TITLE: Lenalidomide plus Melphalan as a Preparative Regimen for Autologous Stem Cell Transplantation in Relapsed or Refractory Multiple Myeloma:A Phase 1 / 2 Study

Principal Investigator: Roger Pearse, MD
Weill Cornell Medicine
425 E. 61st Street, 8th Floor
Phone: 646-962-6500
Fax: 212-746-8961
Email: rnp2001@med.cornell.edu

NCT01054196

Current Protocol Amendment Version (8): 05.27.2021

Prior versions:

Protocol A(7) clean 04.14.17

Protocol A(6) dated 5.25.16

Protocol A(5) dated 9.11.13

Protocol A(4) dated 8.1.12

Protocol A(3) dated 4.7.11

IRB Protocol Number: 0909010623
Amendment 8, Revision Date: May 27th , 2021
Celgene Tracking Number: RV-MM-PI-0458

Weill Cornell Medical College

TITLE: Lenalidomide plus Melphalan as a Preparative Regimen for Autologous Stem Cell Transplantation in Relapsed or Refractory Multiple Myeloma: A Phase 1 / 2 Study

Principal Investigator: Roger Pearse, MD
Weill Cornell Medicine
425 E. 61st Street, 8th Floor
Phone: 646-962-6500
Fax: 212-746-8961
Email: rnp2001@med.cornell.edu

Statistician:
Paul Christos, DrPH, MS Weill Cornell Medical College
Division of Biostatistics and Epidemiology New York, NY 10065
Phone: 646-962-8018
Fax: 646-962-0281
Email: pac2001@med.cornell.edu

TREATMENT SCHEMA

Transplant Phase:

(LMWH, 40mg daily, given days -5 to +14, held if platelets < 50K)

Planned dose levels of lenalidomide in Phase 1 portion of study:

Dose Level	Lenalidomide Dose / Schedule
-1	25mg daily x 5 days
1	25mg twice daily x 5 days
2	25mg qAM, 50mq qPM x 5 days
3	50mg qAM, 75mg qPM x 5 days
4	75mg qAM, 100mg qPM x 5 days
5	100mg qAM, 150mg qPM x 5 days
6	150mg qAM, 200mg qPM x 5 days

Maintenance Phase:

Starting Day + 100 (post stem cell infusion):
Start 25 mg of Lenalidomide daily for days 1-21 of a 28-day cycle until progression of disease.
Aspirin 81 mg daily continuously during the maintenance phase.

TABLE OF CONTENTS

1. OBJECTIVES

1.1. Primary Objectives

A) Phase 1: To determine the maximal tolerated dose (MTD) of lenalidomide that can be safely added to high-dose melphalan prior to autologous stem cell transplantation (ASCT).

B) Phase 2: To determine whether the addition of high-dose lenalidomide to ASCT followed by maintenance standard-dose lenalidomide improves the response rate and duration of response for relapsed or refractory multiple myeloma (RMM) as compared to historical data for standard ASCT using melphalan conditioning alone.

1.2 Phase 1 Study Endpoints

- Maximum Tolerated Dose of Lenalidomide prior to autologous stem cell transplantation

1.3 Phase 2 Study Endpoints

Primary:

- Duration of response (DOR)

Secondary:

- Response rate
- Determination of regimen toxicities
- Overall Survival (OS)
- Quality of Life

2. BACKGROUND

2.1 Disease

Multiple myeloma (MM) is a usually fatal neoplasm of the plasma cell that is currently the second most common hematologic malignancy in the United States, with an incidence of approximately 19,000 new cases per year.[1]MM is characterized by the secretion of a monoclonal immunoglobulin, the M-protein, into the blood and is complicated by the development of end-organ damage, including lytic lesions of the skeleton, renal failure, and bone marrow suppression.[2] For many years, the traditional therapies for multiple myeloma consisted of alkylating agents, most commonly melphalan, combined with corticosteroids. While the response rate to these therapies ranged at about 50%, the average survival of MM remained unchanged at 3-5 years.[3] MM is uniquely sensitive to melphalan in a dose-response relationship, however the maximal effective dose could not be safely used, due to the severe myelosuppression and pancytopenia that high-dose melphalan could induce.[4]The development of the technology for autologous stem cell transplant (ASCT) in the 1980's allowed high dose melphalan to be used as a conditioning regimen in MM and was the first therapy shown to improve survival vs. traditional chemotherapy.[5,6] The success achieved with high-dose melphalan and ASCT made this regimen the standard of care for all patients with MM who could tolerate the rigors of

transplantation.

The advent of the immunomodulatory drugs (IMiD® compounds) and proteasome inhibition with bortezomib in the late 1990s once again revolutionized treatment for MM. Thalidomide, the first IMiD used, was shown to induce responses in relapsed RMM (RMM), a state of advanced disease that is typically resistant to traditional chemotherapy (including high-dose melphalan), and is associated with high morbidity and mortality.[7]While the mechanism of action of thalidomide is not entirely known, it is postulated that it targets the bone marrow environment through a combination of angiogenesis inhibition, T-cell stimulation, and cytokine modulation.[8]Lenalidomide is a second generation IMiD that has been shown to be directly toxic to myeloma cells and several thousand-fold times more potent than thalidomide for certain mechanisms of action.[9]Lenalidomide has been shown in two large phase three studies to improve the improve the disease-free and overall survival in RMM.[10,11]

Recent trials of the combination of the IMiD® compounds with traditional chemotherapy have demonstrated a remarkable synergy in anti-myeloma efficacy. In elderly patients who are not considered to be candidates for ASCT, the combination of thalidomide with traditional melphalan and prednisone treatment (MPT) was shown to be superior to MP, with increases in both disease response rate (76% vs. 47.6%) and overall survival at three years (80% vs. 64%).[12] The combination of lenalidomide with melphalan plus prednisone (RMP) has shown to be similarly, if not slightly more, effective in preliminary trials.[13]

Lenalidomide has a dose-response relationship in its anti-myeloma efficacy that is limited by myelosuppression that hearkens the melphalan experience. In a phase I trial of lenalidomide, the dose-limiting toxicity of myelosuppression was seen in nearly all patients who were treated with 50mg daily of lenalidomide after 28 days, making 25 mg daily the maximal tolerated dose and the reference for future trials.[14]Yet, in this study nearly all patients treated with 50mg lenalidomide daily had a dramatic improvement in their MM, with a response rate of 85% to the single agent. This result suggests that the 50mg dose may be more active, albeit more toxic to the bone marrow.

The majority of patients receiving first line treatment for myeloma will have a drop in the M-protein and at least a partial remission; however, disease relapse is the rule. As with most malignancies, when MM progresses after each successive therapy, the treatment response wanes, and thus there is a continuing need to discover novel effective therapies for patients with RMM. Although the novel agents lenalidomide, thalidomide, and bortezomib have all provided new hope for thousands of patients with RMM, new strategies are needed to help manage and delay disease progression and morbidity.

2.2 Investigational Agents

Lenalidomide

Lenalidomide (Revlimid®) is an analog of thalidomide with greater potency to activate immunomodulatory effects and inhibit angiogenesis when compared to thalidomide. Both lenalidomide and thalidomide are members of the Celgene Corporation's proprietary class of compounds called IMiDs® which are characterized by their immunomodulatory and anti-angiogenic activity.

Lenalidomide differs structurally from thalidomide by the addition of an amino group, making it a 4-amino-glutamyl analog of thalidomide.[9]It was initially developed with the focus on further inhibition of TNF-α secretion, and it does so 50,000 times more effectively than thalidomide *in vitro* and 2000 times more potently in activated monocytes. Moreover, lenalidomide has also been shown to be directly cytotoxic to MM cell lines and patient cells in culture.[15]

Lenalidomide achieves a peak plasma concentration in MM patients between 0.5 to 4 hours after oral administration. Administration with food does not affect the AUC (total exposure time) to the drug, but it does reduce the maximum serum concentration by approximately one-third. The majority of lenalidomide is excreted via the kidney and the half-life of the drug is approximately 3 hours. Serum concentration and AUC is affected by varying degrees of renal insufficiency, which can affect the risk of adverse effects when taking lenalidomide.[16]

Phase I studies of heavily pretreated subjects with relapsed or refractory multiple myeloma was conducted to identify the MTD and to evaluate the safety of oral lenalidomide.[17]Myelosupression was found to be the DLT and the MTD was determined to be 25 mg/day. No significant somnolence, constipation, or neuropathy was observed. Seventeen (71%) of 24 evaluable patients achieved >25% reduction of the myeloma paraprotein and 20% of patients achieved a > 50% paraprotein reduction (responders received 25-50 mg/day). The results from phase II trials of lenalidomide given at 30 mg per day for 21 days every 28 days suggest that oral lenalidomide is active in advanced multiple myeloma and well tolerated. Of 46 evaluable subjects with relapsed or refractory MM, 39 (85%) achieved at least stable disease, including 2 subjects with complete resolution of paraprotein.[17]

Two randomized, phase III studies have been conducted to investigate the effectiveness and safety of lenalidomide at 25 mg combined with high-dose dexamethasone compared to high-dose dexamethasone to treat patients with relapsed or refractory multiple myeloma.[10-11] The results of these study revealed 59.4% of heavily pretreated patients with relapsed / refractory multiple myeloma responded to the combination of 25mg lenalidomide and high-dose dexamethasone compared to a 21.1% response rate to high-dose dexamethasone alone. Furthermore, a survival benefit was seen in the lenalidomide-containing arm. This data led to the approval of lenalidomide in combination with dexamethasone in patients with relapsed / refractory multiple myeloma in 2006.

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the RevAssist® program of Celgene Corporation. Per standard RevAssist® requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the RevAssist® program. Prescriptions must be filled within 7 days. **Only enough lenalidomide for one cycle of therapy (either in the stem cell transplant conditioning phase or the later maintenance phase) will be supplied to the patient each cycle**.

Melphalan

Melphalan is commercially available and is the primary agent used for conditioning in

autologous stem cell transplantation for multiple myeloma. It is a derivative of nitrogen mustard and classified as an alkylating agent. Melphalan intercalates within ribonucleic acid base pairs and thus interferes with DNA replication and transcription of RNA, leading to death in actively replicating cells. When used for ASCT, it is given intravenously. Melphalan is incompletely and erratically absorbed, has a prolonged plasma half-life, and is excreted largely unchanged in the urine. Intravenous melphalan results in very high plasma levels followed by an initial rapid decay curve (half-life 30-60 minutes). Most of the administered dose is recovered unchanged in the urine and the drug does not need to be metabolized to be active. The peak concentration achieved in the plasma is directly related to creatinine clearance (CrCl) and thus the dose is usually reduced in those patients with a CrCl < 70 cc/min.

The major toxicity of melphalan is myelosuppression, which is dose-related. Other toxicities which may occur at high-doses include nausea and vomiting, mucositis, and diarrhea. Antiemetics are therefore routinely given prior to and after administration, along with oral care to prevent and ameliorate mucositis, and anti-diarrheals as needed. Further details of action and pharmacology can be found in the package insert.

Melphalan's efficacy when used in high doses as a preparative regimen for autologous stem cell transplantation was established by the landmark study of Attal, et al. in 1996, in which 200 patients with MM were randomized to receive either high-dose melphalan with autologous stem cell support versus standard combination chemotherapy.[5]The standard combination therapy consisted of alternating cycles of VCMP (Vincristine, Cyclophosphamide, oral Melphalan, Prednisone) and BVAP (Carmustine, Vincristine, Adriamycin, Prednisone) every three weeks for a total of 18 cycles. The ASCT conditioning regimen consisted of four to six cycles of VCMP and BVAP, followed by 140mg/m^2 of intravenous melphalan plus 8Gy of total body irradiation. The results were clearly favorable for the ASCT arm, with an improvement in event-free survival (28% vs. 10%) and overall survival at five years (52% vs. 12%). A second larger randomized study of conventional chemotherapy versus high-dose melphalan confirmed a survival benefit of approximately one year with ASCT.[6]Furthermore, this study showed that the benefit was achievable with 1) omitting the total body irradiation and increasing the dose of melphalan to 200mg/m2 and 2) using peripheral blood stem cells (PBSC) instead of bone marrow. Following the results of these two trials, and other similar studies, autologous stem cell transplantation become the gold standard treatment for multiple myeloma in patients deemed fit for intensive therapy.

2.3 **Rationale**

Patients with RRMM have usually undergone several prior lines of therapy and tend to respond poorly to further treatment. Thus, patients with RRMM are particularly vulnerable to their disease and there is a need to develop new treatment strategies to improve their disease response and survival. The use of ASCT has allowed the effective and safe delivery of high-dose melphalan and has shown to have a positive impact on survival in MM. Similarly, lenalidomide may have greater efficacy in higher doses and has been shown to have synergistic activity when combined with melphalan. The use of ASCT support is the logical next step to allow the safe incorporation of high-dose lenalidomide with high-dose melphalan conditioning prior to ASCT. This new proposed therapy should provide greater anti-myeloma efficacy compared to high-dose melphalan alone, especially in the RRMM setting. If there is significant improvement in MM

clinical outcomes seen in patients with RRMM, this treatment may be extended to the up-front treatment of newly diagnosed MM as well and potentially improve the quality and length of the lives thousands of patients a year.

3. PATIENT SELECTION

3.1 Inclusion Criteria

3.1.1 Patients must have histologically confirmed multiple myeloma that is either refractory to or has relapsed following at least one prior line of therapy. Per the International Myeloma Working Group Consensus Panel 1, relapsed myeloma is defined as previously treated myeloma that progresses and requires the initiation of salvage therapy but does not meet criteria for either "primary refractory myeloma" or "relapsed-and-refractory myeloma". Primary refractory myeloma is defined as disease that is non-responsive in patients who have never achieved a minimal response (MR) or better with any therapy. It includes patients who never achieve MR or better in whom there is no significant change in M-protein and no evidence of clinical progression, as well as primary refractory/progressive disease where patients meet criteria for true progressive disease. Relapsed and refractory myeloma is defined as disease that is non-responsive while on salvage therapy, or progresses within 60 days of last therapy, in patients who have achieved MR or better at some point before then progressing.

3.1. 2 Age $\geq$18 years.

3.1.3 Life expectancy of greater than 12 weeks.

3.1.4 ECOG performance status $\leq$ 2.

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

3.1.6 Patients must have normal organ and marrow function as defined below:

- ANC $\geq$1,000/µL
- platelets $\geq$50,000/µL
- total bilirubin $\leq$ 1.5 X upper limit of normal
- AST(SGOT)/ALT(SGPT) $\leq$ 2.5 X upper limit of normal
- Cardiac Ejection Fraction $\geq$ 45%
- Creatinine clearance > 60 cc/min

(Creatinine clearance can be calculated either by 24 hour urine collection, or if urine is not available, by Cockcroft-Gault formula∗).

∗ The Cockcroft-Gault formula to estimate the creatinine clearance[19]:

3.1.7 Patients must have an adequate number of CD34+ stem cells collected to allow for transplantation. This number is defined as $\geq 2x10^6$ CD34+ cells / kg body weight. If not previously collected and stored, the patient must be willing to undergo stem cell mobilization and collection as per standard practice.

3.1.8 The effects of lenalidomide on the developing human fetus at the recommended therapeutic dose are unknown; however, it has been shown to be teratogenic other primates. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix D: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. The treating physician will follow the adverse reporting guidelines as outlined in further detail below for pregnancies.

3.1.9 Lenalidomide has been shown to carry a risk of thromboembolic events, especially when used in combination with either corticosteroids or alkylating chemotherapeutic agents.[20] All patients who participate in this study must be willing and able to tolerate prophylactic anticoagulation with low-molecular weight heparin (LMWH) for the required dates in treatment protocol. (See treatment schema for LMWH usage plan). Patients also must be able to tolerate low-dose aspirin, 81 mg daily, during the maintenance phase of the treatment protocol.

3.1.10 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had myeloma therapy within 14 days prior to entering the study or those who have not recovered from adverse events due to agents

---

$$\text{CrCl} = \frac{(140 - \text{age})(\text{Weight in kg})(0.85 \text{ if female})}{(72 * \text{Creatinine in mg/dL})}$$

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

administered more than 2 weeks earlier. Patients may have received bisphosphonate therapy as part of routine myeloma care at any time prior to study entry.

3.2.2 Patients may not be receiving any other investigational agents.

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to lenalidomide (including thalidomide) or melphalan.

3.2.4 Known positive for HIV or infectious hepatitis, type B or C.

3.2.5 Uncontrolled illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.

3.2.6 Pregnant and lactating women are excluded from the study because the risks to an unborn fetus or potential risks in nursing infants are unknown.

3.2.7 History of thrombosis or thromboembolic event within last 60 days prior to study entry.

4. REGISTRATION PROCEDURES

Central Patient Registration

Patients will be centrally registered with the Weill Cornell Medical College (WCMC), Division of Hematology and Medical Oncology Clinical Research Office. To register a patient, fax the following documents to the Clinical Research Office at 646-962-1610:

- WCMC Patient registration form
- First and last page of the full executed informed consent form, plus additional pages in checkboxes for correlative studies are required.
- Fully executed HIPAA research authorization form
- Eligibility checklist signed and dated by investigator and research nurse
- Documentation of any eligibility waivers granted
- Confirmation of sponsor registration, when applicable
- For inpatients, signed consent documentation template

Central registration information is reviewed and entered into the HemOnc centralized research database. Documentation of patient registration will be faxed to the Investigational Pharmacy to allow for release of study agent.

5. TREATMENT PLAN

5.1 Study Design / Agent Administration

This is a phase 1/2 study of the incorporation of high-dose lenalidomide into high-dose melphalan conditioning prior to autologous stem cell transplantation (ASCT) for relapsed/refractory multiple myeloma (RRMM). About 21 subjects will participate in phase 1 of the study at Weill Cornell Medical College. Phase 1 of the study will dose escalate lenalidomide in a series of subjects in a 3+3 design through 6 dose levels of lenalidomide (as per modified Fibonacci escalation) to determine the maximal tolerated dose (MTD)of lenalidomide prior to ASCT. The lenalidomide dosing in the phase 1 portion of the study is shown in **Table 1** below:

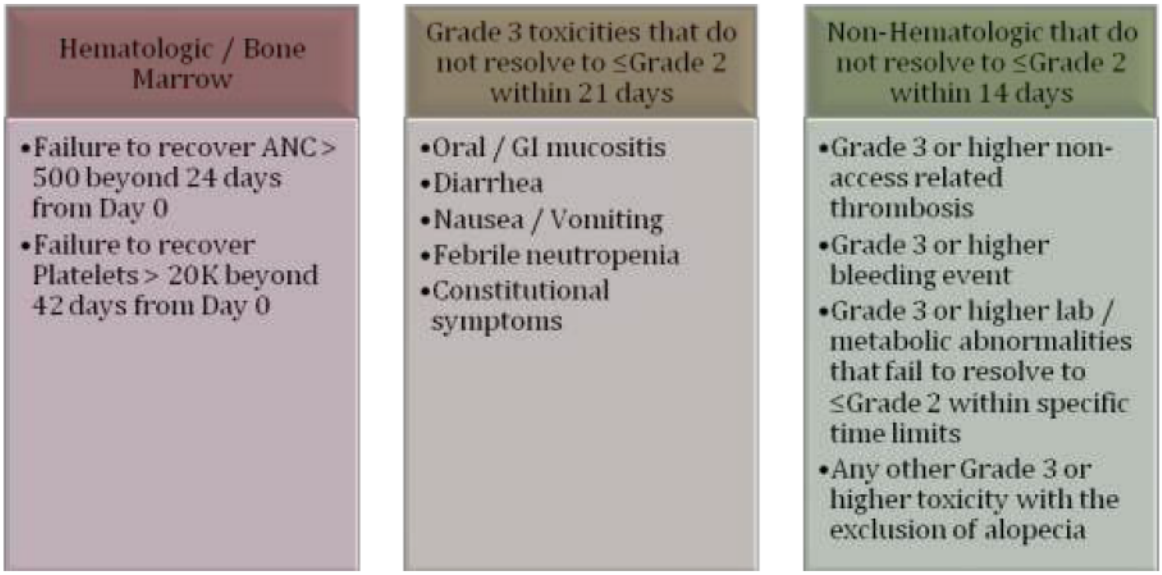
Table 1: Planned dose levels of lenalidomide in Phase 1 portion of study

Dose Level	Lenalidomide Dose / Schedule
-1	25mg daily x 5 days
1	25mg twice daily x 5 days
2	25mg qAM, 50mq qPM x 5 days
3	50mg qAM, 75mg qPM x 5 days
4	75mg qAM, 100mg qPM x 5 days
5	100mg qAM, 150mg qPM x 5 days
6	150mg qAM, 200mg qPM x 5 days

Finding the dose-limiting toxicity (DLT) will determine the MTD. The potential DLTs are defined by the criteria in **Table 2**.

Table 2: Dose limiting toxicities (DLT). [Note that Day 0 is defined as the day of stem cell infusion]. Toxicity is graded as per NCI Common Terminology Criteria for Adverse Events (CTCAE) version

3



The phase 1 trial starts at dose level 1 (50mg daily dose) as per the treatment schema (page i). Escalation commences to the next dose level after three patients are treated with no DLT. If 1 patient at a dose level experiences DLT, an additional three patients are treated at that dose level. If 2 patients experience a DLT at dose level 1, then the trial will recommence at dose level -1. MTD of lenalidomide is defined by the dose level that has less than 2/6 DLTs (See **Table 3**).

Table 3:3+3 dose escalation schema to determine maximum tolerated dose (MTD) based on dose-limiting toxicity (DLT).

# DLT / # Subjects	**Decision**
0/3	Escalate to the next higher dose
1/3	Add 3 patients to the same dose cohort
1/6	Escalate to the next higher dose / trial ends if already at Dose level 4
≥ 2/3 or ≥ 2/6	Decrease dose for ongoing study
The MTD is defined as the maximum dose with < 2/6 DLT's. If there are 2 or more DLT's at dose level -1, all test doses will be declared to have exceeded the MTD.	

In more detail, in the transplant phase of the study, all participants will receive oral lenalidomide (at the pre-determined dose level in the phase 1 portion, and at the MTD for lenalidomide in the phase 2 portion) for 5 days (designated as days -5 to -1 in the Treatment Schema above). On days-2 and -1, all patients will receive 100mg/m^2 of intravenous melphalan once daily for a total of 2 doses (200mg/m^{2}total). After a period of 24-72 hours has elapsed from the last melphalan dose (designated as Day 0) each patient will receive infusion of at least 2.0 x 10^6/kg of autologous CD34+ stem cells. As per conventional New York Presbyterian Hospital (NYPH)

autologous transplantation protocol, all patients will receive daily filgrastim (G-CSF) starting on day +1 post infusion of stem cells until stem cell engraftment. Engraftment is defined as an absolute neutrophil count of 500 / cu. mm and platelet count of 20,000/mm^3 untransfused. Concomitant medications and other supportive care for the transplant phase of the study are described below in section 5.2. Bone marrow biopsy will be performed for all patients on Day -2, just prior to melphalan infusion. Toxicity will be assessed on a continuing basis during the course of the ASCT and thereafter on a biweekly basis for the first two months and thereafter on a monthly basis. Bone marrow biopsy as well as other laboratory studies to determine the extent of myeloma will be performed on Day 100 to define the response rate to the lenalidomide + melphalan ASCT.

In the maintenance phase of the study, all patients will begin lenalidomide at a dose of 25mg daily for days 1-21 of a 28 day cycle on Day +100. This therapy will continue until there is either progression of disease (as defined by IURC, Appendix C) or intolerability to lenalidomide develops, even after dose reduction (dose reduction schedule outlined below in section 6.)Response rate and duration of response will be measured every 28 days as defined by the IURC **(see Appendix C)** until disease relapse/progression or 36 months have elapsed from day 0, which ever occurs first.[18]

Phase 2 of the study will expand the number of participants in the MTD arm of the trial and follow the treatment plan outlined above. Up to 29 patients will be enrolled at Weill Cornell Medical College and Cedars-Sinai Medical Center in phase 2 of the study.

The autologous transplant will be performed on an inpatient basis.Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications for lenalidomide are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.2 General Concomitant Medication and Supportive Care Guidelines

Transplant Phase: Patients will receive supportive care according to institutional guidelines for autologous transplant recipients. All patients will be treated in private rooms with hepafilters. Patients will receive antibacterial, antiviral and antifungal prophylaxis. All patients will receive thromboprophylaxis with low-molecular weight heparin (LMWH) at a dose of 40mg subcutaneously once daily, starting from day -5 until day +14 or until platelet count has dropped to < 50K, whichever comes first. All patients will also receive prophylactic antibiotics, antivirals, and antifungals as per usual NYPH transplant protocol which usually, but not in all cases, consists of levofloxacin 500mg daily and fluconazole 100 mg daily, until engraftment, as well as either valacyclovir 500mg twice daily or acyclovir 400 mg twice daily from Day +1 to 6 months post-transplant. Levofloxacinbacterial infection prophylaxis will start at 500 mg once a day on Day - 1. Diflucan 400 mg daily and valacyclovir 500 mg two times per day will be started upon admission. Broad-spectrum antibiotics and antifungals will be instituted for fever and signs of infection. All blood products will be irradiated and leukodepleted. Patients will be screened for CMV viremia by pcr weekly and those who test positive will receive ganciclovir. Patients will have daily blood counts and electrolytes while in hospital. This can be decreased to CBC 3x per week until engraftment and then routinely with follow up appointments. The electrolytes are done daily while in hospital but can be decreased to be decreased to routine monitoring at follow

up appointment once discharged and the liver function tests should be done 2x per week in hospital but decreased to routine monitoring at follow up appointments once the patient is discharged. Liver function tests will be done at least twice a week. Antiemetics will be used prophylactically and on an as needed basis. Patients will receive full transfusion support.

5.3 Duration of Therapy and Criteria for Removal From Study

In the absence of treatment delays due to adverse event(s), treatment may continue until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Pregnancy or a positive pregnancy test,
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

5.4 Early Termination of Study

We plan to recruit 3 patients initially and observe treatment side effects and adverse events for two full cycles of therapy. If there are serious or life-threatening side effects, the study will be terminated and no further patients will be accrued. Study-terminating events are listed below:

- Abrupt or unexpected patient death
- Grade 4 rash or neuropathic drug toxicity
- Intolerability of study drug regimen

5.5 Duration of Follow Up

Patients will be followed for 3 years after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

6. DOSING DELAYS/DOSE MODIFICATIONS

The dose levels and escalation strategy for lenalidomide in the phase 1 portion of the study are outlined in detail above.

In the maintenance phase (starting Day +100), lenalidomide will be given daily for days 1-21 of a 28 day cycle. The dose of lenalidomide will be modified for toxicity as listed below. Doses must be adjusted for adverse events deemed related to lenalidomide by the investigator. Doses may be adjusted for adverse events related to study medications not listed below at the discretion of the investigator.

Lenalidomide doses during the maintenance phase will be modified due to toxicity as follows:

Dose Level	*Agent* Dose
-4	Lenalidomide 5 mg/day PO on days 1-21 of 28 day cycle.
-3	Lenalidomide 10 mg/day PO on days 1-21 of 28 day cycle.
-2	Lenalidomide 15 mg/day PO on days 1-21 of a 28 day cycle
-1	Lenalidomide 25 mg/day PO on days 1-21 + G-CSF 5µg/kg/day (or equivalent pegylated G-CSF dosage).
0	Lenalidomide 25 mg/day PO on days 1-21 of a 28 day cycle.

If neutropenia is the only toxicity for which dose reduction is necessary, the first dose reduction step is Dose Level –1. For all other toxicities requiring dose reduction, the first dose reduction step is Dose level –2. Toxicities and dose reduction guidelines are listed in the following table:

Dose Modification Schedule for Lenalidomide		
NCI CTC v3.0 Toxicity Grade	Day 2-14 of Cycle	≥Day 15 of Cycle
Grade 3 neutropenia (ANC < 1000 cells/mm^3) associated with fever (temperature ≥ 38.5°C) or Grade 4 neutropenia (ANC < 500 cells/mm^3)	• Hold (interrupt dose). • Follow cbc weekly. • If neutropenia has resolved to ≤ grade 2, restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remained for cycle. • If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the dose maintained for the next cycle at the treating physician's discretion.
Thrombocytopenia ≥ Grade 3 (platelet count < 50,000 / mm^3)	• Hold (interrupt dose). • Follow cbc weekly. • If thrombocytopenia resolves to ≤ grade 2, restart at next lower dose level and continue the cycle until day 21. • Hold anticoagulation for platelet count < 50,000/mm^3	• Omit lenalidomide for remainder of cycle. • Restart at next lower dose level for next cycle • Hold anticoagulation for platelet count < 50,000/mm^3
Anemia ≥ Grade 3 (Hgb < 8g/dL)	• Hold (interrupt dose). • Follow cbc weekly. • If anemia resolves to ≤ grade 2, restart at next lower dose level and continue the cycle until day 21.	• Omit lenalidomide for remainder of cycle • Restart at next lower dose level for next cycle
Non-blistering rash Grade 3	• If Grade 3 hold (interrupt) dose. Follow weekly. • If the toxicity resolves to ≤	• Omit lenalidomide for remainder of cycle. • Restart at next lower dose level for next

	grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. • Discontinue lenalidomide study drug.	cycle
Desquamating (blistering) rash of any grade	• Discontinue lenalidomide	• Discontinue lenalidomide
Erythema multiforme ≥ Grade 3	• Discontinue lenalidomide	• Discontinue lenalidomide
Sinus bradycardia / other arrhythmia = Grade 2	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for the remainder of the cycle and restart at next lower dose for next cycle
Grade ≥ 3	• Discontinue lenalidomide	• Discontinue lenalidomide
Hyper or Hypothyroidism Grade ≥ 2	• Omit lenalidomide for the remainder of the cycle • Evaluate etiology and initiate appropriate therapy • Restart Lenalidomide at next lower dose level for next cycle	• Omit lenalidomide for the remainder of the cycle • Evaluate etiology and initiate appropriate therapy Restart Lenalidomide at next lower dose level for next cycle

7. ADVERSE EVENT REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The investigator will be required to provide appropriate information concerning any findings that suggest significant hazards, contraindications, side effects, or precautions pertinent to the safe use of the drug under investigation. Safety will be monitored by evaluation of adverse events reported by patients or observed by investigators or research staff, as well as by other investigations such as clinical laboratory tests, x-rays, electrocardiographs, etc.

7.1 Study Agent / Method Risks:

A. Melphalan

1. Myelosuppression is the major dose-limiting toxicity, occurring regularly at doses >20mg/m^2.

2. Nausea, vomiting, diarrhea - occasional, rarely severe.

3. Transient hepatic transaminase elevations are occasionally seen, but rarely severe.

4. Mucositis is occasionally seen and can potentially be as severe as WHO grade 4 (unable to tolerate oral intake of solids or liquids). Care is generally supportive with mouthwashes, oral viscous lidocaine, and, in some cases, intravenous narcotics are used until healing

occurs.

5. Miscellaneous- there is the rare possibility that cataract formation, secondary malignancies, sterility, coronary artery disease and hypothyroidism may occur.

B. Autologous Peripheral Blood Stem Cell Infusion

The volume of the peripheral blood stem cell (PBSC) infusate is approximately 800-1000cc for the average adult. Infusions of marrow may produce volume overload and subsequent pulmonary edema which can be prevented and treated by diuretic administration. Stem cell infusion is rarely associated with allergic reactions. Small, subclinical pulmonary emboli may occur, but these rarely if ever require any intervention. Rarely, renal failure due to hemoglobinuria can be seen. Standard pre-medications for blood products may be used before administration of the marrow graft, generally consisting of diphenhydramine or acetaminophen; in some cases, corticosteroids are given, especially if the patient has had allergic reactions to blood products in the past.

In very rare circumstances, an autologous stem cell graft may fail to engraft either as a primary failure to recover marrow function, manifested by failure of early recovery of myeloid and erythroid elements in the marrow, or as an abrupt onset of marrow hypoplasia during the post-transplant period. a) If ANC$<0.2 \times 10^9$ on day 28 of the second transplant the patients will receive GM-CSF (instead of the usually received G-CSF that is given from Day 0 until engraftment) at a dose of 500 ug/m^2/day SC. If ANC $<0.5 \times 10^9$ on day 35, the patient will receive re-infusion of backup. In addition, the GM-CSF will continue.

C. Blood Product Infusions

Infusions of fractionated blood products may produce volume overload, which can be managed with diuretics. They may also induce allergic reactions of variable severity, many of which can be prevented or mitigated by premedication with antipyretics, antihistamines, and corticosteroids. These products may also serve as vectors of serious infection [e.g., CMV, hepatitis, HIV]. To circumvent this, prospective blood donors will be screened for evidence of hepatitis B, HIV, HTLV-I/II and CMV infection. CMV will be prevented by WBC depletion. HIV[-] and hepatitis B_sAg[-] and C Ab [-] blood products determined by currently available serologic testing will be used at all times. All blood products are irradiated [3000r,^{137}Cs] to circumvent the risk of GvHD caused by contaminating lymphocytes in the transfused fractions.

D. Pneumocystis Carinii Prophylaxis – Trimethoprim/Sulfamethoxasole

The risk of trimethoprim and sulfamethoxazole in the doses given are primarily hypersensitivity reactions and signs of folate deficiency. Any patient with known hypersensitivity to these compounds will not receive these drugs and will receive an alternative agent, either dapsone or pentamidine up to the discretion of the investigator.

E. Herpes Zoster Prophylaxis – Acyclovir / Valacyclovir

Either acyclovir or valacyclovir will be used for this indication. The serious risks involved with the use of acyclovir include seizure and renal failure, however these are rarely seen. More commonly, acyclovir has been associated with nausea / vomiting, diarrhea, headache, and rash. Valacyclovir has been rarely associated with renal failure, aplastic anemia, anaphylaxis, thrombotic thrombocytopenia purpura / hemolytic-uremic syndrome, psychosis, and seizure. More common side effects of valacyclovir that are seen include nausea / vomiting, abdominal pain, elevated liver function tests, and rash. Any subject sensitive to one of these agents may receive the other, or no agent at all, at the discretion of the investigator.

H. G-CSF (filgastrim)

The only side-effect observed frequently is bone pain. Mild hair thinning has been reported but the combination of chemotherapy and radiotherapy of the present program will cause universal alopecia. Splenomegaly has been rarely reported. Flare-up of pre-existing auto-immune diseases and psoriasis have also been reported.

Investigational Agent Risks

Lenalidomide

Lenalidomide has been studied in healthy volunteers and in patients with cancer of the blood and other organs of the body as well as in patients with other diseases. As with any other experimental treatment there may be side effects or risks associated with lenalidomide, some of which are not yet known.

The following is a list of the most medically significant or most common side effects reported in completed and ongoing studies considered to be related to lenalidomide. In some cases, side effects can be serious, long-lasting, may never go away, or can cause death. This list is not complete but your Study Doctor will answer any questions you might have and provide you with more information.

Very Common (Greater than 10% chance this will happen)

Low number of white blood cells (with or without fever) [Leukopenia, Neutropenia, Febrile neutropenia, Granulocytopenia, Lymphopenia]; Anemia; Decrease in cells that help your blood clot [Thrombocytopenia]; Vision Blurred; Diarrhea; Pain [Upper abdominal pain, Abdominal pain, Toothache], Constipation; Indigestion [Dyspepsia]; Nausea; Vomiting; Feeling weak and unwell [Asthenia]; Tired [Fatigue]; Swelling [Edema, Peripheral edema]; Fever [Pyrexia]; Chills; Pneumonia or other infections [Pneumonia, Bronchitis, Upper respiratory tract infection, Urinary tract infection, Erysipelas, Gastroenteritis, Herpes simplex, Herpes zoster, Influenza, Lower respiratory tract infection, Sinusitis, Sepsis, Bacteremia]; Sore throat [Nasopharyngitis, Pharyngitis]; Stuffy nose [Rhinitis]; Weight loss ; Decreased appetite; High blood sugar [Hyperglycemia]; Chemical imbalance in blood [Hypokalemia, Hypocalcemia, Hypophosphatemia, Hypomagnesemia, Hyponatremia]; Pain including muscles, joints, and non-cardiac chest pain [Pain in extremity, Pain in limb, Arthralgia, Back pain, Bone pain, Muscle spasms, Musculoskeletal pain, Muscle cramp, Chest pain and Myalgia]; Dizziness; Altered sense of taste [Dysgeusia], Headache; Eye lens cloudy [Cataract]; Abnormal sense of touch [Hypoaesthesia]; Pain and decreased sensation in nerves [Neuropathy, Peripheral neuropathy,

Peripheral sensory neuropathy]; Shaking [Tremor]; Cough; Shortness of breath [Dyspnea]; Nosebleed [Epistaxis]; Blood clot in lower extremities, lungs, heart, brain, and other organs [Pulmonary embolism, Deep vein thrombosis]; Dry skin; Itching [Pruritus]; Allergic reaction [Rash, Hypersensitivity (in uncommon category)]; Feeling sad [Depression], Not sleeping well [Insomnia].

Common (between a 1-10% chance that this will happen):

Abnormally low number of blood cells [Pancytopenia]; Destruction of red blood cells [Hemolytic anemia]; Heart attack [Acute myocardial infarction]; Abnormal heart beats [Atrial fibrillation, Palpitations, Tachycardia]; Heart stops working [Cardiac failure, Congestive cardiac failure]; Low oxygen to heart tissue [Myocardial ischemia]; Dry mouth; Decreased action of intestine [Gastrointestinal motility disorder]; Bile flow from liver slowed or blocked [Cholestasis]; Gout; Fall; Bruise [Contusion]; Lowered level of consciousness with drowsiness, listlessness, and apathy [Lethargy]; Abnormal liver lab tests [Abnormal liver function tests, Alanine aminotransferase increased, Gamma-glutamyltransferase increased]; Increase in liver protein that indicates inflammation in body [C-Reactive protein increased]; Loss of fluid [Dehydration]; Diabetes [Diabetes mellitus]; High uric acid in blood [Hyperuricemia]; Iron build up in body [Iron overload]; Muscle weakness; Cancer [Acute myeloid leukemia, B-cell lymphoma, Basal Cell Carcinoma, Squamous cell carcinoma]; Stroke [Cerebrovascular accident]; Tingling of skin [Paresthesia]; Fainting [Syncope]; Vertigo (problem with inner ear which leads to feeling that everything is spinning) Moody [Mood altered]; Kidney failure [Renal failure]; Breathing disorder [Respiratory distress]; Excessive sweating [hyperhidrosis]; Night sweats; Skin redness [Erythema]; Swelling of skin filled with blood [Hematoma]; Swelling of blood vessels [Vasculitis]; High or low blood pressure [Hypertension, Hypotension]; Blood not getting to extremities [Peripheral ischemia]; Clot in vein [Thrombosis], Sudden increase in tumor size [Tumor flare], Rapid death of cancer cells where the accumulating contents of dying cancer cells cause an imbalance in the chemistry of the body which can lead to kidney damage [Tumor lysis syndrome (TLS)]; Blood cancer that causes decreased number of red blood cells, white blood cells, and platelets because they do not develop normally [Myelodysplastic syndrome].

Furthermore, the following risks have been reported after marketing of lenalidomide and are considered by Celgene to be related:

- Swelling of lungs [Pneumonitis]
- Over and underactive thyroid [Hyperthyroidism and Hypothyroidism],
- Severe allergic conditions including
    - swelling under skin [angioedema]
    - Severe skin reactions involving lining of the nose, mouth, stomach and intestines or rash leading to the separation of the top layer of skin [Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis],
- TLS.
- Acute Graft versus Host Disease- after a bone marrow transplant, new cells attack the body which can result in abdominal pain or cramps, nausea, vomiting, diarrhea, jaundice (yellowing of skin), or skin rash.

Second new cancers

- In clinical trials of newly diagnosed multiple myeloma, an increased rate of second new cancers have been seen in patients receiving lenalidomide compared with patients in the other arm (not receiving lenalidomide). These new cancers including acute leukemia (blood cancers), lymph node cancers, and solid tumors were seen in patients receiving lenalidomide taken together with melphalan or immediately after high dose melphalan and stem cell transplantation. An increase of blood and lymph node cancers was also seen in the clinical trials where patients received lenalidomide after stem cell transplant. When lenalidomide is given with dexamethasone a higher number of skin cancers and solid tumors have been reported. Patients should make their doctors aware of their medical history and any concerns they may have regarding their own increased risk of other cancers. Your doctor will be checking you for any possible new cancers that may develop during your treatment.
- Other Risks
- Lenalidomide has been shown to increase the level of digoxin in the blood in some patients; please tell your doctor if you are taking digoxin.
- Your condition may not get better or may become worse while you are in this study. For more information about risks and side effects, ask your Study Doctor.

7.2 **Adverse Event Characteristics**

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 3.0 will be utilized for AE reporting. A copy of the CTCAE version 3.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **Attribution** of the AE:
  - Definite – The AE *is clearly related* to the study treatment.
  - Probable – The AE *is likely related* to the study treatment.
  - Possible – The AE *may be related* to the study treatment.
  - Unlikely – The AE *is doubtfully related* to the study treatment.
  - Unrelated – The AE *is clearly NOT related* to the study treatment.

7.3 Recording of Adverse Events

All adverse events will be recorded on a patient specific adverse event log. The AE log will be maintained by the research staff and kept in the patient's research chart.

7.4 Serious Adverse Event (SAE) Reporting

7.4.1. Definition of SAE

SERIOUS ADVERSE EVENTS include death, life threatening adverse experiences, hospitalization or prolongation of hospitalization, disability or incapacitation, overdose, congenital anomalies, pregnancy, and any other serious events that may jeopardize the subject or require medical or surgical intervention to prevent one of the outcomes listed in this definition.

7.4.1.1 Pregnancies:

Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on study drug or within 4 weeks after the subject's last dose of study drug are considered expedited reportable events. If the subject is on study drug, the study drug is to be discontinued immediately and the subject is to be instructed to return any unused portion of the study drug to the Investigator. The pregnancy must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

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

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

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

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

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

7.4.2. Reporting of SAE to IRB

All SAEs occurring on this study will be reported to the IRB according to the IRB policy. The following procedure will be followed for reporting SAE to the IRB:

- Complete the SAE Cover Sheet (See Appendix B)
- Complete the IRB Unexpected, Study-related Adverse Events, Incidents, and Information Reporting Form. This form should be submitted within 7 calendar days of investigator notification of the event.
- If the event is not immediately reportable as per the IRB policy, only the SAE Cover Sheet must be completed. These events will be reported to the IRB at the time of continuing renewal on the Adverse Event & IND Safety Reporting Cumulative Table.

Forms may also be downloaded from the IRB website at:
http://weill.cornell.edu/research/forms_and_policies/irb_forms/index.html

7.4.3. Reporting of SAE to FDA

If an SAE occurs on this study, the event will be filed on a MedWatch form with the FDA (Form 3500A).

Adverse drug reactions that are serious, unlisted/unexpected, and at least possibly associated to the drug, and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) in writing by Dr. Tomer Mark (the principal sponsor-investigator). A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

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

The principal sponsor-investigator must also call the FDA as soon as an adverse reaction occurs. The phone number is (301) 594-5778. A recorder is available after hours. Report these reactions to the FDA within ten (10) working days both verbal and written.

The address of the FDA is:

FDA
Division of Oncology
HFD-150
1451 Rockville Pike
Rockville, MD 20852-1448

The phone number of the FDA is: (301) 594-5778

Please ask to speak with the Division of Oncology.

7.4.4. Reporting of SAE to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene within 24 hours / 1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-MM-PI-0458) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

The contact information for Celgene is: Celgene Corporation
Drug Safety
86 Morris Avenue
Summit, NJ 07901

Toll Free: 800-640-7854
Phone: 908-673-9667
Fax: 908-673-9115
Email: drugsafety@celgene.com

7.4.5 Provisions for Adverse Events

Necessary prophylaxis will be administered. Anti-emetics and will be prescribed if necessary. Blood and platelet transfusions will be given as clinically indicated. Pamidronate or Zoledronic acid may be given monthly as part of standard care.

7.4.6 Adverse event updates/IND safety reports

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

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

The Investigator shall notify his/her IRB promptly of these new serious and unexpected AE(s) or significant risks to subjects.
The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB, on file.

7.4.7 Annual Reports

If this study meets the FDA requirements for IND exemption, the Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follow:

Celgene Corporation
Attn: Clinical Science Research
86 Morris Avenue
Summit, NJ 07901
Tel: (908) 673-9000

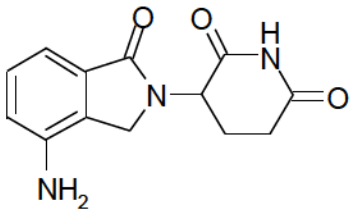
All adverse experience reports must include the patient number, age, sex, weight, severity of reaction (mild, moderate, severe), relationship to drug (probably related, unknown relationship, definitely not related), date and time of administration of test medications and all concomitant medications, and medical treatment provided. The investigator is responsible for evaluating all adverse events to determine whether criteria for "serious" and as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described in section 7.4.4.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with the study agents can be found in Section 7.1. The properties of the investigational agent in this study, lenalidomide, are listed below.

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

Chemical Structure of Lenalidomide



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

The empirical formula for lenalidomide is C13H13N3O3, and the gram molecular weight is 259.3.

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

REVLIMID® (lenalidomide) is available in 5 mg, 10mg, 15mg, and 25 mg capsules for oral administration. Each capsule contains lenalidomide as the active ingredient and the following inactive ingredients: lactose anhydrous, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

8.1.1 Clinical Pharmacology

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

8.1.2 Pharmacokinetics and Drug Metabolism

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

Pharmacokinetic sampling in myelodysplastic syndrome (MDS) patients was not performed. In multiple myeloma patients maximum plasma concentrations occurred between 0.5 and 4.0 hours post-dose both on Days 1 and 28. AUC and Cmax values increase proportionally with dose following single and multiple doses. Exposure (AUC) in multiple myeloma patients is 57% higher than in healthy male volunteers.

8.1.3 Pharmacokinetic Parameters

In vitro (14C)-lenalidomide binding to plasma proteins is approximately 30%. The metabolic profile of lenalidomide in humans has not been studied. In healthy volunteers, approximately two-thirds of lenalidomide is eliminated unchanged through urinary excretion. The process exceeds the glomerular filtration rate and therefore is partially or entirely active. Half-life of elimination is approximately 3 hours

8.2 Drug Supply and Dosage

The planned dose levels of lenalidomide for phase 1 transplant portion of the investigation is as outlined in on page i. The MTD determine in the phase 1 portion of this study will be used in the transplant phase of the phase 2 portion. The maintenance dose of lenalidomide is the same regardless of study phase. Maintenance lenalidomide will begin at Day +100 at a dose of 25 mg/day, orally for 1-21 days followed by a 7-day rest period (28 day cycles). Subjects experiencing adverse events may need study treatment modifications as outlined above in Section 6.

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the RevAssist®program. All physicians who prescribe lenalidomide for research subjects enrolled into this trial and all research subjects enrolled into this trial must be registered in and must comply with all requirements of Celgene's RevAssist®program.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.
Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

8.3 Ordering and Packaging

Lenalidomide will be shipped directly to patients. Bottles will contain a sufficient number of capsules to last for one cycle of dosing.

8.3.1 Storage and Special Handling Instructions

Study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold. Females of child bearing potential should not handle or administer the clinical dosage forms unless they are wearing gloves.

8.3.2 Prescribing Information

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Lenalidomide will be provided in accordance with the RevAssist®program of Celgene Corporation. Per standard RevAssist®requirements all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of

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.

8.4 Lenalidomide Accountability

Lenalidomide Inventory Records – The investigator, or a responsible party designated by the investigator, will maintain a careful record of the inventory and disposition of all agents received from *Sponsor* on a Drug Accountability Record Form (DARF).

9. STUDY EVALUATIONS

Patients will be followed daily during their inpatient stay during the transplant portion of the study (Day -5 until engraftment). Thereafter, they will be followed in clinic on days +28, +56, +100, and thereafter every 28 days (+/- 2 days).Within two weeks of admission to the hospital for transplant, females of childbearing potential must have a pregnancy test with a sensitivity of at least 50mIU/dL. Thereafter, females of childbearing potential will then have a pregnancy test every 28 days if they have regular or no menstrual cycles or every 14 days if they are irregular (See **Appendix D** for complete pregnancy testing, birth control and counseling). Females of childbearing potential may also need to have a pregnancy test if a period is missed or if there is unusual menstrual bleeding. FCBP will have additional pregnancy tests at discontinuation of study drugs and at Day 28 after discontinuation of study drugs (FCBP with irregular menstrual cycles will also have a pregnancy test at Day 14 after discontinuation of study drugs). During scheduled study visits patients will undergo the following evaluations for assessment of response and toxicity (depicted in **Table 4** below).Baseline evaluations are to be conducted within 6weeks prior to transplant date, unless otherwise noted. A Study Calendar of Assessments is shown on the next page in **Table 4**.

Table 4: Study Calendar

	Screening	Transplant Phase		Maintenance Phase			
	(<6 weeks prior to transplant date: Day 0)	Day +28	Day +56	Day +100 (Cycle 1, Day 1)	Cycle 1, Days 8,15,22	All Other Cycles Day 1	Off Study
Informed Consent	X						
Complete medical history[1]	X[1]	X	X	X	X	X	X
Physical exam, KPS, vital signs, weight[1]	X[1]	X	X	X	X	X	X
CBC[1]	X[1]	X	X	X	X	X	X
Complete metabolic profile[1,2]	X[1]	X	X	X	X	X	X
SPEP, IF, quant immunoglobulins[1]	X[1]	X	X	X		X	X
Serum free light chains[1]	X[1]	X	X	X		X	X
24-hour urine for UTP, UPEP, UIF[1]	X[1]	X	X	X		X	
Serum pregnancy test[1,3]	X[1]	X	X	X	X	X[3]	X[3]
24-hour urine for creatinine clearance	X						
Chest x-ray	X						

Paranasal Sinus X-ray	X						
Dental Clearance	X						
β_2M[1]	X[1]						
CRP, LDH, uric acid[1]	X[1]						
LDH[1], TSH[1]	X[1]						
Echocardiogram or MUGA	X						
Pulmonary Function Testing	X						
Register patient into RevAssist®program[5]	X						
Skeletal survey or whole body PET/CT scan	X			X		X[4]	
Bone marrow biopsy and aspirate[4]	X	X[7]		X		X[4]	
FACT-BMT survey for quality of life	X			X		X[6]	
Concurrent medication use survey[1]	X	X	X	X	X	X	X
Drug dispensation [5]	Continuous						
Adverse event monitoring	Continuous (as defined in detail in Section 5.1)						

1. **Within 4 weeks prior to starting treatment. UTP = urine total protein; UPEP = urine protein electrophoresis; UIF = urine immunofixation; SPEP = serum protein electrophoresis; IF = serum immunofixation; β_2M = beta-2 microglobulin.**
2. **Includes sodium, potassium, chloride, CO_2, calcium, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phospatase, total bilrubine, SGOT/AST, SGPT/ALT.**
3. **Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide(see Appendix III: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).**
4. **To confirm CR or when clinically indicated.**
5. **Lenalidomide must be prescribed through and in compliance with Celgene's RevAssist® program. Prescriptions of lenalidomide must be filled within 7 days.**
6. **To be done Cycle 6, day 1 only. See appendix E for questionairre**
7. **To be done on Day -2 (two days prior to stem cell infusion)**

Labs required as per the study calendar on days +28,+56 and +100 can be done (+/-) 2 days

9.1 Baseline Evaluation

All baseline evaluations are to be done within 6 weeks of start of therapy, unless otherwise specified:

- Complete blood count (CBC) with differential and platelets **(WITHIN 4 WEEKS OF TREATMENT)**
- Complete metabolic profile (including sodium, potassium, chloride, CO2, calcium, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT/AST, SGPT/ALT. **(WITHIN 4 WEEKS OF TREATMENT)**
- TSH **(WITHIN 4 WEEKS OF TREATMENT)**
- CRP, LDH, uric acid **(WITHIN 4 WEEKS OF TREATMENT)**
- Beta-2 microglobulin**(WITHIN 4 WEEKS OF TREATMENT)**
- 24-hour urine collection for total protein, protein electrophoresis, and immunofixation.
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulims, and serum free light chains studies.**(WITHIN 4 WEEKS OF TREATMENT)**
- Physical examination with history, vital signs, and performance status **(WITHIN 4 WEEKS OF TREATMENT)**
- Concurrent medication use survey**(WITHIN 4 WEEKS OF TREATMENT)**
- FACT-BMT quality of life survey
- Whole body PET-CT scan or skeletal survey
- Serum pregnancy test (for females of childbearing potential) **(WITHIN 10-14 DAYS PRIOR TO AND AGAIN WITHIN 24 HRS OF PRESCRIBING LENALIDOMIDE with sensitivity described above)**
- Bone marrow aspirate and core biopsy
- Registration of patient into RevAssist program
- Standard pre-none marrow transplant evaluation, including:
    - Chest x-ray
    - Paranasal sinus x-ray
    - Pulmonary function testing, including spirometry and diffusion capacity
    - 24 hour urine for creatinine clearance
    - Echocardiogram or MUGA scan
    - Dental clearance (written documentation of dental inspection by dentist indicating no active infections or need for tooth extraction)

9.1.1 Day -2 (Two days prior to Melphalan Infusion)

- Bone marrow aspiration and biopsy

9.2 Day+28(+/- 2 days) and Day + 56 (+/- 2 days) visits (Transplant phase)

- Complete blood count (CBC) with differential and platelets
- Complete metabolic profile (including sodium, potassium, chloride, CO2, calcium, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT/AST, SGPT/ALT.

- 24-hour urine collection for total protein, protein electrophoresis, and immunofixation.
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulims, and serum free light chains studies.
- Physical examination with history, vital signs, and performance status
- Concurrent medication use survey
- Serum pregnancy test (for females of childbearing potential)

9.3 Day +100 (+/- 2 days) visit (Cycle 1, Day 1 of Maintenance phase)

- Complete blood count (CBC) with differential and platelets
- Complete metabolic profile (including sodium, potassium, chloride, CO2, calcium, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT/AST, SGPT/ALT)
- 24-hour urine collection for total protein, protein electrophoresis, and immunofixation.
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulims, and serum free light chains studies.
- Physical examination with history, vital signs, and performance status
- Concurrent medication use survey
- Serum pregnancy test (for females of childbearing potential: 10-14 days prior to and again within 24 hrs of prescribing lenalidomide)
- FACT-BMT quality of life survey
- Bone marrow aspirate and core biopsy
- Whole body PET-CT scan or skeletal survey as clinically indicated to confirm complete remission or disease progression.

9.4 Day +108, 115, 122 visits (Cycle 1, Day 8,15, 22 of Cycle 1 in Maintenance phase)

- Complete blood count (CBC) with differential and platelets
- Complete metabolic profile (including sodium, potassium, chloride, CO2, calcium, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT/AST, SGPT/ALT)

9.5 All other cycles on maintenance phase, Day 1 and End-of-study visit

- Complete blood count (CBC) with differential and platelets
- Complete metabolic profile (including sodium, potassium, chloride, CO2, calcium, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT/AST, SGPT/ALT, LDH, uric acid, Phosphorous, Magnesium)
- 24-hour urine collection for total protein, protein electrophoresis, and immunofixation. This test is not required at the end-of-study visit.
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulims, and serum free light chains studies.
- Physical examination with history, vital signs, and performance status

- Concurrent medication use survey
- Serum pregnancy test (for females of childbearing potential)
- Bone marrow aspirate and core biopsy, to confirm complete remission or progression of disease, as clinically indicated. This test is not required at the end-of-study visit unless clinically indicated.
- Whole body PET-CT scan or skeletal survey, to confirm complete remission or progression of disease, as clinically indicated. These tests are not required at the end-of-study.
- FACT-BMT quality of life survey **(CYCLE 6 Day 1, only)**

9.6 Post study follow-up

All attempts will be made to follow patients until progression or death. Subjects who have been discontinued from study will still be followed in a clinic setting to the fullest extent possible on a monthly to bi-monthly basis. Those who choose not to resume regular clinic follow-up will be contacted every 6 months by telephone or electronically to collect post study information. The post-study collection information will consist of telephone interview between the clinical investigator and the discontinued patient. The information requested will be current disease status, current treatment use, and physical status of the patient.

9.7 Criteria for removal from study

Treatment with study drugs is to be discontinued when any of the following occurs:

- Progressive disease (see Appendix C)
- Adverse event(s) that, in the judgment of an Investigator, may cause severe or permanent harm or which rule out continuation of study drug
- Major violation of the study protocol
- Non-compliance or refusal of the patent to continue treatment and/or evaluation
- Withdrawal of consent
- Patient is lost to follow-up
- Death
- Pregnancy or a positive pregnancy test
- The patient achieves a stable plateau and is eligible to proceed to high dose chemotherapy and stem cell transplantation
- The development of any co-morbid condition or excessive toxicity that would make further participation in the protocol unsafe
- At the discretion of the principal investigator and/or Celgene Corporation for any reason

Any possible premature discontinuation would be documented adequately with reasons being stated, and information would have to be issued according to local requirements (e.g., IRB/EC, regulatory authorities, etc.).
The responsible Clinical Investigator as well as the Supporters (Celgene Corporation) have the right to discontinue this study at any time for reasonable medical or administrative reasons in any single center. Possible reasons for termination of the study could be but are not limited to:

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

10 MEASUREMENT OF EFFECT

10.1 Disease Response

Disease response category (e.g. partial response, very good partial response, complete response, stringent complete response) will be as defined by the International Uniform Response Criteria for Multiple Myeloma (Appendix C).

10.2 Duration of Response

Duration of overall response*:* The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

10.3 Overall Survival

Overall survival: The interval between the day of transplantation (Day 0) and date of death. If the date of death is uncertain, the date of last contact with the subject will be used.

10.4 Quality of Life

Quality of life will be evaluated and scored using the questionnaire from the bone marrow transplant subscale of the Functional Assessment of Cancer Therapy available from www.facit.org. See Appendix E for an example questionnaire.

11 DATA REPORTING / REGULATORY CONSIDERATIONS

11.1 Data Collection

The data collection plan for this study is to utilize the RedCap database with support from the institutional CTSA (Clinical Translation Science Award) center to capture all treatment, toxicity, and efficacy data for all enrolled patients.

11.2 Regulatory Considerations

All protocol amendments and consent form modifications will be made by the Principal Investigator. Celgenewill have the opportunity to review and approve the changes prior to submission of these changes to the local IRB and distribution to participating sites.

12. STATISTICAL CONSIDERATIONS

12.1 **Study Design/Endpoints**

This study is designed to occur in two sections: A phase 1 study, in which the primary objective is to determine the maximum tolerated dose (MTD) of lenalidomide to be used with standard melphalan-based autologous stem cell transplantation; and 2) A phase 2 study, in which the primary endpoint is to determine the duration of response to lenalidomide + melphalan conditioning for autologous stem cell transplantation.

For the phase 1 study:

Determination of the dose-limiting toxicity (DLT) and study methods are defined above in Section 5. The design is constructed to reduce the chance of escalating the dose when the probability of DLT is high, and increase the chance of escalating the dose when the probability of DLT is low. The maximum tolerated dose is defined as the highest dose level with an observed incidence of DLT in no more than one out of six patients treated at a particular dose level. The dose escalation scheme is as follows:

The dose escalation scheme provides the following probabilities of escalation based on the true chances of DLT at a specific dose level. One can see that the probability of escalation is high if the toxicity risks are low.

True Probability of Toxicity:	.05	.10	.20	.30	.40	.50	.60
Probability of Escalation:	.97	.91	.71	.49	.31	.17	.08

After the determination of the MTD, a phase 2 trial will be initiated with the dose selected on the basis of the phase 1 study.

For the phase 2 study:

The primary endpoint is measurement of duration of response, as defined in Section 11. The duration of response to the study medications will be compared to historical data for standard ASCT using melphalan conditioning alone. Historically, 50% of patients with relapsed MM will maintain response at 12 months following ASCT. Enrollment of a total of 29 patients in the expanded MTD cohort (phase 2 portion of study) will give an 80% power to detect a 25% difference in the proportion of patients in continued response at 12 months with an two-tailed alpha = 0.05. Duration of response, overall survival and other such time-related endpoints will be analyzed via the Kaplan-Meier method and log-rank test will be used to determine statistical significance.

12.2 **Sample Size/Accrual Rate**

For the phase 1 portion of the study: A minimum of six and a maximum of 36 patients would be treated on this trial. It is expected that the study will accrue 10 patients per year and will take approximately 30 months.

For the phase 2 portion of the study: An enrollment of 29 patients in the expanded MTD cohort will be required. It is expected that the study will accrue 15 patients per year and will take approximately 36 months.

12.3 **Analysis of Secondary Endpoints**

The secondary endpoint of overall response rate will be measured as defined in Section 11. Fisher exact test and Student *t* test (or Wilcocon rank-sum test) will be used to associate category of response with potential risk factors such as sex, disease stage, C-reactive protein (CRP), β-2 microglobulin, lactate dehydrogenase, and albumin. All *P* values will be 2 sided with statistical significance evaluated at the 0.05 α level. The precision of the obtained estimates will be assessed by calculating 95% confidence intervals.

The secondary endpoint of quality of life (QOL) will be measured via FACT-BMT questionnaire (Appendix E). Fisher exact test and Student *t* test (or Wilcoxon rank-sum test) will be used to associate QOL score with category of response, duration of response, as well as the other potential risk factors listed above such as sex, disease stage, C-reactive protein (CRP), β-2 microglobulin, lactate dehydrogenase, and albumin. All *P* values will be 2 sided with statistical significance evaluated at the 0.05 α level. The precision of the obtained estimates will be assessed by calculating 95% confidence intervals.

12.4 **Reporting and Exclusions**

12.4.1 **Evaluation of toxicity.** All patients will be evaluable for toxicity from the time of their first treatment with lenalidomide.

12.4.2 ***Evaluation of response.*** *All patients included in the study will be assessed for response to treatment if they have received at least autologous stem cell transplantation (underwent Day 0 stem cell infusion).*

13. PROTOCOL AMENDMENTS AND DEVIATIONS

Any amendment to this protocol must be agreed to by the Principal Investigator and reviewed by Celgene. Amendments should only be submitted to IRB/EC after consideration of Celgene review. Written verification of IRB/EC approval will be obtained before any amendment, which affects subject safety or efficacy, is implemented. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

All protocol amendments and consent form modifications will be made by the Principal Investigator. Celgene will have the opportunity to review and approve the changes prior to submission of these changes to the local IRB and distribution to participating sites.

14 REGULATORY CONSIDERATIONS

14.1 Institutional Review Board/Ethics Committee approval

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

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

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

All protocol amendments will be reviewed by Celgene Corporation prior to submission and approval by the Institutional Review Board (IRB) before they can be implemented. The investigator is also responsible for notifying the IRB/EC of any serious deviations from the protocol, or anything else that may involve added risk to subjects.

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

14.2 Informed Consent Procedures

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

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form, signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files. At the pre-admission consultation, patients will be fully informed as to the purposes and potential risks and benefits involved in this study. Patients will have ample opportunity to ask questions before consenting. Legal guardians will sign informed consent for legally incompetent patients in accordance with hospital policy.

14.3 Protecting Privacy and Confidentiality

Confidentiality will be maintained within the limits of the law. Patient names or any other identifying information will not be used in reports or publications resulting from this study. Only qualified staff from New York Presbyterian Hospital, Weill Medical College of Cornell

University, the Food and Drug Administration, the Celgene Corporation or other supporters such as the National Cancer Institute will be able to review patient medical records.
Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws. Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

14.4 Study records requirements

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

14.5 Protection of Human Rights

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to Weill Cornell Medical College IRB guidelines.

Patients will be eligible for this trial regardless of gender or racial/ethnic background. All patients must follow the guidelines for pregnancy testing, birth control and counseling related to the risk of fetal exposure to lenalidomide as outlined in Appendix D.

14.6 Premature Discontinuation of Study

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

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

- Serious adverse events, intolerability of drug regimen, or sudden/unexpected death in any of the early trial (up to three patients) participants, as outline in section 9.2.

14.6.1 Study as a whole

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

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

14.7 Benefits of the Protocol

The potential benefit of this study is the development of a safe and effective treatment program for MM patients who have disease relapse. Knowledge will be acquired about this treatment program, its tolerability, and the effectiveness of lenalidomide (Revlimid®) in combination with melphalan prior to autologous stem cell transplant the treatment of relapsed or refractory MM. If effective, this treatment plan may improve disease-free and overall survival MM patients.

14.8 Risks in Relation to Anticipated Benefit

The risks associated with participation in this trial are commensurate with the expected risks of other potential therapies and are reasonable given the potential benefit to patients with newly diagnosed MM. If the combination of lenalidomide with melphalan-based autologous stem cell transplantation demonstrated is as effective against relapsed MM as anticipated, this regimen could become standard of care leading to improved survival.

14.9 Alternative Treatments

Patients who refuse to participate in the study or decided to withdrawal from the study will be given the option to choose standard chemotherapy, other investigation studies, supportive care, or no anti-cancer treatment at all. Some patients treated with standard chemotherapy do benefit. Treatment with either thalidomide or lenalidomide alone or in combination with corticosteroids has prior proven efficacy. Furthermore, therapy with an autologous stem cell transplant using standard melphalan conditioning alone may also be of benefit. While the results of these therapies have been encouraging, long-term remissions are rare, no patients are cured and none of the drugs used in these standard treatments are free of side effects. We believe that this novel regimen will improve response rates and duration of remission.

14.10 Incentives

No incentives will be offered to patients/subjects for participation in the study. Participation is voluntary.

14.11 Costs

Patients and/or their medical insurance coverage will be responsible for paying for their hospitalization, doctor visits, diagnostic tests, chemotherapy drugs, and other medicines used in their care directly. These costs are expected to be equivalent to those of standard treatment.

Lenalidomide (Revlimid®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers in accordance with the RevAssist® program. Lenalidomide will be will be shipped directly to patients.

REFERENCES

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin. 2007;57:43-66.
2. Munshi N, Tricot G, Barlogie B: Plasma cell neoplasms. In: DeVita J, VT., Hellman S, Rosenberg SA, eds. Principles and Practice of Oncology. Philadelphia, PA: Lippincott Williams & Wilkons; 2001:2465-2499.
3. Kyle RA, Rajkumar SV. Multiple myeloma. N Engl J Med. 2004;351:1860-1873.
4. Selby PJ, McElwain TJ, Nandi AC et al. Multiple myeloma treated with high dose intravenous melphalan. Br J Haematol. 1987;66:55-62.
5. Attal M, Harousseau JL, Stoppa AM et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. N Engl J Med. 1996;335:91-97.
6. Child JA, Morgan GJ, Davies FE et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med. 2003;348:1875-1883.
7. Singhal S, Mehta J, Desikan R et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med. 1999;341:1565-1571.
8. Bartlett JB, Dredge K, Dalgleish AG. The evolution of thalidomide and its IMiD derivatives as anticancer agents. Nat Rev Cancer. 2004;4:314-322.
9. Knight R. IMiDs: a novel class of immunomodulators. Semin Oncol. 2005;32:S24-30.
10. Dimopoulos M, Spencer A, Attal M et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. N Engl J Med. 2007;357:2123-2132.
11. Weber DM, Chen C, Niesvizky R et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. N Engl J Med. 2007;357:2133-2142.
12. Palumbo A, Bringhen S, Caravita T et al. Oral melphalan and prednisone chemotherapy plus thalidomide compared with melphalan and prednisone alone in elderly patients with multiple myeloma: randomised controlled trial. Lancet. 2006;367:825-831.
13. Palumbo A, Falco P, Corradini P et al. Melphalan, prednisone, and lenalidomide treatment for newly diagnosed myeloma: a report from the GIMEMA--Italian Multiple Myeloma Network. J Clin Oncol. 2007;25:4459-4465.
14. Richardson PG, Schlossman RL, Weller E et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood. 2002;100:3063-3067.
15. Mitsiades N, Mitsiades CS, Poulaki V et al. Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. Blood. 2002;99:4525-4530.
16. Chen N, Lau H, Kong L et al. Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. J Clin Pharmacol. 2007;47:1466-1475.
17. Richardson PG, Blood E, Mitsiades CS et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. Blood. 2006;108:3458-3464.
18. Durie BG, Harousseau JL, Miguel JS et al. International uniform response criteria for multiple myeloma. Leukemia. 2006;20:1467-1473.
19. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron. 1976;16(1):31-41.

20. Palumbo A, Rajkumar SV, Dimopoulos MA et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008;22:414-423.
21. Knight R, DeLap R, Zeldis J. Lenalidomide and venous thrombosis in multiple myeloma. New England Journ of Med, Vol 354, 2006: 2079.

APPENDIX A

Performance Status Criteria

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. 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).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work.
2	In bed <50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead.	0	Dead.

APPENDIX B

WCMC IRB SAE Reporting Forms

http://weill.cornell.edu/research/forms_and_policies/irb_forms/index.html

Appendix C

International Uniform Multiple Myeloma Response Criteria (IURC)

Stringent Complete Response (sCR) requires all of the following:

- ❑ All of the criteria of complete response
- ❑ Normal serum free light chain ratio
- ❑ Absence of monoclonal cells on bone marrow aspirate by immunohistochemistryor immunofluorescence

Complete Response (CR) requires all of the following:

- ❑ Absence of the original monoclonal protein in serum and urine by inmmunofixation. The presence of oligoclononal bands consistent with oligoclonal immune reconstitution does not exclude CR.
- ❑ ≤5% plasma in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is 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 plasmacytoma.

Very Good Partial Response (VGPR) requires all of the following:

- ❑ Negative serum and urine protein electrophoeresis with persistence of monoclonal protein detectable on immunofixationOR
- ❑ ≤90% reduction in serum monoclonal protein level with urine monoclonal protein level < 100mg in 24 hour collection.

Partial Response (PR) requires all of the following:

- ❑ ≥50% reduction in the level of the serum monoclonal paraprotein.
- ❑ Reduction in 24h urinary light chain excretion either by ≥90% or to <200mg.
- ❑ For patents with light chain only disease, then a 50% reduction in the difference between the involved and uninvolved free light chain level may be substituted for the M-protein measurement.
- ❑ For patients with non-secretory myeloma only, ≥50% reduction in plasma cells in a bone marrow aspirate and on trephine bone biopsy, if biopsy is performed.
- ❑ ≥50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).
- ❑ No increase if size or number of lytic bone lesion (development of a compression fracture does not exclude response)

Stable Disease (SD) requires the following:

- ❑ Not meeting the criteria stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR)

Plateau:

- ❑ Stable values (within 25% above or below value at the time response is addressed)

Patients in which no significant change (<50% decrease or <25% increase from baseline) in the production rate of the monoclonal serum protein or Bence-Jones protein excretion and no new lytic lesions and/or plasmacytomas are detected.

Relapse from CR requires at least one of the following:

- ❑ Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis, comfirmed by at least one further investigation and excluding oligoclonal immune reconstitution.
- ❑ ≥5% plasma in a bone marrow aspirate or trephine bone biopsy.
- ❑ Development of new lytic lesions of 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 >11.5mg/dl or 2.8 mmol/l) not attributable to any other cause.

Progressive disease (PD) 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 5g/L and confirmed by at least one repeated investigation.
- ❑ >25% increase in the 24h urinary light chain excretion, which must also be an absolute increase of at least 200mg/24h and confirmed by at least one repeated investigation.
- ❑ >25% increase in plasma cells in a bone marrow aspirate and on trephine bone biopsy, which must also be an absolute increase of at least 10%.
- ❑ Definite increase in the size of excisting 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 and may not indicate progression).
- ❑ Development of hypercalcemia (corrected serum calcium >11.5mg/dl or 2.8 mmol/l) not attributable to any other cause.

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

Risks Associated with Pregnancy

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

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

Criteria for females of childbearing potential (FCBP)

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

The investigator must ensure that:

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

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 intercourse during the following time periods related to this study: 1) for at least 28 days before starting lenalidomide; 2) throughout the entire duration of lenalidomide treatment; 3) during dose interruptions; and 4) for at least 28 days after lenalidomide discontinuation.

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

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

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

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

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 50 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 lenalidomide

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide. The patient may not receive lenalidomide until the Investigator has verified that the results of these pregnancy tests are negative.

Male Patients:

Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of

lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

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

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.

Additional precautions

- Patients should be instructed never to give lenalidomide to another person.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.

- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.

Appendix E: Functional Assessment of Cancer Therapy – Bone Marrow Transplant

FACT-BMT (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-BMT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-BMT (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C3	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT10	I can remember things	0	1	2	3	4
Be4	I am able to concentrate	0	1	2	3	4
BMT11	I have frequent colds/infections	0	1	2	3	4
BMT12	My eyesight is blurry	0	1	2	3	4
BMT13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT15	I am bothered by skin problems (e.g., rash, itching)	0	1	2	3	4
BMT16	I have trouble with my bowels	0	1	2	3	4
BMT17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT18	The cost of my treatment is a burden on me or my family	0	1	2	3	4