study drug may be held for up to 8 weeks. Contact the Study Chair or Co-Chair for consultation.

8.1.4.5 Venous Thrombosis

Patients who develop signs or symptoms suggestive of thrombosis should be evaluated and treated as clinically indicated. CC-5013 should be held for patients with venous

thrombosis. CC-5013 may resume when patient is adequately anticoagulated. Patients with recurrent thrombosis despite adequate anticoagulation should be removed from protocol therapy.

8.1.4.6 Renal Toxicity

- For creatinine clearance (CrCl) < 30 mL/min skip CC-5013 and reassess in four weeks. If CrCl remains < 30 mL/min after four weeks, then discontinue CC-5013.
- For CrCl < 60 mL/min but ≥ 30 mL/min:
    - **If on 3 capsules per day,** decrease CC-5013 to 1 capsule alternating with 2 capsules daily (1 capsule one day, followed by 2 capsules the next day…etc.). Reassess after four weeks and attempt to re-escalate CC-5013.
    - **If on 2 capsules per day,** decrease CC-5013 to 1 capsule per day. Reassess after four weeks and attempt to re-escalate CC-5013.
    - **If on 1 capsule per day,** decrease CC-5013 to 1 capsule per day for 21 of 28 days. Reassess after four weeks and attempt to re-escalate CC-5013.

8.1.4.6 Pregnancy or Suspected Pregnancy

- Female Subjects

For pregnancy or suspected pregnancy in females taking lenalidomide (CC-5013), discontinue lenalidomide. Refer patient as appropriate for further evaluation and counseling.

- Male Subjects

For pregnancy occurring in partners of males taking lenalidomide, advise partner as appropriate to seek further evaluation and counseling.

8.2 Instructions for Dosing by Corrected Body Weight

High-dose chemotherapy can adversely impact the outcomes of obese patients when dosing is performed according to actual body weight. **Therefore, melphalan therapy and growth factor drug doses only will be determined using a corrected body weight formula.** Patient ideal body weight will be derived from Appendix II using frame size and height. **The corrected body weight is calculated based on the following formula with all weights in kg:**

Corrected Weight = (0.25)(actual weight - ideal weight)+(ideal weight)

For patients whose actual weight is >150% of ideal, their "actual" weight will be capped at 150% of ideal (i.e., their corrected weight will be 112.5% of ideal). For patients whose actual weight is less than ideal, use their actual weight as the corrected weight. Growth factor doses may be rounded to the nearest vial size in 300 mcg and or 480 vial sizes.

9.0 DRUG FORMULATION, AVAILABILITY, AND PREPARATION

Qualified personnel who are familiar with procedures that minimize undue exposure to themselves and to the environment should undertake the preparation, handling, and safe disposal of chemotherapeutic agents in a self-contained, protective environment.

Discard unused portions of injectable chemotherapeutic agents that do not contain a bacteriostatic agent or are prepared with unpreserved diluents (i.e., Sterile Water for Injection USP or 0.9% Sodium Chloride for Injection USP) within eight hours of vial entry to minimize the risk of bacterial contamination.

The total administered dose of chemotherapy may be rounded up or down within a range of 5% of the actual calculated dose.

9.1 Filgrastim (r-met Hug-CSF, G-CSF: Granulocyte Colony-Stimulating Factor, Neupogen®)

AVAILABILITY

G-CSF is commercially available in 1.0 and 1.6 mL vials containing 300 µg and 480 µg G-CSF, and in pre-filled syringes containing 300 µg/0.5mL and 480 µg/0.8mL.

STORAGE & STABILITY

Intact vials and prefilled syringes should be stored under refrigeration. Do not allow the drug to freeze.

ADMINISTRATION

The dose of filgrastim will be based on corrected body weight. The daily dose should be injected subcutaneously in one or two sites. The dose following PBSC infusion is 5 µg/kg/day. The dose of G-CSF may be rounded up to the nearest vial size.

The use of PEG-filgrastim will not be allowed.

TOXICITY

The most common side effect associated with G-CSF is bone pain. Bone pain is usually reported as mild or moderate and, if necessary, may be treated with non-opioid or opiod analgesics.

9.2 Melphalan Hydrochloride

(Alkeran®)

AVAILABILITY

Melphalan for IV use is commercially available in sterile 50 mg vials. The product is a lyophilized powder with 20 mg povidone per vial. Also provided is 10 mL of special diluent for use in reconstituting the product. The special diluent has 0.20 g sodium citrate, 6 mL propylene glycol, 0.5 mL 95% ethanol, and sterile water.

STORAGE & STABILITY

Intact vials should be stored at room temperature (15°-30°C) and protected from light. Reconstituted solutions are chemically and physically stable for at least 90 minutes at room temperature. Solutions further diluted in 0.9% sodium chloride to a concentration of 0.1 mg/mL to 0.45 mg/mL are stable for at least 60 minutes. Solutions diluted to 1 mg/mL are reported to be physically stable for at least 4 hours at room temperature-chemical stability of this dilution is not known. Because of the relative instability of melphalan solutions, it is recommended that administration of the diluted solution be completed within 60 minutes of reconstitution. Reconstituted solutions should not be refrigerated.

PREPARATION

Melphalan should be prepared immediately before intended use. Each vial is reconstituted with 10 mL of the special diluent to yield a concentration of 5 mg/mL. The reconstituted solution may be diluted with 0.9% sodium chloride to a concentration of 0.1 mg/mL to 0.45 mg/mL. Alternatively, when the required concentration necessitates an unacceptable volume of fluid, the reconstituted solution may be administered undiluted.

ADMINISTRATION

See the Treatment Plan (Section 7.0) for instructions on melphalan administration.

TOXICITY

The major toxicity of melphalan is bone marrow suppression, usually lasting four to eight weeks. Other toxicities include nausea, vomiting, diarrhea, and mucositis. Less common toxicities include pulmonary fibrosis, interstitial pneumonitis, vasculitis, alopecia, hemolytic anemia, and allergic reactions.

9.3 Lenalidomide (CC-5013)

(α-[3-aminophthalimido] glutarimide) (NSC # 703813, IND # 70116)

Lenalidomide (CC-5013) a thalidomide analog, is an immunomodulatory agent with a spectrum of activity that is not fully characterized. *In vitro*, it inhibits secretion of the pro-inflammatory cytokines TNF-α, IL-1β, and IL-6 and increases secretion of the anti-inflammatory cytokine IL-10. It also induces T-cell proliferation and IL-2 and IFN-γ production in vitro.

AVAILABILITY

Celgene supplies and CTEP, NCI, DCTD distributes lenalidomide 5 mg (size 2 hard gelatin capsules in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with HDPE caps. Bottles contain either 21 or 28 capsules per container.

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

Sometime after April 1, 2011, Celgene will supply and CTEP, NCI, DCTD will distribute commercially-labeled lenalidomide for investigational use. Available strengths are 5 mg (size 2) hard gelatin capsules in tamper-evident, child-resistant, opaque, high density polyethylene (HDPE) bottles with polypropylene caps. Bottles contain 100 capsules per container. The capsules also contain anhydrous lactose, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

During this transition to commercially-labeled supply, you will likely have both investigationally-labeled and commercially-labeled lenalidomide (designated with "Caution: for investigational use only") bottles on the shelf for NCI trials. Please use the investigationally-labeled supply first and start a new DARF for each new lot of lenalidomide.

Lenalidomide (NSC # 703813/IND # 70116) will be provided free-of-charge by Celgene and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP), Division of Cancer Treatment and Diagnosis (DCTD), National Cancer Institute (NCI).

Each patient-specific bottle will be labeled with:

- the protocol number (i.e., CALGB-100104)
- the bottle number (i.e., “Bottle ____ of ____”)
- the number of capsules (i.e., “28 capsules”)
- the patient ID number (e.g., “99999”)
- the patient initials (e.g., “L,FM” [last initial, first and middle initial])
- the agent identification (i.e., “CC-5013 [Revlimid] 5 mg or Placebo”)
- a blank line for the pharmacist to enter the patient’s name
- administration instructions (i.e., “Take ____ capsules once daily.”)
- storage instructions (i.e., “Store at room temperature [15°-30°C, 59° to 86°F). Protect from moisture.”)
- emergency contact instructions
- a Julian date

The Julian date indicates the day the bottle was labeled and shipped and is composed of the last two digits of the calendar year (e.g., 2004 = 04, 2005 = 05) and a day count (e.g., January 1 = 001, December 31 = 365). For example, a bottle labeled and shipped on January 1, 2004 would have a Julian date of ‘04001’ and a bottle labeled and shipped on December 31, 2005 would have a Julian date of ‘05365.’ The Julian date will be used by PMB for recalls. PMB will determine the last date the expired lot was shipped, and will recall all relevant bottles.

Questions about drug orders, transfers, returns, or accountability should be addressed to the PMB by calling (301) 496-5725, Monday through Friday, between 8:30 am and 4:30 pm, Eastern Time.

DRUG ORDERS **(New Instructions as of 9/15/12)**

Following IRB approval of Update #16, lenalidomide can be ordered from Biologics, Inc. The last day to order lenalidomide supplies for CALGB 100104 from the PMB will be 12/14/12 (3 months from the protocol posting update). Starting 12/15/12, Biologics, Inc. will be the only distributor of lenalidomide for CALGB 100104.

Celgene corporation will supply lenalidomide to patients at no charge through the RevAssist® Program for Study Patients (RASP). Lenalidomide will be provided to study patients 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 of the Celgene Corporation. Per standard RevAssist® requirements, all physicians who prescribe lenalidomide for patients on this trial, as well as patients on this trial, must be registered in and must comply with all requirements of the 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. Supplies will be sent directly to the patients’ home.

All study patients 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 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 during study treatment, and for at least 28 days after discontinuation of lenalidomide. A female of childbearing potential is a sexually mature female who: 1) has 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). FCBP must also agree to ongoing pregnancy testing, as described in Section 6.0. Men must agree to use a latex condom during sexual contact with

a FCBP even if they have had a successful vasectomy. See Appendix VI: Lenalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

The RASP prescription form, and instructions for completing the form, may be found on the CALGB 100104 study web page.

DRUG TRANSFERS

Bottles **MAY NOT** be transferred from one patient to another patient or from one protocol to another protocol. All other transfers (e.g., a patient moves from one participating clinical site to another participating clinical site, the principal investigator at a given clinical site changes) should be approved in advance by the PMB. To obtain an approval transfer, investigators should complete and submit to the PMB (fax number 301-480-4612) a Transfer Investigational Agent Form available on the CTEP home page (http://ctep.cancer.gov) or by calling the PMB at 301-496-5725. The patient ID number (e.g., "99999") and the patient initials (e.g., "L,FM") should be entered in the "Received on NCI Protocol No." and the "Transferred to NCI Protocol No." fields in addition to the protocol number (i.e., "CALGB-100104").

DRUG RETURNS (**New instructions as of 9/15/12)**

Any unused lenalidomide must be returned as instructed through RASP. Information about the RASP program is available on the CALGB 100104 study web page.

ACCOUNTABILITY (**New instructions as of 9/15/12)**

Once patients begin receiving lenalidomide through the RASP, institutions will no longer be responsible for maintaining drug accountability records. Old DARFs should not be discarded. Information about the RASP program is available on the CALGB 100104 study web page.

UNBLINDING PROCEDURES

Treatment assignments were unblinded on 12/17/09. As of 12/17/09 no further emergency unblinding procedures will be performed.

STORAGE & STABILITY

The capsules should be stored at room temperature (15°-30°C, 59°-86°F), away from moisture and direct sunlight.

ADMINISTRATION

Only a 28-day supply may be dispensed to a patient at one time. Sites may not mail lenalidomide to patients.

NOTE: Before lenalidomide is dispensed, patients must 1) have a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. Pharmacists may be trained counselors (see Lenalidomide Counselor Program Site Counselor Identification Form, Appendix IV). The counseling requirements for investigational-use lenalidomide are separate from the RevAssist program.

Lenalidomide should be taken by mouth with or without food. Lenalidomide should not be crushed, chewed, and the capsules should not be opened.

Before lenalidomide is dispensed, patients must 1) have a negative pregnancy test (if applicable) and 2) be counseled by a trained counselor. Pharmacists may be trained counselors (see Lenalidomide Counselor Program Site Counselor Identification form in Appendix V). The

counseling requirements for investigational-use lenalidomide are separate from the RevAssist program.

For this study, the starting dose of lenalidomide will be will be two capsules orally once daily for three months. Dose escalation is described in Section 7.3.2 and dose modifications in Section 8.0.

Patient Care Implications and Counseling

Risks Associated with Pregnancy

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

Definition of female of childbearing potential (FCBP)

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

Before starting study drug:

Female Subjects:

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

Male Subjects:

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

All Subjects:

- Only a 28-day supply may be dispensed at one time. Sites may not mail lenalidomide to patients.
- If pregnancy or a positive pregnancy test does occur in a female study subject or the partner of a male study subject during study participation, lenalidomide must be immediately discontinued.

Counseling

- Patients must be counseled by a qualified healthcare professional (including, but not limited to, nurses, pharmacists, and non-investigator physicians). Two healthcare professionals at each site will be trained by Celgene in the requirements specific to counseling of subjects (investigators cannot be trained as counselors).

- To become a counselor, refer to the Lenalidomide Counseling Program Site Counselor Identification Form in Appendix VI. The Lenalidomide Counseling Program is available on the Internet for each person who has completed the site counselor identification form and registered with Celgene prior to completing the training. Counselors who wish to counsel patients for different protocols at the same site or for the same protocol at different sites should indicate this on the site counselor identification form. After completing the training, send the training certification and a copy of the Lenalidomide Counseling Program Site Counselor Identification Form to the CTSU Operations Office) fax # 1-888-691-8039. Documentation of two trained counselors at each site is required for drug ordering. For questions, please contact the CTSU Help Desk at 1-888-823-5923.

- Once trained, these healthcare staff will counsel subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP), and that the subject understands the risks associated with lenalidomide. This step will be documented with a completed Lenalidomide Education and Counseling Guidance Document (Appendix VII) and no drug will be dispensed until this step occurs. Counseling includes verification with the female patient that required pregnancy testing was performed and results were negative. Each patient must be counseled prior to dispensing lenalidomide and documentation is kept in the patient's records. Both the training certificates and the completed Lenalidomide Education Counseling Guidance Documents are auditable documents and must be produced upon request. A Lenalidomide Information Sheet (Appendix VIII) will be supplied each time medication is dispensed.

Drug distribution for CC-5013 (lenalidomide) will be transitioned from CTEP/DCTD/NCI to Biologics, Inc during the period of September 15, 2012 through December 14, 2012 ('transition period').

During the transition period each site should exhaust their existing lenalidomide CTEP drug supply. Starting Sept 15, 2012, sites may begin registering patients to the RevAssist® for Study Participants (RASP) program once they have IRB approval of protocol update 16.

During the transition period CTEP/DCTD/NCI will only distribute drug to sites that have not yet received IRB approval and/or are not yet registered to the mandatory RevAssist® for Study Participants (RASP) program.

Beginning December 15, 2012, CTEP/DCTD/NCI will no longer distribute lenalidomide and all the sites must be participating in the RevAssist® for Study Participants (RASP) program utilizing Biologics Inc. for the duration of the study.

TOXICITY

The most common toxicity reported with lenalidomide to date is myelosuppression. In a phase I dose-finding trial, grade 3 neutropenia was seen in 60% and grade 4 in 15% of 25 patients. Grade 3 thrombocytopenia occurred in 20%. Myelosuppression frequently occurred after the

first 28 days of single daily dose treatment. It has been suggested that myelosuppression may not be completely reversible in heavily pretreated patients. No other grade 3 or 4 toxicities were noted in this trial. Mild (grade 1) lightheadedness, fatigue, rash, itching, diarrhea, and leg cramps were reported in as many as 40% of patients. Abnormal kidney function and thyroid function tests have been noted. In contrast to thalidomide, lenalidomide is thought not to cause significant somnolence, constipation, or neuropathy. Rarely, tumor lysis syndrome (TLS) has been seen. Preliminary data also indicate that anemia may occur, in addition to thrombocytopenia and neutropenia, and may be severe. In trials with lenalidomide, in a small number of patients, cardiac arrhythmias have been described. In addition, a small increase in the risk of arterial thrombosis (e.g., myocardial infarction, CNS thromboembolic events) has been reported.

Recent data indicate that like thalidomide, lenalidomide may be associated with an increased risk of venous thrombosis and pulmonary embolus. It appears that the risk is increased when lenalidomide is used concurrently with dexamethasone or epoetin. Prophylactic aspirin or low molecular weight heparin are to be given for patients with a high risk of developing DVT/PE or arterial thromboses during maintenance therapy unless contraindicated. Coumadin (Warfarin) may be utilized as well. High risk will be defined as a history of DVT/PE, significant family history, performance status ≥ 2, smoking history, use of oral contraceptives, and concurrent use of epoetin. Patients with diabetes mellitus or coronary artery disease are considered to be at high risk for arterial thromboembolic events.

Lenalidomide should not be administered to pregnant or nursing women. Women of child-bearing potential must have a negative serum or urine pregnancy test within seven days of starting study drug. In addition, sexually active women of child-bearing potential must agree to use adequate contraceptive measures (oral, injectable or implantable hormonal contraceptive; tubal ligation, IUD; barrier contraceptive with spermacide; or vasectomized partner) while on study drug.

For a comprehensive adverse events and potential risks (CAEPR) list, see Section 14.3. Also refer to the lenalidomide Investigator Brochure for additional information about toxicities.

DRUG INTERACTIONS

Lenalidomide may increase the effect of the drug warfarin. Patients taking both lenalidomide and warfarin should have INR monitored more frequently.

REGULATORY INFORMATION

The agent (hereinafter referred to as Agent), lenalidomide, used in this protocol is provided to the NCI under a Clinical Research and Development Agreement (CRADA) or Clinical Trials Agreement (CTA) between Celgene, Inc. (hereinafter referred to as Collaborator) and the NCI DCTD. The following obligations/guidelines apply to the use of the Agent in this study:

1. Agent may not be used outside the scope of this protocol, nor can Agent be transferred or licensed to any party not participating in the clinical study.
2. Collaborator data for Agent are confidential and proprietary to Collaborator and should be maintained as such by the investigators. Neither the institution nor the investigator shall charge any third party or patient enrolled in the study for the Agent, neither shall the institution nor the investigator include the cost of the drug in any cost report to third party payors.
3. Further information on the terms of award additions/intellectual property option to collaborator may be found at ctep.dev.cancer.gov/industry.ipo.html.
4. The NCI encourages investigators to make data from clinical trials fully available to Collaborator for review at the appropriate time (see #5). The NCI expects that clinical trial

data developed under a CTA or CRADA will be made available exclusively to Collaborator, and not to other parties.

5. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair) of Collaborator's wish to contact them.
6. Any manuscripts reporting the results of this clinical trial should be provided to CTEP for immediate delivery to Collaborator for advisory review and comment prior to submission for publication. Collaborator will have 30 days from the date of receipt for review. An additional 30 days may be requested in order to ensure that confidential and proprietary data, in addition to Collaborator intellectual property rights, are protected. Copies of abstracts should be provided to Collaborator for courtesy review following submission, but prior to presentation at the meeting or publication in the proceedings. Copies of any manuscript and/or abstract should be sent to:

   Regulatory Affairs Branch, CTEP, DCTD, NCI
   Executive Plaza North, Room 7111
   Bethesda, Maryland 20892
   Fax: 301-402-1584

The Regulatory Affairs Branch will then distribute them to Collaborator.

10.0 ANCILLARY THERAPY

10.1 Supportive Care

Patients should receive *full supportive care*, including transfusions of blood and blood products, epoetin, antibiotics, antiemetics, etc., when appropriate. The reason(s) for treatment, dosage, and the dates of treatment should be recorded on the flow sheets. Patients receiving epoetin during maintenance therapy may be at an increased risk of developing DVT/PE and must receive prophylaxis with aspirin or low molecular weight heparin unless contraindicated. Coumadin (Warfarin) also may be used.

10.2 Completion of Autologous Transplant

Following completion of autologous transplant, pamidronate 90 mg/month or zoledronate 4 mg/month is recommended. The minimum yearly bisphosphanate therapy is every other month for a minimum of 6 total doses annually. Dose adjustments should be considered for patients who do not tolerate bisphosphanates or have renal insufficiency.

11.0 CRITERIA FOR RESPONSE, PROGRESSION, AND RELAPSE (34)

11.1 Time of Response Evaluation

For all patients not demonstrating disease progression, response status will be evaluated at the following time points:

- At 90 to 100 days following autologous transplant.
- To be obtained every 3 months until 4 years post autotransplant and every 6 months from year 4 to 5 post autotransplant.

11.2 Response Criteria

11.2.1 Complete Response (CR)

Complete response requires **all** of the following:

- Absence of the original monoclonal paraprotein in serum and urine by immunofixation, maintained for a minimum of 6 weeks. The presence of oligoclonal bands consistent with oligoclonal immune reconstitution does not exclude CR.
- <5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy performed. If absence of monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow, except in patients with non-secretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR.
- No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).
- Disappearance of soft tissue plasmacytomas.

Patients in whom some, but not all, the criteria for CR are fulfilled are classified as PR, providing the remaining criteria satisfy the requirements for PR (see Section 11.2.2). This includes patients in whom routine electrophoresis is negative but in whom immunofixation has not been performed.

11.2.2 Partial Response (PR)

Partial response requires **all** of the following:

- ≥50% reduction in the level of the serum monoclonal paraprotein, maintained for a minimum of 6 weeks.
- Reduction in 24 hour urinary light chain excretion either by ≥90% or to <200 mg, maintained for a minimum of 6 weeks.
- For patients with non-secretory myeloma only, ≥50% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if biopsy is performed, maintained for a minimum of 6 weeks.
- ≥50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
- No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response).

Patients in whom some, but not all, the criteria for PR are fulfilled are classified as Minimal Response (MR), provided the remaining criteria satisfy the requirements for MR (see Section 11.2.3 below).

11.2.3 Minimal Response (MR)

Minimal response requires **all** of the following:

- 25-49% reduction in the level of serum monoclonal paraprotein maintained for a minimum of 6 weeks.
- 50-89% reduction in 24 hour urinary light chain excretion, which still exceeds 200 mg/24 hours, maintained for a minimum of 6 weeks.
- For patients with non-secretory myeloma only, 25-49% reduction in plasma cells in a bone marrow aspirate and on trephine biopsy, if a biopsy was performed, maintained for a minimum of 6 weeks.

- 25-49% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
- No increase in the size or the number of lytic bone lesions (development of a compression fracture does not exclude response).

MR also includes patients in whom some, but not all, the criteria for PR are fulfilled, provided the remaining criteria satisfy the requirements for MR.

11.2.4 No Change (NC)

No change is defined as neither meeting the criteria for minimal response or progressive disease.

11.2.5 Progressive Disease (PD)

Progressive disease (for patients not in CR) requires one or more of the following:

- >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL and confirmed by at least one repeated investigation.
- >25% increase in the 24 hour urinary light chain excretion, which must also be an absolute increase of at least 200 mg/24 hour and confirmed by at least one repeated investigation.
- >25% increase in plasma cells in a bone marrow aspirate or trephine biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response).
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.8 mmol/L) not attributable to any other cause.

11.2.6 Relapsed Disease [35]

Relapsed disease (for patients who were in CR) requires at least one or more of the following (to be used for analyzing disease free survival).

- Reappearance of serum or urine monoclonal paraprotein by immunofixation or electrophoresis.
- Development of at least 5% plasma cells in the bone marrow.
- A difference between involved and uninvolved FLC levels of >10 mg/dL, only in patients without measurable paraprotein in the serum and urine.
- Development of new lytic bone lesions or soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).
- Development of hypercalcemia (corrected serum calcium > 11.5 g/dL or 2.8 mmol/L) not attributable to any other cause.
- Appearance of any other sign of progression.

Patients with relapsed disease (recurrence of disease after attaining a CR) should continue on treatment if they do not fulfill criteria for progressive disease (Section 11.2.5). This

would apply to patients at randomization or at any time following initiation of maintenance therapy.

12.0 REMOVAL OF PATIENTS FROM PROTOCOL THERAPY

If, at any time the constraints of this protocol are detrimental to the patient's health, the patient experiences disease progression, and/or the patient no longer wishes to continue protocol therapy, protocol therapy shall be discontinued. In this event:

- Notify the Study Chair.
- Document the reason(s) for discontinuation of therapy on flow sheets.
- Follow the patient for toxicity, survival, progression, relapse, and secondary malignancies.

13.0 STATISTICAL CONSIDERATIONS

13.1 Primary Objective

The primary endpoint of this study is the time to progression (TTP), starting at transplant, with progression as defined in Section 11.2.5, in MM patients. Time to progression will start at Day 0 of start of transplant. Any death will be considered as an event (i.e., will not be censored). We hypothesize that the treatment arm will be superior with respect to this endpoint.

Throughout these discussions, we will assume that the laws of the time-to-event in both arms are exponential. The hypothesis of interest may be canonically presented as testing $H_0:\Delta=1$ versus the general alternative $H_1:\Delta>1$, where Δdenotes the treatment to control hazard ratio. In particular, we hypothesize that the median TTP is M_c=2 years (24 months) for the control arm and M_e=2.8 years (33.6 months) for the treatment arm. This corresponds to testing $H_0:\Delta=1$ versus the local alternative $H_1:\Delta=1.4$.

Given that the observed accrual pattern has differed considerably from that assumed in the original design, an amendment to the statistical considerations was necessitated so as to comply with the CTEP low accrual policy. We note that the study team has not carried out any interim analyses for the primary endpoint (TTP). Furthermore, the TTP distribution assumptions in this amendment and the targeted number of events (309) are identical to those of the original design. What is subject to amendment is only the assumed distribution of the administrative censoring mechanism. As such, the proposed amendment should have no effect on the risk to benefit ratio of the original design.

In the original design, we had planned to randomize n=462 patients over a period of 33 months. We had expected that this would require, to account for the drop-out rate of 15%, that we registered about N=544 patients over this period. Under an equal allocation randomization scheme (i.e., 231 patients randomized to each arm) and a planned follow-up period of 30 months at the α=0.05 level of significance, this design would have had a power of at least 0.9 for the one-sided log-rank test. The total study period was expected to be 63 months.

The study was opened on December 15, 2004. Accrual to the study did not begin until April 2005. We propose to continue accrual to the study for an additional 30 months, starting April 2007. We will assume that accrual to the study will be 5 per month in April and May 2007, and then will ramp up from 6 per month in June 2007 to 16 per month in December 2007. Thereafter, the accrual rate is assumed to remain constant at 16 per month for another 21 months. Given that the study has been open for 28 months (December 2007 through March 2007), we plan to accrue for another 30 months (starting April 2007) and we plan to follow-up the last patient for 30 months, the total study period is expected to be 28+30+30=88 months (compared to 63 months in the original design).

A total of 117 patients were accrued up to including March 2007. We will accrue an additional 421 patients. This will result in accruing a total of 538 patients (compared to 544 in the original design).

The assumed censoring distribution of the original design was uniform on the interval (30, 30+33)=(30, 63) months. The proposed accrual period is 28+30=58 months long. For the amendment we will assume that the censoring distribution for a patient accrued in month i=1,...,58 is uniform on the interval (30, 30+58-i). Based on this assumption on the censoring distribution and the distributional assumptions on TTP, we expect that this design will yield 367 events. Furthermore, given that it is assumed that at most 15% of the registered patients will not be randomized, this design is expected to yield at least 309 events (target specified in the original design).

If the median monthly accrual in the third quarter following activation of this amendment is below 10 patients, then consideration of another amendment will be necessitated.

The stratification factors for randomization (described in Section 5.3) will consist of B2microglobulin, prior therapy with thalidomide and/or CC-5013. A randomized permuted block procedure, as described in [36], will be employed.

Interim analyses of TTP will be conducted on a semiannual basis to coincide with the semiannual meetings of the CALGB Data and Safety Monitoring Board (DSMB). Under the alternative hypothesis, the number of events expected at the end of the study is about 309. The first formal interim analysis will be conducted for the first DSMB meeting after which at least 20% of the events have occurred. A group sequential test design due to Emerson and Fleming [31,32] will be used to stop the trial early for superiority of the experimental drug. The study will also be monitored for futility. In particular, at each of the seven interim analyses the hypothesis that the hazard ratio is at least 1.4 will be tested at a fixed one side significance level of 0.005. The upper boundary will be truncated by the 1-0.005 quantile of a standard normal distribution. For calculating the futility bound, we will assume that the standardized log-rank statistic, after the d-th event has occurred, is normally distributed with the unit variance and mean log [1.4] $(d/4)^{0.5}$. Note that among other things, this assumption not only depends on asymptotic results but also on approximating the mean of the asymptotic distribution.

We had expected that the first interim analysis were to occur by about 21 months after the trial had opened. In total we had planned to carry out seven interim and one final analysis for a total of eight analyses.

Based on assumptions of the revised design, we expect to carry out the first interim analysis for the June 2008 DSMB meeting. We could expect to carry out up to eight interim analyses in addition to one final analysis (nine analyses all together).

For illustrative purposes, we provide the lower and the upper boundaries (in the so called normalized z-score scale) that would be used under the specific assumptions of the previous paragraph in Table 1. We reiterate that these bounds are for illustrative purposes only as these calculations were based on various assumptions that were rarely realized in practice.

Table 1.

Analysis #	1	2	3	4	5	6	7	8	9
Projected Time of Analysis (in months following start of accrual)	43	49	55	61	67	73	79	85	88
Expected proportion of events realized at time of analysis	0.21	0.31	0.43	0.57	0.70	0.80	0.89	0.97	1.00
Upper Boundary (for superiority)	2.576	2.576	2.576	2.403	2.168	2.028	1.92	1.842	1.814

Lower Boundary (for futility)	-1.221	-0.929	-0.637	-0.343	-0.102	0.0693	0.214	0.337	1.814

This rather extensive monitoring plan, as confirmed by simulations, has, as discussed in Freidlin et al. [3], a negligible impact on the planned Type 1 and II error rates of this trial.

Toxicity Stopping Rules: If > 20% of patients randomized to the CC-5013 arm permanently discontinue the drug due to drug-related toxicity within one year following randomization, the treatment will be considered overly toxic and consideration will be given to terminate the study.

13.2 Secondary Objectives

The rates for the various types of responses pre-randomization, at 3 months and at 12 months will be estimated. The improvement in response (e.g., PR to CR) over the aforementioned time-points will be analyzed as well. The potential discrepancies between the TTP profiles for the CR and non-CR group on the study drug arm will be described. We expect little differences in patient responses by sex or race.

14.0 ADVERSE EVENT REPORTING (AER)

Investigators are required by Federal Regulations to report serious adverse events as defined below. Investigators are required to notify the Investigational Drug Branch, CALGB Central Office, the Study Chair, and their Institutional Review Board if a patient has an adverse event requiring expedited reporting (i.e., a serious adverse event). The description and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting beginning October 2011. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov). All reactions determined to be reportable in an expedited manner must be reported using the NCI Adverse Event Expedited Reporting System (AdEERS).

All new malignancies must be reported through AdEERS. In addition, all new malignancies must be reported using Study Form C-1001. Progression or recurrence of the disease under study is not considered a new malignancy.

Second or Secondary Malignancies

All new malignancies must be reported through AdEERS, whether or not they are thought to be related to either previous or current treatment. All new malignancies must be reported, including solid tumors (including non-melanoma skin malignancies) hematologic malignancies, myelodysplastic syndrome (MDS) / acute myelogenous leukemia (AML), and *in situ* tumors.

- In CTCAE version 4.0, the new malignancies (both second and secondary) may be reported as one of the following: (1) leukemia secondary to oncology chemotherapy; (2) myelodysplastic syndrome; (3) treatment-related secondary malignancy; or (4) neoplasm other, malignant (grade 3 or 4).

Pregnancy or Suspected Pregnancy

All pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) occurring in female subjects or in the partner of a male subject during lenalidomide therapy, or within 28 days after the subject's last dose, must be reported via AdEERS.

- In CTCAE version 4.0, use the event term, "pregnancy, puerperium and perinatal conditions-other: fetal exposure (grade 4)."

- AdEERS reports should be amended upon completion of the pregnancy to report pregnancy outcomes (e.g. normal, spontaneous or therapeutic abortion, fetal death, and congenital abnormalities).

- The AdEERS report should be amended for any neonatal deaths or complications occurring within 28 days of birth, independent of attribution. Infant deaths occurring after 28 days considered to be related to *in utero* exposure to lenalidomide should also be reported via AdEERS.

CALGB requires investigators to route all adverse event reports (AERs) through the Central Office for CALGB-coordinated studies.

14.1 CALGB 100104/ECOG 100104 Reporting Requirements

Phase 2 and 3 Trials Utilizing an Agent under a CTEP IND: AdEERS Expedited Reporting Requirements for Adverse Events That Occur Within 30 Days[1] of the Last Dose of the Investigational Agent

	Grade 1	Grade 2	Grade 2	Grade 3		Grade 3		Grades 4 & 5[2]	Grades 4 & 5[2]
				Unexpected		Expected			
	Unexpected and Expected	Unexpected	Expected	with Hospitalization	without Hospitalization	with Hospitalization	without Hospitalization	Unexpected	Expected
Unrelated Unlikely	Not Required	Not Required	Not Required	10 Calendar Days	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days
Possible Probable Definite	Not Required	10 Calendar Days	Not Required	10 Calendar Days	10 Calendar Days	10 Calendar Days	Not Required	24-Hrs; 5 Calendar Days	10 Calendar Days

[1] **Adverse events with attribution of possible, probable, or definite that occur <u>greater</u> than 30 days after the last dose of treatment with an agent under a CTEP IND require reporting as follows:**

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

- Grade 4 and Grade 5 unexpected events

AdEERS 10 calendar day report:

- Grade 3 unexpected events with hospitalization or prolongation of hospitalization
- Grade 5 expected events

[2] Although an AdEERS 24-hour notification is not required for death clearly related to progressive disease, a full report is required as outlined in the table.

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Note: All deaths on study require both routine and expedited reporting regardless of causality. Attribution to treatment or other cause should be provided.

- Expedited AE reporting timelines defined:
  - "24 hours; 5 calendar days" – The investigator must initially report the AE via AdEERS within <u>24 hours</u> of learning of the event followed by a complete AdEERS report within <u>5 calendar days</u> of the initial 24-hour report.
  - "10 calendar days" - A complete AdEERS report on the AE must be submitted within <u>10 calendar days</u> of the investigator learning of the event.
- Any medical event equivalent to CTCAE grade 3, 4, or 5 that precipitates hospitalization (or prolongation of existing hospitalization) must be reported regardless of attribution and designation as expected or unexpected with the exception of any events identified as protocol-specific expedited adverse event reporting exclusions (see below).

- Any event that results in persistent or significant disabilities/incapacities, congenital anomalies, or birth defects must be reported via AdEERS if the event occurs following treatment with an agent under a CTEP IND.
- Use the NCI protocol number and the protocol-specific patient ID provided during trial registration on all reports.

14.2 Additional Instructions or Exclusions

Additional instructions or exclusions to AdEERS expedited reporting requirements for phase 2 and 3 trials utilizing an agent under a CTEP-IND:

- CALGB 100104 is conducted under a CTEP-held IND for lenalidomide. Therefore, the reporting requirements for investigational agents under a CTEP-held IND apply for all enrolled patients during maintenance therapy.
- During mobilization and transplant, all grade 5 events must be reported via AdEERS within 10 calendar days.
- During mobilization and transplant, grade 4 unexpected events that are at least possibly related to treatment must be reported via AdEERS within 10 calendar days.
- During mobilization and transplant, any unexpected medical event equivalent to CTCAE grade 4 that precipitates hospitalization or prolongs an existing hospitalization must be reported via AdEERS within 10 calendar days.
- All adverse events reported via AdEERS (i.e., serious adverse events) should also be forwarded to your local IRB.
- For the purposes of expedited adverse event reporting, the CAEPR for lenalidomide may be found in Section 14.3 below. **Note** that the ASAEL column of the CAEPR has been replaced with the specific protocol exceptions to expedited reporting (SPEER) list. This list now includes “expected” severity grades in addition to event terms.
- A discussion of adverse events associated with agents used in this trial can be found in Section 9.0 (Drug Formulation, Availability and Preparation).
- New malignancies occurring at any time during treatment or follow-up should be reported through AdEERS and on form C-1001 as described above in Section 14.0.
- Whenever possible, the AdEERS reports for new malignancies should include tumor pathology, history of prior tumors, prior treatment/current treatment including duration, any associated risk factors or evidence regarding how long the new malignancy may have been present, when and how the new malignancy was detected, molecular characterization or cytogenetics or the original tumor (if available) and of any new tumor, and new malignancy treatment and outcome (if available).
- AdEERS reports are to be submitted electronically (http://ctep.info.nih.gov/reporting/adeers.html) to the CALGB Central Office (calgb@uchicago.edu). In the rare event when Internet connectivity is disrupted, a 24-hour notification is to be made to the NCI by telephone at 301-897-7497. An electronic report MUST be submitted immediately upon re-establishment of the Internet connection. Please note that all paper AdEERS forms have been removed from the CTEP website and will NO LONGER be accepted.
- Grade 3/4 myelosuppression is expected during mobilization and transplant. Grade 3/4 myelosuppression and hospitalization resulting from such do not require AdEERS, but should be submitted as part of study results.

- The reporting of adverse reactions described in the table above is in addition to and does not supplant the reporting of adverse events as part of the report of the results of the clinical trial, e.g., study summary forms or cooperative group data reporting forms (see Section 5.4 for required CALGB forms).

14.3 Comprehensive Adverse Events and Potential Risks List (CAEPR) for CC-5013

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

Version 2.3, June 27, 2011[1]

Adverse Events with Possible Relationship to Lenalidomide (CC-5013) (CTCAE 4.0 Term) [n= 4081]			**Specific Protocol Exceptions to Expedited Reporting (SPEER)** (formerly known as ASAEL)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
Anemia			***Anemia (Gr. 3)***
ENDOCRINE DISORDERS			
	Hypothyroidism		***Hypothyroidism (Gr. 3)***
GASTROINTESTINAL DISORDERS			
Constipation			***Constipation (Gr. 3)***
Diarrhea			***Diarrhea (Gr. 3)***
	Nausea		***Nausea (Gr. 3)***
		Pancreatitis	
	Vomiting		***Vomiting (Gr. 3)***
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
	Chills		***Chills (Gr. 2)***
	Edema limbs		***Edema limbs (Gr. 2)***
Fatigue			***Fatigue (Gr. 3)***
	Fever		***Fever (Gr. 2)***
IMMUNE SYSTEM DISORDERS			
		Anaphylaxis	
INFECTIONS AND INFESTATIONS			
	Infection[2]		***Infection[2] (Gr. 3)***
INVESTIGATIONS			
		Lipase increased	
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr. 3)***
Neutrophil count decreased			***Neutrophil count decreased (Gr. 3)***
Platelet count decreased			***Platelet count decreased (Gr. 3)***

	Weight loss		***Weight loss (Gr. 2)***
	White blood cell decreased		***White blood cell decreased (Gr. 3)***
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		***Anorexia (Gr. 3)***
		Tumor lysis syndrome	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
	Back pain		
	Musculoskeletal and connective tissue disorders - Other (Muscle cramp/muscle spasm)		***Musculoskeletal and connective tissue disorders - Other (Muscle cramp/muscle spasm) (Gr. 2)***
	Myalgia		***Myalgia (Gr. 2)***
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)			
		Leukemia secondary to oncology chemotherapy[3]	
		Myelodysplastic syndrome[3]	
		Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Tumor flare)[4]	
		Treatment related secondary malignancy[3]	
NERVOUS SYSTEM DISORDERS			
	Dizziness		
	Headache		
		Leukoencephalopathy	
PSYCHIATRIC DISORDERS			
	Insomnia		***Insomnia (Gr. 2)***
RENAL AND URINARY DISORDERS			
		Acute kidney injury	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Cough		***Cough (Gr. 2)***
	Dyspnea		***Dyspnea (Gr. 2)***
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme	
	Hyperhidrosis		***Hyperhidrosis (Gr. 2)***
	Pruritus		***Pruritus (Gr. 2)***
	Rash maculo-papular		***Rash maculo-papular (Gr. 2)***
	Skin and subcutaneous tissue disorders - Other (pyroderma gangrenosum)		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

VASCULAR DISORDERS			
	Thromboembolic event		***Thromboembolic event (Gr. 2)***

[1] This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

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

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

[4] Tumor flare has been observed only in patients with Chronic Lymphocytic Leukemia (CLL).

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

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

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

Also reported on lenalidomide (CC-5013) trials but with the relationship to lenalidomide (CC-5013) still undetermined:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Blood and lymphatic system disorders - Other (eosinophilia); Blood and lymphatic system disorders - Other (monocytosis); Blood and lymphatic system disorders - Other (pancytopenia); Disseminated intravascular coagulation; Febrile neutropenia; Hemolysis; Spleen disorder

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

EAR AND LABYRINTH DISORDERS - Tinnitus

ENDOCRINE DISORDERS - Cushingoid; Hyperthyroidism

EYE DISORDERS - Blurred vision; Conjunctivitis; Dry eye; Flashing lights; Retinopathy

GASTROINTESTINAL DISORDERS - Abdominal distension; Abdominal pain; Anal mucositis; Ascites; Colonic perforation; Dry mouth; Dyspepsia; Dysphagia; Flatulence; Gastritis; Gastroesophageal reflux disease; Gastrointestinal disorders - Other (Crohn's Disease aggravated); Gastrointestinal disorders - Other (diverticulitis); Gastrointestinal disorders - Other (pale feces); Gastrointestinal hemorrhage[5]; Gastrointestinal obstruction[6]; Ileus; Mucositis oral; Rectal mucositis; Small intestinal mucositis

GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - General disorders and administration site conditions - Other (edema NOS); Malaise; Multi-organ failure; Non-cardiac chest pain; Pain

HEPATOBILIARY DISORDERS - Cholecystitis; Hepatic failure

IMMUNE SYSTEM DISORDERS - Allergic reaction

INFECTIONS AND INFESTATIONS - Infections and infestations - Other (Opportunistic infection associated with >=grade 2 lymphopenia)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS - Bruising; Fall; Fracture; Hip fracture; Vascular access complication
INVESTIGATIONS - Activated partial thromboplastin time prolonged; Alanine aminotransferase increased; Alkaline phosphatase increased; Aspartate aminotransferase increased; Blood bilirubin increased; Cholesterol high; Creatinine increased; Electrocardiogram QT corrected interval prolonged; INR increased; Investigations - Other (hemochromatosis)
METABOLISM AND NUTRITION DISORDERS - Acidosis; Dehydration; Hypercalcemia; Hyperglycemia; Hyperkalemia; Hyperuricemia; Hypocalcemia; Hypoglycemia; Hypokalemia; Hypomagnesemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Arthritis; Bone pain; Chest wall pain; Generalized muscle weakness; Joint effusion; Muscle weakness lower limb; Neck pain; Osteonecrosis of jaw[7]; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Tumor pain
NERVOUS SYSTEM DISORDERS - Ataxia; Cognitive disturbance; Depressed level of consciousness; Dysgeusia; Dysphasia; Edema cerebral; Encephalopathy; Intracranial hemorrhage; Ischemia cerebrovascular; Memory impairment; Myelitis; Nervous system disorders - Other (hyporeflexia); Nervous system disorders - Other (spinal cord compression); Peripheral motor neuropathy; Peripheral sensory neuropathy; Seizure; Somnolence; Syncope; Transient ischemic attacks; Tremor
PSYCHIATRIC DISORDERS - Agitation; Anxiety; Confusion; Depression; Psychosis
RENAL AND URINARY DISORDERS - Renal and urinary disorders - Other (chromaturia); Urinary frequency; Urinary incontinence; Urinary tract pain
REPRODUCTIVE SYSTEM AND BREAST DISORDERS - Reproductive system and breast disorders - Other (hypogonadism); Vaginal hemorrhage
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Adult respiratory distress syndrome; Allergic rhinitis; Atelectasis; Bronchopulmonary hemorrhage; Epistaxis; Hypoxia; Laryngeal mucositis; Pharyngeal mucositis; Pleural effusion; Pneumonitis; Pulmonary hypertension; Respiratory failure; Tracheal mucositis; Voice alteration
SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Nail loss; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome); Urticaria
VASCULAR DISORDERS - Hot flashes; Hypertension; Hypotension; Phlebitis; Vascular disorders - Other (hemorrhage NOS)
Note: Lenalidomide (CC-5013) in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

15.0 WRITING COMMITTEE

A Writing Committee will be responsible for the publication of a manuscript that will describe the results of this study in a peer-reviewed journal. The members of this Writing Committee will be the co-authors of this manuscript. Dr. McCarthy, the Study Chair, will be the primary author; Dr. Anderson, Study Co-Chair, will be second author; Dr. Owzar, the CALGB Statistician, will be the third author; and Dr. Linker, the Transplant Committee Chair of the CALGB will be the senior (last) author.

The other members of the Writing Committee will be determined according to the level of participation in the study as measured by patient accrual from each group. The number of investigators on the Writing Committee from each of the participating cooperative groups (CALGB and ECOG) will be based on the following accrual formula. Each group that enrolls at least 5% of the entire study population will have one member on the Writing Committee. Each group will be entitled to an additional member of the Writing Committee for each additional 10% of the overall accrual. For example, if a group enrolled 15% of the study patients, that group would have 2 co-authors on the Committee; if 25% of the study patients were enrolled, that group would have 3 co-

authors. The CALGB will be assigned additional members of the Writing Committee only after that group accrues >25% of the total study patients. It will be the responsibility of each cooperating group to name the individual clinical or laboratory investigators to fill their allotted positions. By this method, it is anticipated that the final Writing Committee will include approximately 12-14 of the clinical and/or laboratory investigators who have been most involved in the design, conduct, and analysis of this study.

A smaller number of individuals may warrant acknowledgment (with their group affiliation) in the final manuscript for their support of the conduct of the study and for their critical review of the manuscript. The participation of each cooperative group that enrolls any patients on this intergroup study will be acknowledged in the final manuscript with their respective grant support.

16.0 REFERENCES

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APPENDIX I MODIFIED COCKCROFT AND GAULT FORMULA FOR ESTIMATED CREATININE CLEARANCE (CR_{CL})

For Serum Creatinine Concentration (SrCr) in mg/dL[a]

$$CR_{cl}(mL/min) \quad \frac{(140 - age)\ (weight)^{b}}{(72)\ (SrCr)}$$

FOR FEMALES, USE 85% OF CALCULATED CR_{CL} VALUE.

a Age in years and weight in kilograms
b If the patient is obese (> 30% over ideal body weight), use ideal body weight in calculation of estimated CrCl.

Calculation of Ideal Body Weight Using the Devine Formula

Ideal body weight: Males = 50.0 kg + (2.3 kg x each inch over 5 feet)
Females = 45.5 kg + (2.3 kg x each inch over 5 feet)

Example female, actual body weight = 75.5, height = 62 inches

Ideal body weight = 45.5 + 2.3 (62-60) = 50.1 kg

This patient's actual body weight is > 30% over ideal body weight. Therefore, in this case, the patient's ideal body weight of 50.1 kg should be used in determining the creatinine clearance

APPENDIX II IDEAL BODY WEIGHT TABLE

	Height (Feet/Inch)	Small Frame (kg)	Medium Frame (kg)	Large Frame (kg)
MEN				
	5’2”	54	59	64
	5’3”	56	60	65
	5’4”	57	62	67
	5’5”	59	63	69
	5’6”	60	65	71
	5’7”	62	67	73
	5’8”	64	69	75
	5’9”	66	71	77
	5’10”	68	73	79
	5’11”	70	75	81
	6’0”	72	77	84
	6’1”	74	79	86
	6’2”	76	82	88
	6’3”	78	84	90
	6’4”	79	86	93
WOMEN				
	4’10”	45	49	54
	4’11”	46	50	55
	5’0”	47	51	57
	5’1”	49	53	58
	5’2”	50	54	59
	5’3”	51	55	61
	5’4”	53	57	63
	5’5”	54	59	64
	5’6”	56	61	66
	5’7”	58	63	68
	5’8”	59	65	70
	5’9”	61	67	72
	5’10”	64	69	74
	5’11”	65	70	76
	6’0”	67	72	79

APPENDIX III ECOG (ZUBROD) PERFORMANCE STATUS SCALE

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

APPENDIX IVCANCER TRIALS SUPPORT UNIT (CTSU) PARTICIPATION PROCEDURES

CANCER TRIALS SUPPORT UNIT (CTSU) ADDRESS AND CONTACT INFORMATION:

To submit site registration documents:
CTSU Regulatory Office
1818 Market Street, Suite 1100
Philadelphia, PA 19103
Phone: 1-888-823-5923
Fax: 215-569-0206

For patient enrollments:
CTSU Patient Registration
Phone: 1-888-462-3009
Fax: 1-888-691-8039
Hours: 8:00 AM - 8:00 PM Eastern Time, Monday - Friday (excluding holidays)

[For CTSU patient enrollments that must be completed within approximately one hour, or other extenuating circumstances, call 301-704-2376. Please use the 1-888-462-3009 number for ALL other CTSU patient enrollments.]

Submit study data directly to the Lead Cooperative Group unless otherwise specified in the protocol:

CALGB Statistical Center
Hock Plaza
2424 Erwin Road, Suite 802
Durham, NC 27705
Tel: 919-668-9350
Data Operations Fax: 919-668-9348
Teleform Fax: 919-416-4990

Sites should submit Teleforms via Fax or Mail. See Section 5.4 Data Submission Section for details on forms submission.

Do not submit study data or forms to CTSU Data Operations. Do not copy the CTSU on data submissions.

For patient eligibility or treatment related questions: Contact the CALGB Study Chair.

For questions unrelated to patient eligibility, treatment, or data submission contact the CTSU Help Desk by phone or e-mail:

CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.

The CTSU Registered Member Web site is located at http://www.ctsu.org

REGISTRATION/RANDOMIZATION

Prior to the recruitment of a patient for this study, investigators must be registered members of the CTSU. Each investigator must have an NCI investigator number and must maintain an "active" investigator registration status through the annual submission of a complete investigator registration packet (FDA Form 1572 with original signature, current CV, Supplemental Investigator Data Form with signature, and Financial Disclosure Form with original signature) to the Pharmaceutical Management Branch, CTEP, DCTD, NCI. These forms are available on the CTSU registered member Web site or by calling the PMB at 301-496-5725 Monday through Friday between 8:30 a.m. and 4:30 p.m. Eastern time.

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

All forms and documents associated with this study can be downloaded from the CALGB-100104 Web page on the CTSU registered member Web site (https://www.ctsu.org). Patients can be registered only after pre-treatment evaluation is complete, all eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS.

Note: ECOG and CALGB institutions will participate via their own Group mechanism.

Requirements for CALGB-100104 site registration:

- CTSU IRB Certification
- CTSU IRB/Regulatory Approval Transmittal Sheet
- Sites need to be transplant-approved by and affiliated with either a NCI Cooperative Oncology Group or the Bone Marrow Transplant Clinical Trials Network or be a FACT-credentialed CICRS site.

Prestudy requirements for patient enrollment on CALGB-100104:

- Patient must meet all inclusion criteria, and no exclusion criteria should apply
- Patient has signed and dated all applicable consents and authorization forms, and the patient decision whether to permit use of tissue for future studies has been documented.
- All baseline laboratory tests and prestudy evaluations performed within the time period specified in the protocol.

CTSU PROCEDURES FOR PATIENT ENROLLMENT

Step 1 Registration

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.
2. Complete the following forms:
    - CTSU Patient Enrollment Transmittal Form
    - CALGB-100104 Step 1 Eligibility Checklist
    - CALGB-100104 Step 1 Registration Worksheet
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays). Registration is limited to the operating hours of the CALGB Registration Office (9 AM - 5 PM ET). The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.
4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the CALGB, within the confines of CALGB's registration hours. The

CTSU registrar will access the CALGB's on-line registration system, to obtain assignment of a unique patient ID (to be used on all future forms and correspondence).

Patients must not start protocol treatment prior to registration.

Step 2 Randomization

Note: Randomization occurs as a separate event from registration and must occur between day +90 - +100 post-transplantation.

1. Contact the CTSU Patient Registration Office by calling 1-888-462-3009. Leave a voicemail to alert the CTSU Patient Registrar that an enrollment is forthcoming. For immediate registration needs, e.g. within one hour, call the registrar cell phone at 1-301-704-2376.
2. Complete the following forms:
   - CTSU Patient Enrollment Transmittal Form
   - CALGB-100104 Step 2 Registration Worksheet
3. Fax these forms to the CTSU Patient Registrar at 1-888-691-8039 between the hours of 8:00 a.m. and 8:00 p.m., Mon-Fri, Eastern Time (excluding holidays). Registration is limited to the operating hours of the CALGB Registration Office (9 AM - 5 PM ET). The CTSU registrar will check the investigator and site information to ensure that all regulatory requirements have been met. The registrar will also check that forms are complete and follow-up with the site to resolve any discrepancies.
4. Once investigator eligibility is confirmed and enrollment documents are reviewed for compliance, the CTSU registrar will contact the CALGB, within the confines of CALGB's registration hours. The CTSU registrar will access the CALGB's on-line registration system, to obtain assignment of a unique patient ID (to be used on all future forms and correspondence). Since this is a double-blind study, a specific treatment arm will not be identified. The CTSU registrar will confirm registration by fax.

DATA SUBMISSION AND RECONCILIATION

1. All case report forms (CRFs) and transmittals associated with this study must be downloaded from the CALGB-10104 Web page located on the CTSU registered member Web site (https://www.ctsu.org). Sites must use the current form versions and adhere to the instructions and submission schedule outlined in the protocol.
2. Submit all completed CRFs (with the exception of patient enrollment forms), clinical reports, and transmittals directly to the CALGB Statistical Center, [see contact table and Section 5.4 of protocol] unless an alternate location is specified in the protocol. Do not send study data to the CTSU. A completed CTSU-CALGB coversheet should accompany all data submissions.
3. The CALGB Statistical Center will send (generally via e-mail but may be sent via postal mail or fax) query notices and delinquency reports directly to the site for reconciliation. Please send query responses and delinquent data to the CALGB Statistical Center (via postal mail) and do not copy the CTSU Data Operations. Each site should have a designated CTSU Administrator and Data Administrator and **must keep their CTEP AMS account contact information current**. This will ensure timely communication between the clinical site and the CALGB Statistical Center.

SPECIAL MATERIALS OR SUBSTUDIES

1. Specimen Submission (Protocol Section 5.5)

- Collect, prepare, and submit specimens as outlined in the protocol.
- Do not send specimens, supporting clinical reports, or transmittals to the CTSU.

SERIOUS ADVERSE EVENT (AE) REPORTING (SECTION 14.0)

1. CTSU sites must comply with the expectations of their local Institutional Review Board (IRB) regarding documentation and submission of adverse events. Local IRBs must be informed of all reportable serious adverse reactions.
2. CTSU sites will assess and report adverse events according to the guidelines and timelines specified in the protocol. You may navigate to the CTEP Adverse Event Expedited Report System (AdEERS) from either the Adverse Events tab of the CTSU member homepage (https://www.ctsu.org) or by selecting Adverse Event Reporting Forms from the document center drop down list on the CALGB-100104 Web page.
3. Do not send adverse event reports to the CTSU.
4. Secondary AML/MDS/ALL reporting: Report occurrence of secondary AML, MDS, or ALL via the NCI/CTEP AML-MDS Report Form in lieu of AdEERS. Submit the completed form and supporting documentation as outlined in the protocol.

DRUG PROCUREMENT (SECTION 9.0):

Investigational agents:	CC-5013 and matching placebo, provide free of charge by Celgene and distributed by the Pharmaceutical Management Branch (PMB), Cancer Therapy Evaluation Program (CTEP). No blinded starter supplies will be available for this study.
Commercial agents:	Filgrastim, Melphalan Hydrochloride

1. Information on drug formulation, procurement, storage and accountability, administration, and potential toxicities are outlined in Section 9.0 of the protocol.
2. You may navigate to the drug forms by selecting Pharmacy Forms from the document center drop down list on the CALGB-100104 Web page.

REGULATORY AND MONITORING

Study Audit

To assure compliance with Federal regulatory requirements [CFR 21 parts 50, 54, 56, 312, 314 and HHS 45 CFR 46] and National Cancer Institute (NCI)/Cancer Therapy Evaluation Program (CTEP) Clinical Trials Monitoring Branch (CTMB) guidelines for the conduct of clinical trials and study data validity, all protocols approved by NCI/CTEP that have patient enrollment through the CTSU are subject to audit.

Responsibility for assignment of the audit will be determined by the site's primary affiliation with a Cooperative Group or CTSU. For Group-aligned sites, the audit of a patient registered through CTSU will become the responsibility of the Group receiving credit for the enrollment. For CTSU Independent Clinical Research Sites (CICRS), the CTSU will coordinate the entire audit process.

For patients enrolled through the CTSU, you may request the accrual be credited to any Group for which you have an affiliation provided that Group has an active clinical trials program for the primary disease type being addressed by the protocol. Per capita reimbursement will be issued by the credited Group provided they have endorsed the trial, or by the CTSU if the Group has not endorsed the trial.

Details on audit evaluation components, site selection, patient case selection, materials to be reviewed, site preparation, on-site procedures for review and assessment, and results reporting and follow-up are available for download from the CTSU Operations Manual located on the CTSU Member Web site.

Health Insurance Portability and Accountability Act of 1996 (HIPAA)

The HIPAA Privacy Rule establishes the conditions under which protected health information may be used or disclosed by covered entities for research purposes. Research is defined in the Privacy Rule referenced in HHS 45 CFR 164.501. Templated language addressing NCI-U.S. HIPAA guidelines are provided in the HIPAA Authorization Form located on the CTSU website.

The HIPAA Privacy Rule does not affect participants from outside the United States. Authorization to release Protected Health Information is NOT required from patients enrolled in clinical trials at non-US sites.

Clinical Data System (CDS-Web) Monitoring

This study will be monitored by the Clinical Data System (CDS-web). Cumulative CDS data will be submitted quarterly to CTEP by electronic means. The sponsoring Group fulfills this reporting obligation by electronically transmitting to CTEP the CDS data collected from the study-specific case report forms.

APPENDIX V SITE COUNSELOR IDENTIFICATION FORM

Celgene Corporation	**Celgene Pregnancy Prevention & Counseling Program** **Site Counselor Identification Form** **for NCI Studies** **NCI Protocol #: _____**

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

General Information
Principal Investigator: _____
Institution Name: _____

Counselor Information

CTEPpersonID:_____
CTEPsiteID: _____

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

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

Email Address:
_____
____

Phone:_____
Fax: _____

Institution Street Address:
_____

City:_____
State/Region: _____

Zip/Post Code: _____
Country: _____

Previously approved as a Counselor? □ No □ Yes

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

If yes, please list the protocols #(s), corresponding CTEPsiteID(s) and institution names(s) *for*

***protocols Celgene has already associated you with*:**

Protocol#:	CTEPsiteID	Institution

Document A_Version2.1 May 17, 2011

APPENDIX VI LENALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

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

Criteria for females of childbearing potential (FCBP)

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

Counseling

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

She understands the potential teratogenic risk to the unborn child

She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment

She should be capable of complying with effective contraceptive measures

She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy

She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test

She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol

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

The investigator must ensure that for females of childbearing potential:

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

Acknowledge the aforementioned requirements

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

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

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

Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential

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

Contraception

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

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

Highly effective methods:

Intrauterine device (IUD)

Hormonal (birth control pills, injections, implants)

Tubal ligation

Partner's vasectomy

Additional effective methods:

Male condom

Diaphragm

Cervical Cap

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

Pregnancy testing

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

Before starting study drug

Female Patients:

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

Male Patients:

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

During study participation and for 28 days following study drug discontinuation

Female Patients:

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 discontinuation, and at day 28 following study drug discontinuation. 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 study drug discontinuation.

At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.

Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.

If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.

Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study treatment must be discontinued during this evaluation.

Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.

If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

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

Female patients should not donate blood during treatment and for at least 28 days following discontinuation of lenalidomide.

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

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

APPENDIX VII LENALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT

To be completed prior to each dispensing of study drug.

Protocol Number: _____

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

(Check the appropriate box to indicate risk category)

Female: □

If female, check one:

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

□ NOT FCBP

Male: □

Do Not Dispense study drug if:

The patient is pregnant.

No pregnancy tests were conducted for a FCBP.

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

FCBP:

I verified that the required pregnancy tests performed are negative.

I counseled FCBP regarding the following:

Potential risk of fetal exposure to lenalidomide: If lenalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid

pregnancy while taking lenalidomide. The teratogenic potential of lenalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking lenalidomide.

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

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

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

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

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

Frequency of pregnancy tests to be done:

- Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
- If the patient missed a period or has unusual menstrual bleeding.
- When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.

- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.

- NEVER share study drug with anyone else.

- Do not donate blood while taking study drug and for 28 days after stopping study drug.

- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.

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

- Return unused study drug to the study doctor.

Provide Lenalidomide Information Sheet to the patient.

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

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

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

- NEVER share study drug with anyone else.

- Do not donate blood while taking study drug and for 28 days after stopping study drug.

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

- Return unused study drug capsules to the study doctor.

Provide Lenalidomide Information Sheet to the patient.

MALE:

I counseled the Male patient regarding the following:

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

- To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 28 days after stopping study drug.

- Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant.

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

Provide Lenalidomide Information Sheet to the patient.

Counselor Name (Print): _____

Counselor Signature: _____ Date: _____/_____/_____

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

APPENDIX VIII LENALIDOMIDE INFORMATION SHEET

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

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

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

Lenalidomide may cause birth defects (deformed babies) or death of an unborn baby.

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

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

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

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

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

You must have pregnancy testing done at the following times:

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

Stop taking study drug if you become pregnant during treatment

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

Do not breastfeed while taking study drug

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

If you are a female not of childbearing potential:

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

If you are a man:

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

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

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

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

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

Restrictions in sharing lenalidomide and donating blood:

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

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

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

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

Return unused study drug capsules to your study doctor.

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