IRB PROTOCOL NUMBER	CUMC AAAJ2355
TITLE	A Randomized Clinical Trial of Lenalidomide (CC-5013) and Dexamethasone With and Without Autologous Peripheral Blood Stem Cell Transplant in Patients With Newly Diagnosed Multiple Myeloma
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PRINCIPAL INVESTIGATOR	Suzanne Lentzsch, M.D.
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ClinicalTrials.gov Registration	NCT01731886

PROTOCOL SIGNATURE PAGE

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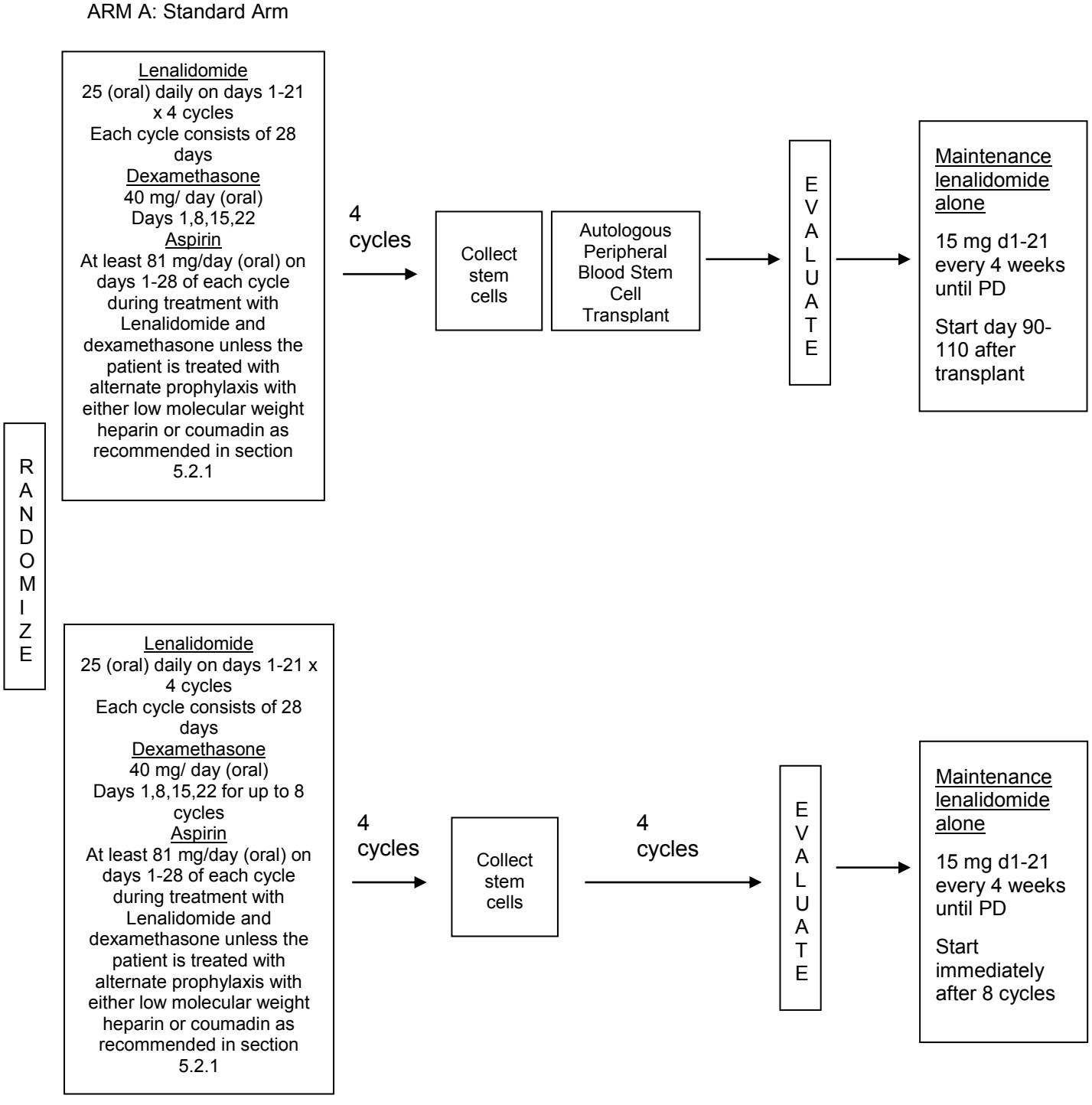
I have read this protocol and agree that it contains all necessary details for carrying out this study. I will conduct the study as outlined herein and will complete the study within the time designated, in accordance with all stipulations of the protocol and in accordance with Good Clinical Practices, local regulatory requirements, and the Declaration of Helsinki.

I will provide copies of the protocol and all pertinent information to all individuals responsible to me who assist in the conduct of this study. I will discuss this material with them to ensure that they are fully informed regarding the study agent(s) and the conduct of the study.

Printed Name of Investigator	Signature of Investigator	Date


ARM A: Standard Arm
Lenalidomide
25 (oral) daily on days 1-21 x 4 cycles
Each cycle consists of 28 days
Dexamethasone
40 mg/ day (oral)
Days 1,8,15,22
Aspirin
At least 81 mg/day (oral) on days 1-28 of each cycle during treatment with Lenalidomide and dexamethasone unless the patient is treated with alternate prophylaxis with either low molecular weight heparin or coumadin as recommended in section 5.2.1
4 cycles
Collect stem cells
Autologous Peripheral Blood Stem Cell Transplant
EVALUATE
Maintenance lenalidomide alone
15 mg d1-21 every 4 weeks until PD
Start day 90-110 after transplant
RANDOMIZE
Lenalidomide
25 (oral) daily on days 1-21 x 4 cycles
Each cycle consists of 28 days
Dexamethasone
40 mg/ day (oral)
Days 1,8,15,22 for up to 8 cycles
Aspirin
At least 81 mg/day (oral) on days 1-28 of each cycle during treatment with Lenalidomide and dexamethasone unless the patient is treated with alternate prophylaxis with either low molecular weight heparin or coumadin as recommended in section 5.2.1
4 cycles
Collect stem cells
4 cycles
EVALUATE
Maintenance lenalidomide alone
15 mg d1-21 every 4 weeks until PD
Start immediately after 8 cycles
ARM B: Treatment Arm

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1 BACKGROUND AND RATIONALE

1.1 Disease Under Study

Multiple myeloma is a malignant plasma cell proliferative disorder responsible for 11, 000 deaths each year in the United States.[1] Approximately one third of myeloma patients develop hypercalcemia and about two thirds present with anemia. As the second most common hematologic malignancy, myeloma remains incurable. In the last forty years, options for therapy have included melphalan-prednisone, anthracyclines, and vinca alkaloids; however, relapse with those regimens continues to be inevitable with a median survival of 3 years.

1.2 Role of Autotransplant with Non-Thalidomide Chemotherapy

In 1996, Attal et al. through the Intergroupe Francais du Myelome confirmed in a randomized trial that high dose chemotherapy combined with autologous bone marrow transplantation as opposed to conventional-dose chemotherapy improved the response rate, event-free survival, and overall survival in previously untreated myeloma patients less than 65 years old.[2] Complete response was seen in 22% of those receiving high dose therapy who, in addition, underwent autologous bone marrow transplantation. Median overall survival exceeded 5 years after high dose chemotherapy with autologous peripheral blood stem cell transplantation (PBSCT). However, there was no significant difference in overall survival (OS) whether autologous PBSCT was performed as first-line therapy or as rescue treatment after receiving monthly courses of vincristine, melphalan, cyclophosphamide, and prednisone.[3] These data suggest that transplant given for the first relapse or as primary therapy results in the same OS. The Medical Research Council Myeloma VII Trial found an increase in median survival of one year and in progression-free survival among subjects randomized to receive high dose therapy followed by autologous PBSCT as compared to those receiving conventional chemotherapy.[4] However, Blade et al via PETHEMA showed that subjects randomized to HDT followed by autologous PBSCT as opposed to conventional chemotherapy had no impact on progression free survival and overall survival but was associated with a significantly increased complete response of 30%.[5] Taken together as a result of several randomized trials, autologous stem cell transplant currently is recommended for newly diagnosed multiple myeloma patients.

1.3 Role of Maintenance

Over the last years, many studies provided evidence that continuation of Lenalidomide treatment beyond 8 cycles increases response rates and prolongs PFS. During the 2009 ASH Annual Meeting Palumbo et al reported significant increase of the PFS for subjects receiving Lenalidomide maintenance after melphalan, prednisone and lenalidomide (MPR-R) in comparison to subjects without maintenance (MPR).[6] In addition at the November 2009 CALGB group meeting, the CALGB Data and Safety Monitoring Board reviewed follow-up interim analysis of the CALGB 100104, "A Phase II Double Blind Study of Maintenance Therapy with CC-4047 (NSC #703813) or Placebo Following Autologous Stem Cell Transplantation for Multiple Myeloma." The results of the analysis indicated a statistically

significant improvement in the time to progression for subjects receiving lenalidomide compared to the placebo group. Based on these findings the study was un-blinded to subjects and their physicians. The CALGB recommended that subjects receiving lenalidomide maintenance therapy should continue until disease progression. Subjects who were receiving placebo maintenance were to stop placebo treatment and switch to lenalidomide maintenance therapy. It was further recommended to discuss the initiation of maintenance therapy beyond day 110 post transplant with the subject in cases where the subject was still in remission.

Based on these data, we think that an amendment of our current protocol which does not include maintenance is necessary in order to continue testing our hypothesis and at the same time providing the best available care.

1.4 Lenalidomide

CC-5013 (lenalidomide) is an immunomodulatory derivative of thalidomide that is potentially safer, with significantly more potent immunomodulatory effects, and has shown synergy in preclinical studies with dexamethasone.[7] In pre-clinical models, Lenalidomide is 50 to 2,000 times more potent compared to thalidomide in T-cell proliferation and 50 to 100 times more potent than thalidomide in increasing IL-2 and IFN-gamma production.[7] Lenalidomide showed high anti-myeloma activity in human xenograft mice models.[8] Based on these laboratory results, two phase I clinical trials with Lenalidomide were initiated in 2001.These studies showed that the maximum tolerated dose of Lenalidomide was 25mg daily. In a University of Arkansas study, 8 of 15 subjects with relapsed refractory myeloma (53%) responded to therapy.[9] In the Dana-Farber study, 17 of 24 subjects (71%) responded to therapy. Specifically, 7 of 24 subjects (29%) had at least a 50% reduction in paraprotein.[7] These results were impressive because subjects selected had failed to respond to at least two prior regimens of treatment. Specifically, 11 of the 24 subjects (46%) had failed prior thalidomide. Another trial compared two doses of Lenalidomide: 30mg once a day versus 15mg twice daily. Lenalidomide was administered for 3 weeks (days 1-21) followed by one-week rest. Of 101 subjects treated, at least a 25% reduction in paraprotein levels was observed in 39% of subjects, including complete responses in 5 subjects with advanced, refractory disease.[10] The mechanism of action of Lenalidomide is unclear, but preclinical studies show that it decreases binding of myeloma cells to stroma, and inhibits IL-6, VEGF, and TNF-alpha production. [7,11,12,13,14] It also appears to block angiogenesis, and stimulate natural killer cell mediated immune responses to myeloma cells.[14] In murine myeloma models, Lenalidomide inhibited tumor growth and angiogenesis, prolonging host survival.

Lenalidomide is administered orally. It is dispensed as 5, 10 or 25 mg hard gelatin capsules. The dosing used in ongoing trials is 25 mg given orally daily on days 1-21 and repeated every 28 days (days 22-28 are rest days). Doses are modified based on toxicity. Unlike thalidomide, Lenalidomide causes no significant sedation, constipation or neuropathy. In animal models it has shown no teratogenicity. The main side effects are Grade 3 to 4 thrombocytopenia (20%) and neutropenia (30%).[10] The activity appears to be further enhanced with the addition of dexamethasone. Dimopolous and colleagues presented preliminary data regarding 351 subjects with relapsed and refractory subjects treated with Lenalidomide and dexamethasone compared with dexamethasone as a single agent and

showed a complete response rate of 15.0% for the combination versus 3.4% for dexamethasone alone. Similarly, Weber et al showed a complete response rate of 12.9% in relapsed and refractory subjects receiving lenalidomide and dexamethasone as opposed to 0.6% complete response rate in those receiving dexamethasone alone. In the Dimopoulos study, the incidence of DVT was comparable to that of thalidomide.[15,16] In a phase 2 trial of 34 newly diagnosed myeloma subjects, Rajkumar and colleagues further demonstrated that lenalidomide plus dexamethasone achieved an overall objective response in 31 of 34 subjects (91%) with 2 subjects (6%) achieving complete response.[1]

During 2010 ASH Annual meeting, Palumbo et al reported an increase in secondary malignancies with lenalidomide maintenance therapy, when used in combination with melphalan. Currently the data are under further evaluation. [16]

1.5 Low Dose Dexamethasone

Dexamethasone in combination with thalidomide is known to produce several toxicities. When comparing thalidomide plus dexamethasone with dexamethasone alone, Rajkumar and colleagues demonstrated greater toxicity with the combination.[17] Dexamethasone in both arms was given at a dose of 40 mg orally on days 1 to 4, 9 to 12, and 17 to 20. Cycles were repeated every 4 weeks. The incidence rates of grade 3 or higher deep vein thrombosis, rash, bradycardia, peripheral neuropathy, and any grade 4 to 5 toxicities in the first four months were significant increased with thalidomide plus dexamethasone (45%) as opposed to dexamethasone alone (21%). The incidence of DVT was higher in the combination arm (17%) than in the single arm (3%). Grade 3 neutropenia was seen in 9% of subjects receiving combination and 6% of subjects receiving dexamethasone alone.

In an ongoing phase III randomized trial (ECOG4A03,) Rajkumar and colleagues are comparing low-dose dexamethasone (40 mg orally on days 1, 8, 15, and 22) and lenalidomide with high-dose dexamethasone (40 mg orally 4 days on, and 4 days off) and lenalidomide. Preliminary results as presented at ASCO 2007[18] demonstrated a statistically significant increased one-year survival probability with low-dose dexamethasone and lenalidomide (0.96; 95%CI 0.82,0.92) as compared to with high-dose dexamethasone and lenalidomide (0.87; 95%CI 0.94,0.99). In addition, the high-dose dexamethasone/lenalidomide combination was associated with a statistically significant increased incidence of neutropenia, DVT/PE, infections and pneumonia compared those seen with the low-dose dexamethasone/lenalidomide regimen.

1.6 Melphalan

Melphalan 200 mg/m^2 intravenously will be used as the conditioning regimen prior to autologous peripheral blood stem cell transplant. In a prospective and randomized trial, the Intergroupe Francophone du Myelome compared 200 mg/m^2 melphalan (HDM200) and 8 Gy total body irradiation plus 140 mg/m^2 melphalan (HDM140 + TBI) as a conditioning regimen in newly diagnosed myeloma subjects who had received 4 cycles of VAD.[19] HDM200 was significantly associated with lower rates of grade 3-4 mucositis, duration of neutropenia and thrombocytopenia, number of red blood cell and platelet transfusions, numbers of days on antibiotics, and duration of hospitalization. Event-free survival and survival after relapse rates were equivalent in both groups. Overall survival was increased at

45 months in those receiving HDM200 although this was of borderline significance (p=0.05). Thus, HDM200 is a less toxic but as effective conditioning regimen compared to HDM140 + TBI.

1.7 Vein Thrombosis and Anticoagulation

Lenalidomide has now been used in a number of phase I, II, and III trials. One of the most common side effects associated with lenalidomide is venous thromboembolism. Rajkumar and colleagues reported a 3% incidence in deep vein thrombosis/pulmonary embolism in subjects receiving lenalidomide/dexamethasone for newly diagnosed myeloma.[1] Ongoing analyses have implicated that erythropoietin as well as high dose dexamethasone might contribute to the development of TEE. Knight and colleagues in a multivariate analysis of two placebo-controlled studies demonstrated that there was an independent correlation between the presence of thrombosis and treatment with higher dose dexamethasone and thrombosis erythropoietin.[20] Rajkumar et al also reported thromboembolic events from their ongoing randomized ECOG trial comparing lenalidomide plus high-dose dexamethasone and lenalidomide plus low-dose dexamethasone.[21,22] Venous thromboembolic events were reported in 18% of subjects receiving lenalidomide/high-dose dexamethasone and 3.7% of subjects receiving lenalidomide/low-dose dexamethasone. The trial has since changed to include ASA 81-325 mg daily as prophylaxis unless the subject is already being treated with low molecular weight heparin or warfarin. Second, LMWH or warfarin is recommended for subjects randomized to the high-dose dexamethasone arm. Third, use of concomitant erythropoietin use is being limited in that study regardless of arm. For this reason, we recommend using ASA 325 mg daily as routine thromboprophylaxis. Subjects with risk factors such as strong family history or prior history of a thromboembolic event should receive prophylaxis with warfarin or low molecular weight heparin. (Please see Section 5.2.)

1.8 Study Rationale

Due to the fact that lenalidomide alone can achieve similar response rates as transplant, more and more subjects treated with lenalidomide refuse transplant after achieving CR. Currently it is unclear whether transplant will result in a longer duration of remission, even if transplant and lenalidomide alone achieve similar initial RR. Therefore, it is most important to define the role of <u>transplant in newly diagnosed patients</u>.

By analyzing complete response and furthermore survival achieved by lenalidomide, this randomized clinical trial is designed to determine if there is ultimately a need for autologous peripheral blood stem cell transplant in subjects receiving lenalidomide and low-dose dexamethasone with newly diagnosed myeloma. Using a lower dose of dexamethasone and using lenalidomide instead of thalidomide are two ways in which this trial builds on the potency and minimizes the toxicity of the currently used thalidomide/dexamethasone induction regimen.

As a primary goal, the trial will compare complete response rates and duration of complete response of subjects receiving at least 8 cycles of therapy with lenalidomide plus low-dose dexamethasone and followed by lenalidomide maintenance until disease progression (ARM B) versus subjects receiving 4 cycles of therapy with lenalidomide plus low-dose

dexamethasone followed by autologous peripheral blood stem cell transplant conditioned with 200 mg/m2 melphalan and followed by lenaliidomide maintenance until disease progression (ARM A). Cyclosphosphamide followed by granulocyte colony stimulating factor (G-CSF) with or without AMD3100 will be used to mobilize peripheral blood stem cells in both arms. This will optimize further reduction of malignant cells in the autograft with a concomitant anti-myeloma effect. By comparing the two CRRs and the durations of complete response, the study will determine whether the CR achieved by a non-transplant regimen such as lenalidomide and dexamethasone is equal to the CR achieved by autologous transplant. In ARM A, subjects will undergo autologous peripheral blood stem cell transplant if CR or PR is achieved after completing the 4 cycles of lenalidomide/dexamethasone therapy. Regarding ARM B, subjects will undergo stem cell collection as described above. Stem cell collection after cyclophosphamide mobilization will make both arms more comparable for effect of transplant or response.

As a second goal, the trial will determine if there is a benefit in progression-free survival in those subjects receiving autologous peripheral blood stem cell transplant after undergoing 4 cycles of lenalidomide/dexamethasone versus in those receiving 8 cycles of lenalidomide and dexamethasone without transplant followed by maintenance. Also, the trial will compare overall survival in subjects receiving autologous peripheral blood stem cell transplant after undergoing induction therapy with lenalidomide and dexamethasone versus in those receiving only lenalidomide and dexamethasone. The estimation of sample size for this trial is based on the 6% complete response rate with lenalidomide and dexamethasone in subjects with newly diagnosed myeloma[1] and the 30% complete response rate with autologous stem cell transplantation in subjects with multiple myeloma.[5].

2 OBJECTIVES

2.1 Primary Objective

▪ To determine and compare the complete response rates of 8 cycles lenalidomide and low-dose dexamethasone versus that 4 cycles lenalidomide and low-dose dexamethasone followed by autologous peripheral blood stem cell transplant in subjects with newly diagnosed multiple myeloma.

2.2 Secondary Objectives

▪ To compare the duration of complete response induced by lenalidomide and dexamethasone versus that of lenalidomide and dexamethasone followed by autologous peripheral blood stem cell transplant, followed by lenalidomide maintenance in both arms.
▪ To compare the overall response rate induced by lenalidomide and dexamethasone versus that induced by lenalidomide and dexamethasone followed by autologous peripheral blood stem cell transplant, followed by lenalidomide maintenance in both arms.
▪ To determine if there is a benefit in progression-free survival in subjects receiving autologous peripheral blood stem cell transplant after undergoing 4 cycles of lenalidomide and dexamethasone vs in those receiving 8 cycles of lenalidomide and dexamethasone, followed by lenalidomide maintenance in both arms.
▪ To compare overall survival and time to progression in subjects receiving autologous

peripheral blood stem cell transplant after undergoing induction therapy with lenalidomide and dexamethasone versus in those receiving only lenalidomide and dexamethasone, followed by lenalidomide maintenance in both arms.

▪ To analyze the time to transplant in both arms

▪ To compare the toxicity of lenalidomide and dexamethasone followed by autologous peripheral blood stem cell transplant versus lenalidomide and dexamethasone alone, followed by lenalidomide maintenance in both arms.

3 SUBJECT SELECTION

3.1 Inclusion Criteria

▪ Subjects must have histologically or cytologically confirmed Multiple Myeloma, Salmon-Durie Stage II or III or International Staging System II or III that has not been previously treated. (See Appendix E)

▪ Bone marrow plasmacytosis with > or = 10% plasma cells, or sheets of plasma cells or a biopsy-proven plasmacytoma which must be obtained up to 6 weeks prior to registration.

▪ Measurable levels of monoclonal protein (M protein): 1 g/dL IgG or .5 g/dL IgA on serum protein electrophoresis or > 200 mg of monoclonal light chain on a 24 hour urine protein electrophoresis which must be obtained within 4 weeks prior to registration. If both serum and urine monoclonal components are present, both must be followed in order to evaluate response.

Serum free light chains (FLC) should be measured with each SPEP and is recommended to monitor for subjects with light chain disease. Non-secretory MM subjects will be included if they have measurable parameters to follow, e.g. extramedullary plasmocytoma or measurable bone marrow infiltration, or FLC level ≥ 10 mg/dL (≥ 100 mg/L) provided serum FLC ratio is abnormal.[29]

Both SPEP and UPEP must be performed within 28 days prior to registration.

For subjects presenting with aggressive disease or requiring immediate intervention, up to two weeks or two pulses of high dose dexamethasone (40 mg x 4 days = 1 pulse) is allowed, prior to the start of study treatment. If dexamethasone is given at reduced dose, the total allowed dose is 320 mg prior to enrollment. Prior systemic glucocorticosteroid use for the treatment of non-malignant disorders is permitted; concurrent use after subject is on study treatment of non-malignant disorders is permitted; concurrent use for non-malignant disorders after a subject is on study treatment is permitted, but should be restricted to the equivalent of prednisone 10mg per day. Prior or concurrent topical or localized glucocorticosteroid therapy to treat non-malignant comorbid disorders is permitted.

Subjects should not have received any radiation for the preceding 4 weeks before entry onto the study. Exception: local radiation therapy for symptomatic bone lesions (eg, uncontrolled pain or high risk of pathologic fracture), superior or inferior vena cava syndrome, spinal cord compression or extramedullary soft tissue lesions, as clinically indicated to relieve severe symptoms. Subjects with prior solitary plasmacytoma treated with radiation therapy with curative intent are eligible if the disease has now progressed to active multiple myeloma meeting all the eligibility criteria for this protocol.

▪ Age ≥18 years.

▪ Life expectancy of greater than 12 months.

▪ ECOG performance status ≤2 (Karnofsky ≥60%) (See Appendix B).
▪ Subjects must have adequate organ and marrow function as defined below, obtained within 4 weeks prior to registration:

Hgb	≥ 9 g/dL (which may be supported by transfusion or growth factors)
Absolute Neutrophil Count	≥1,500/ ml (use of growth factors to meet screening requirements is not permitted)
Platelets	≥50,000/mm^3 (administration of platelet transfusions during screening to meet eligibility criteria is not allowed. However, platelet transfusions may be administered as clinically indicated to subjects in both treatment arms who have begun lenalidomide therapy)
Total Bilirubin	≤1.5 mg/dL
AST(SGOT) / ALT(SGPT)	≤2.5 X institutional upper limit of normal
Creatinine	<2.0 mg/dL (subjects with creatinine ≥ 2 should receive lenalidomide according to the dosing schedule (Appendix C).
Creatinine Clearance	≥50 ml/min (estimated). Subjects with creatinine clearance ≤ 50 ml/min should receive lenalidomide according to the dosing schedule (Appendix C).

▪ All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.
▪Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program.
Ability to understand and the willingness to sign a written informed consent document. Subject must be informed of the investigational nature of this study.
▪ Subjects with a history of prior malignancy are eligible provided there is no active malignancy and a low expectation of recurrence within 6 months.
▪ Subjects must be willing and able to take prophylaxis with either aspirin at 81 mg/day or alternative prophylaxis with either low molecular weight heparin or warfarin as recommended.
▪ Subjects who are eligible for transplant with an age up to and including 75 years.
▪ Subjects in ARM A who are refusing transplant can go onto ARM B and will be evaluated separately.
▪ All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of Revlimid REMS®.
▪ Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of prescribing lenalidomide (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Males 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)

3.2 Exclusion Criteria

▪ Subjects who have had chemotherapy or radiotherapy for multiple myeloma prior to entering the study. Subjects should not have received any radiation for the preceding 4 weeks before entry onto the study. Exception: local radiation therapy for symptomatic bone lesions (e.g., uncontrolled pain or high risk of pathologic fracture), superior or inferior vena cava syndrome, spinal cord compression or extramedullary soft tissue lesions, as clinically indicated to relieve severe symptoms. Subjects with prior solitary plasmacytoma treated with radiation therapy with curative intent are eligible if the disease has now progressed to active multiple myeloma meeting all the eligibility criteria for this protocol.
▪ Subjects receiving any other investigational agents or therapy within 28 days of baseline.
▪ Subjects with known brain metastases will be excluded from this clinical trial because of their poor prognosis and because they often develop progressive neurologic dysfunction that would confound the evaluation of neurologic and other adverse events.
▪ Subjects who are pregnant or breast feeding. Due to the potential teratogenic properties of lenalidomide, the use of this drug in subjects that are pregnant is absolutely contraindicated. Further, all women of childbearing potential and sexually active males must agree to avoid conception while participating in this study. Specifically, women of childbearing potential must either agree to refrain from sexual intercourse or employ a dual method of contraception, one of which is highly effective (IUD, birth control pills, tubal ligation or partners vasectomy), and another additional method (condom, diaphragm, or cervical cap) for 4 weeks prior to receiving lenalidomide, and for four weeks after discontinuing this therapy. Sexually active males cannot participate unless they agree to use a condom (even if they have undergone a prior vasectomy) while having intercourse with a woman of child bearing potential while taking lenalidomide and for four weeks after stopping treatment. Women of child bearing potential (those who have not had a hysterectomy or the absence of menstrual periods for at least 24 consecutive months) must have a negative pregnancy test 10-14 days prior to the initiation of therapy and a repeat negative pregnancy test 24 hours prior to the initiation of lenalidomide.
▪ Inability to comply with study and/or follow-up procedures.
▪ Subjects with a history of previous deep vein thrombosis or pulmonary embolism must be on anticoagulation therapy with low molecular weight heparin or warfarin at therapeutic dosages (e.g. INR 2-3).
▪ If a subject is on full-dose anticoagulants, the following criteria should be met for enrollment:
Must not have active bleeding or pathological conditions that carry high risk of bleeding (e.g. tumor involving major vessels, known varices).
Must not have thrombocytopenia requiring transfusion.
Must have a platelet count >50,000.
Must have stable INR between 2-3.
▪ Subjects with smoldering myeloma or monoclonal gammopathy of undetermined significance are not eligible.
▪ Subjects must not have active, uncontrolled infection.

▪ Subjects must not have active, uncontrolled seizure disorder. Subjects must have had no seizures in the last 6 months.
▪ Concurrent use of other anti-cancer agents or treatments.
▪ Known positive for HIV or infectious hepatitis, type B or C.
▪ Known hypersensitivity to thalidomide.
▪ Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

3.3 Inclusion of Women

Both men and women and members of all races and ethnic groups are eligible for this study.

Breastfeeding women are excluded as this regimen may be harmful to a developing fetus or nursing child. Pregnant women are excluded from this study because lenalidomide is related to an agent, thalidomide, with teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with lenalidomide or, breastfeeding should be discontinued if the mother is treated with lenalidomide. These potential risks may also apply to other agents used in this study. Women of child bearing potential (those who have not had a hysterectomy or the absence of menstrual periods for at least 24 consecutive months) must have a negative pregnancy test 10-14 days prior to the initiation of therapy and a repeat negative pregnancy test 24 hours prior to the initiation of lenalidomide. During therapy with lenalidomide, pregnancy tests will be obtained weekly for the first four weeks, and then every 4 weeks if the subject has regular menstruation, or every 2 weeks if their periods are irregular.

4 SUBJECT REGISTRATION

4.1 Registration Guidelines

Eligible subjects will be block randomized to ARM A or ARM B by the CUMC Research Pharmacy. Treatment cannot begin prior to registration. However, if good medical practice dictates the subject needs to receive some form of therapy prior to registration, up to two weeks or two pulses of dexamethasone (without Melphalan or bortezomib) may be given.

4.2 Assignment of Study Numbers

Each subject enrolled in the study will be registered in Velos eResearch at the Herbert Irving Comprehensive Cancer Center (HICCC) at study entry. Velos eResearch is a web based comprehensive clinical research information system to manage clinical trials. eResearch employs standardized data elements that define protocols, subject characteristics, visits and procedures. Velos eResearch is available for use by researchers at outside institutions, if those institutions are enrolling subjects on a trial for which Columbia University Medical Center (CUMC) is the coordinating site. If the outside institutions are unable to access Velos eResearch remotely, the outside institutions should submit their information, source documents and Case Report Forms to the CUMC researchers via telephone and shipment. The CUMC researchers will enter the subject information on behalf of the outside institutions. Each subject enrolled will be assigned a sequential study identifier by Velos

eResearch.

4.3 RevLimid REMS® Designed for Clinical Studies Program
Lenalidomide (Revlimid®) is approved for marketing under a special restricted Distribution program called Revlimid REMS®. Subjects enrolled in this study will also be enrolled in the Revlimid REMS® Designed for Clinical Studies Program.

5 TREATMENT PLAN

Treatment will be administered on an outsubject basis. Each treatment cycle will be 28 days. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

Subjects are randomized to ARM A or ARM B as follows:

ARM A
Lenalidomide Administered orally at a dose 25 mg daily on days 1-21 of each cycle.
Dexamethasone Administered orally at a dose of 40 mg daily on days 1, 8, 15, 22 of each cycle.
Stem Cell Mobilization Subjects may receive up to the maximum recommended high-dose of cyclophosphamide at 4 gm/m^2 intravenously with mesna at a total of 2.4 gm/m^2 intravenously or orally divided over 3 doses. Subjects then will receive mobilization using daily filgrastim (G-CSF) at 10 mcg/kg subcutaneously starting 24 hours after cyclophosphamide is completed and until stem cell collection. The use of AMD3100 (Plerixafor) is permitted. Peripheral stem cell collection will be performed at marrow recovery, usually when WBC is >2500 x 10^9 cells/liter; platelet count is >20 x 10^3/mm^3.
Autologous peripheral blood stem cell transplant Subjects deemed suitable by the principal investigator will receive melphalan 200 mg/m^2 intravenously on days -2 and -1 or only on day -2, and will undergo autologous peripheral blood stem cell transplantation on day 0. Subjects will receive G-CSF subcutaneously daily beginning on day 5 and until blood counts recover.

Maintenance will be started on day 90-110 after transplant. Subjects will receive lenalidomide 15 mg/day on day 1-21 every 28 days until disease progression. Dose can be reduced to 10 mg per treating physician discretion in case subject doses not tolerate 15 mg/day. If subject does not tolerate 10 mg/day lenalidomide, discontinue maintenance. Maintenance with 5 mg/day is not recommended except due to impaired renal function. Subjects may receive up to total 2 years maintenance therapy.

ARM B
Lenalidomide Administered orally at a dose 25 mg daily on days 1-21 of each cycle for 8 cycles. After cycle four, subjects will have peripheral stem cell collection. The final four cycles of lenalidomide and dexamethasone will be started within 4 weeks after stem cell collection.

Dexamethasone Administered orally at a dose of 40 mg daily on days 1, 8, 15, 22 of each cycle.
Stem Cell Mobilization Subjects may receive up to the maximum recommended high-dose of cyclophosphamide at 4 gm/m^2 intravenously with mesna at a total of 2.4 gm/m^2 intravenously or orally divided over 3 doses. Subjects then will receive mobilization using daily filgrastim (G-CSF) at 10 mcg/kg subcutaneously starting 24 hours after cyclophosphamide is completed and until stem cell collection. The use of AMD3100 (Plerixafor) is permitted. Peripheral stem cell collection will be performed at marrow recovery, usually when WBC is >2500 x 10^9 cells/liter; platelet count is >20 x 10^3/mm^3

After 8 cycles with lenalidomide/ dexamethasone, maintenance will be started 15 mg/day on days 1-21 every 28 days until disease progression. Dose can be reduced to 10 mg per treating physician discretion in case subject doses not tolerate 15 mg/day. If subject does not tolerate 10 mg/day lenalidomide, discontinue maintenance. Maintenance with 5 mg/day is not recommended except due to impaired renal function. Subjects may receive up to total 2 years maintenance therapy.

For subjects on maintenance therapy of lenalidomide at a dose 10mg/day at the time protocol v11-30-10 is approved, lenalidomide dose will be increased to 15 mg/day on next cycle.

In ARM A, lenalidomide/dexamethasone therapy will be given through 4 cycles followed by melphalan-based autologous peripheral blood stem cell transplant. In ARM B, lenalidomide/dexamethasone therapy will be given through 8 cycles. If complete response (CR) or partial response (PR) is achieved after 8 cycles, subjects will continue with lenalidomide alone (maintenance) until disease progression or severe toxicity occurs despite dose reduction.

Subjects who progress in either arm may be offered to end protocol treatment and proceed to alternate therapy. Subjects who progress in ARM B will be off treatment and have the option ultimately to undergo autologous peripheral blood stem cell transplant. Subjects refusing transplantation in ARM A have the option to go onto ARM B and will be evaluated separately.

Subjects will come off treatment for unacceptable toxicity, withdrawal of consent, non-compliance, and completion of protocol therapy.

Subjects who progress in either arm will end protocol treatment and proceed to alternate therapy.

The start of the next cycle can be delayed by 2 weeks at the discretion of the treating physician.

5.1 Study Agents

Lenalidomide (CC-5013) will be administered orally at a dose of 25 mg PO daily on days 1-21 of cycle. Administration will be during cycles 1-4 in Arm A and cycle 1-8 in Arm B. Maintenance will be lenalidomide 15 mg/day for a maximum of 2 years or until disease progression.

Supply

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

Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.

Packaging

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

Storage

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

Route and Method of Administration

Oral. Clinical studies have shown that Lenalidomide administration coincident with food intake appears to delay absorption to some degree, although the extent of absorption is not altered. Therefore, Lenalidomide can be taken with or without food.

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.

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

Dexamethasone will be administered 40 mg PO on days 1, 8, 15, 22.

Supply

Decadron, Hexadrol, Dexameth, Dexone, DXM, others

Commercially available in 0.25, 0.5, 0.75, 1, 1.5 , 2, 4, and 6 mg tablets
Route of Administration
Oral. 40 mg PO will be administered on days 1, 8, 15, 22.

5.2 General Concomitant Medication and Supportive Care Guidelines

Thrombosis

All patients will receive enteric coated aspirin, at least 81 mg, QD while on study (thrombosis prophylaxis, see Section 5.4.1 below). Aspirin can be held per treating physician's discretion if clinically indicated, such as for procedures. If patient is unable to tolerate aspirin, patient should receive other types of anti-coagulation such as warfarin or low molecular weight heparin. There is an increased risk of deep vein thrombosis (DVT) with thalidomide/dexamethasone therapy for myeloma, which is higher than the baseline risk of DVT in newly diagnosed myeloma (approximately 3% with dexamethasone alone and 4-10% with VAD). Data on prophylaxis is limited, but it appears that fixed dose (1 mg warfarin) may not be effective. Low molecular weight heparin at prophylactic doses (enoxaparin 40 mg once a day subcutaneously or equivalent) appears effective in decreasing the risk of DVT associated with Thal/Dex therapy. Given the potential risk of DVT in myeloma in general, the increased risk seen previously with Thal/Dex, and recently reported increased risk with lenalidomide, enteric coated aspirin 81-325 mg once daily is recommended for all patients. Enoxaparin 40 mg subcutaneously once daily and full dose warfarin with a therapeutic INR 2-3 are acceptable alternatives and should be given to patients with a higher risk of venous thromboembolism. Patients with high risk are shown in the below table.

Risk Factors for VTE During Lenalidomide Plus Dexamethasone Treatment[23]	
Central Venous Line	Ongoing infection/inflammation
Concomitant Chemotherapy	Older age
Doxorubicin use	Previous VTE
Erythropoietin use	Pre-existing coagulation disorders
High-dose dexamethasone use	Thrombophilia
High tumor mass	
Immobilization	

For information on the risk of venous thromboembolism with combined oral contraception see Appendix D: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

Gastrointestinal

All patients will receive prophylaxis with either an H-2 blocker or proton pump inhibitor (PPI) while on Dexamethasone. Suggested medications included ranitidine 150 mg PO BID or omeprazole 20 mg PO daily or equivalent. Antiemetic therapy may be necessary if vomiting occurs. Diarrhea and constipation are frequent toxicities with lenalidomide. Diarrhea may be treated with loperamide (Imodium). Constipation may be treated with

lactulose or any other laxatives according to the choice of the physician.

Fever and Infection

Routine prophylaxis with one double-strength tablet of trimethoprim/sulfamethoxazole orally three times per week is recommended for all patients on lenalidomide/dexamethasone. If trimethoprim/sulfamethoxazole is not tolerated, then dapsone 100 mg orally daily, atovaquone 1500 mg orally daily with food, pentamidine 4 mg/kg IV monthly, or nebulized pentamidine 300 mg inhaled monthly are acceptable alternatives. In case of a history of zoster or fungal infection, prophylaxis with acyclovir 200 mg orally tid or fluconazole 100 mg orally daily should also be considered. For autologous peripheral stem cell transplant, ciprofloxacin 500 mg orally bid, acyclovir 400 mg orally tid, and fluconazole 200 mg orally daily are recommended for prophylaxis starting no later than day -2 of transplant.

Myelosuppression

Growth factors, specifically filgrastim (granulocyte-colony stimulating factor; G-CSF) or pegfilgrastim only, can be used to treat neutropenia that occurs as a result of lenalidomide therapy and also starting day +5 from autologous peripheral stem cell transplant. The usual dose of filgrastim is 5 micrograms/kg/day given for neutropenia and 10 μg/kg for stem cell mobilization subcutaneously until the ANC is greater than 1,000 x 2 subsequent readings. G-CSF can be rounded to the nearest vial size. The usual dose of pegfilgrastim is a single dose of 6 mg administered subcutaneously. No additional doses of pegfilgrastim are permitted in the next 28-day period. The major adverse event with filgrastim and pegfilgrastim is bone pain. Other side effects are rare and include nausea, fatigue, diarrhea, vomiting, constipation, fever, anorexia, headache, taste perversion, dyspepsia, myalgia, insomnia, abdominal pain, arthralgia, generalized weakness, peripheral edema, and dizziness. Reversible elevations in LDH, alkaline phosphatase, and uric acid, not requiring therapy have also been observed.

Bone Disease

All patients with bone involvement should receive pamidronate (90 mg intravenously over 2-4 hours) or zoledronate (4 mg intravenously over 15 minutes) every 4 weeks as part of standard supportive care for myeloma, unless in the discretion of the treating physician such therapy produces toxicity or is felt to be medically unsafe. Dose modification may be necessary if hypocalcemia or renal insufficiency. Patients receiving bisphosphonates may receive an oral calcium supplement of 500 mg and a multiple vitamin containing 400 IU of vitamin D daily. Serum creatinine should be monitored prior to bisphosphonate infusion since the drugs can cause nephrotoxicity.

Local radiation therapy for symptomatic bone or extramedullary lesions (eg, uncontrolled pain, high risk of pathologic fracture), superior or inferior vena cava syndrome, spinal cord compression is permitted.

Hyperglycemia

Hyperglycemia, sometimes severe, including diabetic coma or ketoacidosis can occur with dexamethasone therapy. Therefore blood sugars should be monitored in diabetic patients, borderline patients, and in patients at risk for hyperglycemia or diabetes.

Anemia
Patients with chronic anemia that is transfusion dependent should be considered for erythropoietin replacement. Patients with hemoglobin <8 mg/dl and/or symptomatic should receive transfusion. The risk of DVT may be significant increased when erythropoietin is administered concurrent with lenalidomide therapy. Thus, we recommend that the use of erythropoietin be minimized as much as possible.

Thrombocytopenia
Administration of platelet transfusions during screening to meet eligibility criteria is not allowed. However, platelet transfusions may be administered as clinically indicated to subjects in both treatment arms who have begun lenalidomide therapy.

Secondary malignancies
Recent data show increase in secondary malignancies with lenalidomide maintenance therapy. The data are under evaluation. [16-2] We will closely follow up for secondary malignancies during the patients' lifetime.

Pregnancies

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

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

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the

male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

5.3 Dosing Delays and Dose Modifications

LENALIDOMIDE
Dosage of lenalidomide must be adjusted according to renal function throughout protocol treatment. Patients with creatinine clearance ≤50mL/min (estimated) should receive lenalidomide according to the dosing schedule in Appendix C.

The start of the next cycle may be delayed by 2 weeks at the discretion of the treating physician.

All other treatment modifications are based on adverse events, which are possibly, probably, or definitely related to drug. Al adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE, v.4.0).

Lenalidomide Treatment Adjustments
If Grade 3 or 4 neutropenia is the only adverse event present for which treatment adjustment is necessary, then the first dose reduction step is Dose Level -1. For all other adverse events requiring treatment adjustment, the first treatment adjustment step is Dose Level -2.

For subjects experiencing a ≥ grade 3 adverse events (AE), lenalidomide will be held until resolution of the AE as described in the below table: Lenalidomide Dose Modifications based on Adverse Events. For all labs related to AE ≥ grade 3, recheck must occur in ≤ 7 days. For Grade 3 or 4 AEs which occur prior to Day 15 of a cycle and resolve to ≤ grade 1 in severity prior to Day 15 of the cycle, administration of lenalidomide during the current cycle is to be continued until Day 21 with a one-level dose reduction according to the table below (Lenalidomide Treatment Adjustment Steps). The next cycle will then continue with this reduced dose level. For grade 3 or 4 AEs which occur on or after Day 15 of a cycle, the subject's study drug is to be held for the remainder of the cycle and will be reduced by one dose level beginning with the next cycle. Once a subject's dose has been reduced, no dose-re-escalation is permitted. Exception: Patients with renal impairment (Appendix C).

If a dose reduction of lenalidomide is indicated both as a result of decreased renal function and ≥ grade 3 AE, please consult with the principal investigator.

When lenalidomide needs to be held at time of re-treatment for adverse events, dexamethasone should also be held unless the subject requires continued dexamethasone treatment per investigator's discretion. As noted in the table, lenalidomide can be introduced after resolution of certain toxicities, midway through the cycle, provided the toxicity revolves prior to day 15. If both need to be held at the time of re-treatment for adverse events, then the date when treatment is resumed with either drug is considered day 1 of the new treatment cycle. Patients requiring a treatment delay of both agents beyond 6 weeks will end protocol treatment.

During maintenance phase, in case of toxicity, hold dose of lenalidomide for any grade 3 AE possible related to lenalidomide. Restart lenalidomide when AE resolves to grade 1 or baseline.

If the grade 3 event occurred at 15mg, reduce dose to 10mg. If the grade 3 event occurred at 10mg, restart dose at 10mg. However, a recurrence in any subsequent cycle of the same grade 3 event requires the patient be taken off maintenance permanently. Dose reduction is not necessary in the event of grade 3 hypokalemia that is adequately treated and has resolved. If the next cycle is delayed by more than 28 days due to grade 3 AE, the subject should be taken off maintenance.

LENALIDOMIDE TREATMENT ADJUSTMENT STEPS

Starting Dose	25 mg D 1-21 every 28 days
Dose Level -1*	Maintain lenalidomide dose and add growth factor (see also Section 5.2)
Dose Level -2	15 mg daily for 21 days every 28 days
Dose Level -3	10 mg daily for 21 days every 28 days
Dose Level -4	5 mg daily for 21 days every 28 days

LENALIDOMIDE DOSE MODIFICATION BASED ON ADVERSE EVENTS

CTCAE Category	At re-treatment and Day 2-14 of cycle	≥ Day 15 of cycle
Sustained (> 7 days) Grade 3 neutropenia or ≥ Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia (see section 5.3.2 if neutropenia is the only adverse event) Thrombocytopenia ≥ Grade 3 (Plt < 50,000/mm3)	Hold lenalidomide and follow CBC weekly. If the toxicity resolves to baseline or ≤ grade 1 prior to Day 14, restart at next lower dose level and continue the cycle until Day 21.	Omit lenalidomide for remainder of cycle.
Non-blistering rash Grade 2	Add Benadryl or comparable orally administered medication per treating physician's discretion and maintain treatment.	Add Benadryl or comparable orally administered medication per treating physician's discretion and maintain treatment.
Non-blistering rash Grade 3	Hold lenalidomide, start Benadryl or comparable orally administered per treating physician's	Omit lenalidomide for remainder of cycle and start Benadryl or comparable orally

	discretion and follow. If the toxicity resolves to ≤ grade 1 prior to Day 14, restart at next lower dose level and continue the cycle until Day 21.	administered per treating physician's discretion.
Non-blistering rash Grade 4	Discontinue lenalidomide and do not resume.	Discontinue lenalidomide and do not resume.
Desquamating (blistering) rash and Grade, or Erythema multiforme ≥ Grade 3	Discontinue lenalidomide.	Discontinue lenalidomide and do not resume.
Sinus bradycardia/other cardiac arrhythmia Grade 2	Hold lenalidomide and follow. If the toxicity resolves to ≤ grade 1 prior to Day 14, restart at next lower dose level and continue the cycle until Day 21.	Omit lenalidomide for remainder of cycle.
Sinus bradycardia/other cardiac arrhythmia Grade 3-4	Discontinue lenalidomide.	Discontinue lenalidomide and do not resume.
Allergic Reaction or Hypersensitivity Grade 2-3	Hold lenalidomide and follow. If the toxicity resolves to ≤ grade 1 prior to Day 14, restart at next lower dose level and continue the cycle until Day 21.	Omit lenalidomide for remainder of cycle.
Allergic Reaction or Hypersensitivity Grade 4	Discontinue lenalidomide.	Discontinue lenalidomide and do not resume.
Venous Thrombosis/embolism ≥ Grade 3	Hold dose of lenalidomide and start anticoagulation, restart at investigators discretion after adequate anticoagulation (maintain dose level).	Omit lenalidomide for remainder of cycle and start anticoagulation. Restart at investigato s discretion after adequate anticoagulation (maintain dose level).
Hepatic or other non-hematologic toxicity assessed as lenalidomide related ≥ Grade 3	Hold lenalidomide and follow. If the toxicity resolves to ≤ grade 1 prior to Day 14, restart at next ower dose level and continue the cycle until Day 21.	Omit lenalidomide for remainder of cycle.

Hyperthyroidism or Hypothyroidism	Continue lenalidomide and initiate appropriate therapy per treating physician's discretion.	Continue lenalidomide and initiate appropriate therapy per treating physician's discretion.

DEXAMETHASONE
Dexamethasone Dose Modification based on Interval Toxicity. It is expected given the low dose of dexamethasone that few dose modifications related to dexamethasone will be necessary.

CTCAE Category	Adverse Event	Dexamethasone Treatment Adjustment
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis	All patients will be treated with H2 Blockers, ranitidine, or omeprazole as per Section 5.2.2.
	Grade 1-2	If symptoms persist despite above measures, decrease dexamethasone dose by 50% permanently
	≥ Grade 3 (requiring hospitalization or surgery)	Hold dexamethaso e until symptoms are adequately controlled. Restart at 50% of current dose. If symptoms persist, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema ≥ Grade 3	Diuretics as needed, and decrease dexamethasone dose by 25%, if edema persists despite above measures, decrease dose to 50% of initial dose; discontinue dexamethasone and do not resume if symptoms persist despite 50% reduction.
Psychiatric	Depression, anxiety, agitation or confusion ≥ Grade 2 (limiting instrumental ADL or self-care ADL)	Hold dexamethasone until symptoms resolve, restart at 50% of current dose. If symptoms persist despite above measures, discontinue dexamethasone and do not

		resume.
Musculoskel tal	Muscle Weakness ≥ Grade 2 (symptomatic and interfering with function and/or ADLs)	Decrease dexamethasone dose by 25%, if weakness persists despite above measures, decrease dose to 50% of initial dose; discontinue dexamethasone and do not resume if sym toms persist despite 50% reduction.
Metabolic	Hyperglycemia ≥ Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by 25% decrements until levels are satisfactory.

All other treatment modifications are based on adverse events, which are possibly, probably, or definitely related to drug. All adverse events should be graded according to the Common Terminology Criteria for Adverse Events (CTCAE, v. 4.0).

5.4 Duration of Treatment

In arm A, therapy will be given through 4 cycles followed by melphalan-based autologous peripheral blood stem cell transplant if CR or PR is achieved after the 4 cycles. In arm A, lenalidomide maintenance will begin between day 90 and 110 following PSCT for a maximum of 24 months or until disease progression. Therapy will be given in arm B, per schema to include 8 cycles lenalidomide and dexamethasone followed by maintenance lenalidomide for a maximum of 24 months or until disease progression. Patients who progress in either arm may be offered to end protocol treatment and proceed to alternate therapy. Patients who progress in arm B will be off treatment and have the option ultimately to undergo autologous peripheral blood stem cell transplant. Patients will come off treatment for unacceptable toxicity, withdrawal of consent, non-compliance, and completion of protocol therapy.

5.5 Duration of Follow Up

Patients will be followed for response until disease progression and death. Duration of follow up will vary according to the overall survival of the patient or, at the most, 5 years from randomization. All patients must also be followed through completion of all protocol therapy. For patients randomized to Arm A, it is recommended that a bone marrow biopsy/aspiration be performed between day 80-100 following autologous PBSCT. Patients removed from study for unacceptable adverse events will be monitored until resolution or stabilization of the adverse event. At treatment discontinuation, subjects will undergo a safety assessment approximately 30 days post the last dose of protocol therapy. Safety assessments can occur by phone contact or office visit per treating physician's discretion.

6 STUDY CALENDAR

The pre-study bone marrow aspirate/biopsy and bone survey may be done up to 6 weeks before registration. Pre-study CBC (with differential and platelet count) and all required pre-study chemistries will be done < 4 weeks prior to registration. If any required lab values are abnormal, they should be repeated < 48 hours prior to registration. Assessments can be performed on day 22 through day 1 of the planned cycle. Cycle four bone marrow biopsy should be performed days 14-21 of cycle four for subject participating in correlative studies. Cycles will be counted consecutively through maintenance phase. Stem Cell Harvest and Stem Cell transplant will not be counted as a cycle.

Study Parameters: Arm A (All assessments can be done +/- 2 days except cycle 4)	Baseline	Cycle 1-3 (day 22 to day1 of next cycle)[9]	Cycle 4 [9]	Stem cell harvest and transplant	Post SCT (day 80 to 100)	Maintenance phase (day 22 to day1 of next cycle)[9] (start at day 90-110)[16]	Discontinuation of therapy[8]
History & Physical Examination	X	X	X		X	X	X
Vital Signs, Adverse Events assessment	X	X	X		X	X	X
Response Assessment	X	X	X		X	X	X
Performance Status	X	X	X		X	X	X
CBC (with diff and platelets)[1]	X	X	X		X	X	X
Calcium, Electrolytes, serum creatinine, BUN	X	X	X		X	X	X
TSH	X	X	X		X	X	X
Glucose	X	X	X		X	X	X
Total Bilirubin, LDH	X	X	X		X	X	X
AST/ALT	X	X	X		X	X	X
Alkaline Phosphatase	X	X	X		X	X	X
Albumin	X	X	X		X	X	X
SPEP including M-spike, FLC	X	X	X		X	X	X
UPEP	X	X	X		X	X	X
24 hour urine collection for total protein, quantitative light chains	X	X	X		X		X
Immunofixation of serum and urine	X[6]	X[6]	X[6]		X[6]		X[6]
Bone Marrow Aspirate/Biopsy	X[7]		X[7]		X[7]		X[7,8]
Beta 2 Microglobulin,	X	X	X		X	X	X
Ig A, G, M	X	X	X		X	X	X

Cytogenetics (bone marrow)	X		X				
Skeletal Survey[3]	X		X				
Pregnancy test[4,]	X[4]	X[4,]	X[4]		X[4,]	X[4]	X[4]
Stem Cell Harvest[14]				X			
Stem Cell Transplant[15]				X			
Register patient into Revlimid REMS® program	X						
Prescribe lenalidomide		X[11] if applicable	X[11]		X[11]	X[11]	

Study Parameters: Arm B (All assessments can be done +/- 2 days except cycle 4 and 5)	Baseline	Cycle 1-3 (day 22 to day1 of next cycle)[9]	Cycle 4[9]	Stem cell harvest	Post Stem Cell Harvest visit (Within 7 days of C5D1)	Cycle 5-8	Maintenance phase[16] (start at day 90-110) (day 22 to day1 of next cycle)[9]	Discontinuation of therapy[8]
History & Physical Examination	X	X	X		x	X	X	X
VS, AE assessment	X	X	X		x	X	X	X
Response Assessment	X	X	X			X	X	X
Performance Status	X	X	X		x	X	X	X
CBC (with diff and platelets)[1]	X	X	X		x	X	X	X
Calcium, Electrolytes, serum creatinine, BUN	X	X	X		x	X	X	X
TSH	X	X	X			X	X	X
Glucose	X	X	X		x	X	X	X
Total Bilirubin, LDH	X	X	X		x	X	X	X
AST/ALT	X	X	X		x	X	X	X
Alkaline Phosphatase	X	X	X		x	X	X	X
Albumin	X	X	X		x	X	X	X
SPEP including M-spike, FLC	X	X	X		x	X	X	X
UPEP	X	X	X		X	X	X	X
24 hour urine collection for total protein, quantitative light chains	X	X	X		X	X		X
Immunofixation of serum and urine	X[6]	X[6]	X[6]		X[6]	X[6]		X[6]

Bone Marrow Aspirate/Biopsy	X[7]		X[7]			X[7]		X[7,8]
Beta 2 Microglobulin,	X	X	X		X	X	X	X
Ig A, G, M	X	X	X		X	X	X	X
Cytogenetics (bone marrow)	X		X					
Skeletal Survey[3]	X		X					
Pregnancy test[4,]	X[4]	X[4,]	X[4]		x	X[4,]	X[4]	X[4]
Stem Cell Harvest[14]				X				
Register patient into Revlimid REMS® program	X							
Prescribe lenalidomide		X[11] if applicable	X[11]		x	X[11]	X[11]	

[1] CBC (with differential and platelet count) should be performed <48 hours prior to the chemotherapy treatment cycle and must be performed within 7 days of start of chemotherapy treatment cycle. CBC can be ordered more than once per cycle per physician discretion and this data should be entered into the eCRFs.
[3] Skeletal survey should be repeated as physician's discretion to determine the response or if clinically indicated.
[4] 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: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
[6] Required only to document complete response; if complete response, repeat to confirm response at ≥ 4 weeks.
[7] To be performed in all the patients of both arms during cycle number 4 and before starting maintenance to assess for remission. In the case of a subject from Arm A for this protocol, a biopsy should be performed on Day 80-100 following autologous PBSCT. All subjects will have bone marrow biopsy at end of lenalidomide therapy. At PI's discretion an additional bone marrow aspiration may be done to confirm complete response, progressive disease or relapse.
[8] After discontinuation of therapy, subjects should be followed every 3 months for the first two years, every 6 months for years 2-5, and annually thereafter. Follow up will be for time to next treatment and then for survival for subjects who received maintenance. For subjects not receiving maintenance, follow up will include standard of care labs until progression, then time to next treatment, then survival.
[9] Each cycle consists of 28 days. In cycle 4, physical exam can be done 2 weeks after finishing cycle 4 and with transplant physical exam. All labs can be done the same time with BM biopsy between days 15 and 28 of cycle 4. Per transplant physician discretion, the cycle 4 studies can also occur within 2 weeks after completion of cycle 4 if needed to correctly assess response.
[11] Lenalidomide must be prescribed through and in compliance with the Revlimid REMS® program of Celgene Corporation. Prescriptions must be filled within 7 days. Consideration should be given to prescribing lenalidomide 5 to 7 days in advance of Day 1 of each cycle to allow time for required patient and prescriber surveys, and drug shipment to patient. Any unused Revlimid® (lenalidomide) should be returned to the patient for disposition in accordance with the Revlimid REMS® program
[14]Stem cell harvest can be done up to 6 weeks after finishing cycle 4.
[15] Stem cell transplant can be done up to 8 weeks after finishing cycle 4.
[16] Maintenance phase is for a maximum of 24 months.

7 MEASUREMENT OF EFFECT

7.1 Definitions

Definitions of response are based on those of the International Response Criteria as published in Leukemia in 2006.[24]

M-protein

Synonyms include M-spike, monoclonal protein and myeloma protein, monoclonal paraprotein, M-component.

Response terms

The following response terms will be used: stringent complete response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), stable disease (SD), plateau, and progression or relapse (PD). See section 7.3 for Response Criteria.

Measurable disease

Patients who have one of the following three measurements: serum M-protein >1 g/dL, urine M-protein >200 mg/24hr, serum FLC assay with involved FLC level > 10mg/dL (>100 mg/l provided serum FLC ration is abnormal.

Non-measurable disease

Patients who do not meet any of the criteria for measurable disease as listed above. Patients who do not meet any of the criteria for measurable disease as listed above can only be assessed for stringent CR, and cannot be assessed for any of the other response categories.

Non-secretory myeloma

Patients with multiple myeloma who have never had a detectable serum or urine M-component or an abnormal serum FLC ratio. The baseline bone marrow must have >10% clonal plasma cells.

7.2 Guidelines for Evaluation of Measurable Disease

Bone radiographs

These are not required to document response. If bone radiographs are obtained, their findings must be consistent with the bone response criteria.

Bone progression

Caution must be exercised to avoid rating progression or relapse on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the study chair before removing the patient from the study.

Clarification of test indications

Patients with "measurable disease' as defined above need to be followed by both SPEP and UPEP for response assessment and categorization. Except for assessment of CR, patients with measurable disease restricted to the SPEP will need to be followed only by SPEP; correspondingly, patients with measurable disease restricted to the UPEP will need to be followed only by UPEP. Patients with measurable disease in either SPEP or UPEP or both will be assessed for response only based on these two tests and not by the FLC assay. FLC response criteria are only applicable to patients without measurable disease in the serum or urine, and to fulfill the requirements of the category of stringent CR.

Laboratory tests for measurement of M-protein

Serum M-protein level is quantified using densitometry on SPEP except in cases where the SPEP is felt to be unreliable such as in patients with IgA monoclonal proteins migrating in the beta region. If SPEP is not available or felt to be unreliable (e.g., in some cases of IgA myeloma) for routine M-protein quantitation during therapy, then quantitative immunoglobulin levels on nephelometry or turbidimetry can be accepted. However, this

must be explicitly reported, and only nephelometry can be used for that patient to assess response and SPEP and nephelometric values cannot be used interchangeably.

7.3 Response Criteria

Stringent Complete Response (sCR)

CR as defined below plus normal FLC ratio and absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.

Complete Response (CR)

Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cell in bone marrow.

Note that patients who do not meet any of the criteria for measurable disease as listed above in the definition can only be assessed for stringent CR, and cannot be assessed for any of the other response categories.

Very Good Partial Response (VGPR)

Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level <100 mg/24hr.

Partial Response (PR)

Requires all of the following:

≥50% reduction of the serum M-protein.

Reduction in 24-hour urinary M-protein by >90% or to <200 mg/24hr.

If the serum and urine M-protein are unmeasurable, a >50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.

If serum and urine M-protein are unmeasurable, and serum free light chain assay is also unmeasurable, a >50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was >30%.

In addition to the above criteria, if present at baseline, a >50% reduction in the size of soft tissue plasmacytomas is also required.

Stable disease (STAB)

Not meeting criteria for CR, VGPR, PR or progressive disease.

Disease Plateau (Note: plateau is not a distinct response category)

A patient in sCR, CR, VGPR, or PR (see sections above) will be further classified as being in plateau if the following criteria are met:

Serum and/or urine M-protein values and/or serum FLC ratio must be stable for a period of at least 12 weeks. Stable values are defined as a continued CR or in the case of patients with residual M-protein, absence of progression.

Any patient with measurable disease who is continuing to have "improvement" in serum or urine response criteria would not be considered in plateau. "Improvement" is defined as a decrease in the serum or urine M spike by > 25% He or she might be approaching a better level of response, and therefore, should not yet be deemed in plateau until the improvement has leveled off.

DATE of plateau will be the first date of suspected plateau. Date cannot be assigned until CONFIRMATION that the patient is in plateau (that is at least 12 weeks later).

Progressive Disease (PD)

To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (including primary progressive disease and disease progression on or off therapy)

Requires any or more of the following:
Increase of >25% from baseline in:
Serum M-component and/or (the absolute increase must be >0.5 g/dl)
Urine M-component and/or (the absolute increased must be > 200mg/24hr)
Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dl.
Bone marrow plasma cell percentage: the absolute % must be 10%.
Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder.
Clinical Relapse
Requires one or more of the following:
Direct indicators of increasing disease and/or end organ dysfunction. It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally o for use in clinical practice.
Development of new soft tissue plasmacytomas or bone lesions
Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion.
Hypercalcemia (11.5 mg/dl) [2.65 mmol/l]
Decrease in hemoglobin > 2g/dl [1.25 mmol/l] not attributed to lenalidomide treatment.
Rise in serum creatinine by 2 mg/dl or more [177 μmol/l or more]
Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having "symptomatic deterioration." Every effort should be made to document the objective progression, even after discontinuation of treatment.
Relapse from CR (To be used only if the end point studied is DFS)
Any one or more of the following:
Reappearance of serum or urine M-protein by immunofixation or electrophoresis
Development of >5% plasma cells in the bone marrow. Note the 5% cutoff versus 10% for other categories of relapse.
Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia.

7.4 Confirmatory Measurement and Duration of Response

Confirmed response
In order to be classified as a response, confirmation of serum and urine monoclonal protein results and serum free light chain levels must be made by verification on two consecutive determinations 4-6 weeks apart.
For patients with non-secretory myeloma only, a bone marrow is required to document all response categories; however, a second confirmatory bone marrow is not required to confirm response.
Bone marrow aspirate and biopsy are not required to document or confirm response.
Exception: for patients with non-secretory myeloma only, a bone marrow is required to document all response categories including progression.

Duration of overall response
The duration of overall response is measured from the time measurement criteria are met for achieving at least partial response to the time of disease progression, with deaths owing to causes other than progression not counted, but censored. The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.
Duration of Stable Disease
Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.
Progression-Free Survival
PFS is defined as the duration of time from start of treatment to time of progression or death.

7.5 Response Review
The CUMC Data Safety and Monitoring Plan includes provisions for independent review and confirmation of responding patients on clinical trials. All reported responders on this trial will be subject to independent review and confirmation.

8 CORRELATIVE STUDIES

Part of the blood and bone marrow samples obtained during this trial will be used for correlative studies. Patients will be informed of these studies during the informed consent process.

9 REGULATORY OBLIGATIONS

9.1 Adverse Event Reporting

Serious Adverse Drug Experience
Only Serious Adverse Event (SAE) which meets the definition of an Unanticipated Problem Involving Risks to Subjects or Others will be reported promptly but no later than one week to the CUMC IRB.

"Adverse Event" is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign, symptom or disease, temporally associated with the subject's participation in research, whether or not considered related to the subject's participation in the research.

"Monitoring Entity" is the group that is responsible for overseeing the safety of all subjects enrolled in the study in accordance with the protocol (e.g., a Data Safety Monitoring Board (DSMC), a Data Monitoring Committee (DMC), a coordinating or statistical center, or a sponsor).

"Unanticipated Problem" is any incident, experience or outcome involving risk to subjects or others in any human subjects research that meets all of the following criteria:
▪ Unexpected (in terms of nature, severity or frequency) given (a) the research procedures

that are described in the IRB-approved protocol and informed consent document, and (b) the characteristics of the subject population.
▪ Related or possibly related to participation in such research (i.e. there is a reasonable possibility that the incident, experience or outcome may have been caused by the procedures involved in such research); and
▪ Suggests that the research places subjects or other at a greater risk of harm (including physical, psychological, economic or social harm) than was previously known or recognized.

Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect or a suspected positive pregnancy, Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Unexpected Drug Adverse Experience
Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended.
Associated with the use of the drug: There is a reasonable possibility that the experience may have been caused by the drug.

Disability
A substantial disruption of a person's ability to conduct normal life functions.

Life-threatening adverse drug experience
Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

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

Scoring

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.
The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the patient's outcome.

Reporting
Only events which meet the definition of an Unanticipated Problem (UP) and are considered possibly related to lenalidomide need to be reported to the CUMC IRB after day 31+ of induction. All other unrelated events or events related to the SOC transplant process should be documented, but do not need to be submitted to the CUMC IRB. Starting at Day 1 of maintenance lenalidomide, all events which meet the definition of an UP need to be reported to the CUMC IRB.

ADVERSE EVENT REPORTING
TO: COLUMBIA UNIVERSTIY MEDICAL CENTER IRB
The investigator must inform CUMC Institutional Review Board (IRB) in accordance with their guidelines.
Provide the IRB with a copy of the MedWatch 3500A form within one week of the onset and assessment of the event.

TO SUPPORTER: CELGENE CORPORATION
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 date of awareness should be noted on the report. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). 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-0385) 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 subject records.

PREGNANCY
Pregnancy of a female subject or the female partner of a male subject while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered

expedited reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of lenalidomide to the Investigator. The pregnancy must be reported 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 subject 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 of 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 patient should be referred to an obstetrician/gynecologist experienced in reproductive toxicity for further evaluation and counseling.

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

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

Celgene Drug Safety Contact Information:

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

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

The Investigator shall notify his/her IRB/EC promptly of these new serious and unexpected

AE(s) or significant risks to subjects.
The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file (see Section 11.4 for records retention information).

Expedited Reporting by Investigator 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 by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (RV-MM-PI-0385) 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.

9.2 Data and Safety Monitoring Plan

The data and safety monitoring plan for this study consists of monitoring safety issues in the form of adverse events occurring at this site as well as safety reports regarding external events received from Celgene. All such events that meet the reporting guidelines of Columbia University Medical Center IRB are submitted on an ongoing basis throughout the renewal interval. Events that do not meet the reporting guidelines are reviewed and placed in the regulatory file for this study. All reportable events are entered into Velos eResearch and submitted to the HICCC Data and Safety Monitoring Committee (DSMC) for review. Study progress is also assessed by the study team on a monthly basis during the conduct of this trial. This assessment includes discussion of recruitment, screening and accrual issues as well as study conduct (dosing, study tests and procedures, response data, patient follow-up, deviations, confidentiality, etc.). In addition, new scientific publications or data that suggest changes to the current trial may be warranted will be discussed should they arise. Both safety and study progress assessments are summarized monthly and reported to the HICCC DSMC, which provides oversight to this and all HICCC trials. This cumulative data and safety monitoring plan ensures that the risk-to-benefit ratio will be closely monitored for any changes. Once all patients are off active study treatment (i.e., are on follow-up only), the data and safety monitoring reviews will occur every 6 months rather than monthly. At the time of IRB renewal, the data and safety monitoring activities outlined above will be summarized and included in the IRB renewal report.

The Data and Safety Monitoring Committee (DSMC) is composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the DSMC is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The DSMC may request additional meetings or safety reports as deemed necessary upon discussion with Celgene and its representatives. The DSMC may stop the

study following review of results from each interim analysis. The first interim analysis will examine only safety information; the second interim, conducted when the database is more mature, will examine both safety and efficacy. Appropriate efficacy and safety data summaries will be provided to the DSMC after each interim analysis.

9.3 Record Retention

According to 21 CFR 312.62(c), the investigator/sponsor shall retain required records for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the investigator shall retain these records until 2 years after the investigation is discontinued (IND is withdrawn) and the FDA is notified.

The investigator/sponsor must retain protocols, amendments, IRB/IBC approvals, copies of the Form FDA 1572, completed, signed, dated consent forms, patient source documents, case report forms, quality monitoring reports, drug accountability records and all documents of any nature regarding the study or patients enrolled. All records will be maintained under restricted access by Columbia University's Clinical Research Management Office while the study remains active. Records will be placed in long-term storage after the study is completed. The location of long-term storage will be secure and easily accessed for regulatory purposes.

9.4 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 is implemented.

9.5 Study Monitoring and Auditing

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

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related audits by Celgene or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

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

9.6 Informed Consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per GCPs as set forth in the CFR and ICH guidelines. Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

9.7 Subject Confidentiality

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 representatives of Celgene Corporation 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.

10 STATISTICAL CONSIDERATIONS

10.1 Study Objectives and Endpoints

The primary objectives of this trial are to estimate and compare the complete response rate in newly diagnosed multiple myeloma patients receiving autologous peripheral blood stem cell transplant after undergoing 4 cycles of lenalidomide and low-dose dexamethasone (Arm A) vs. in those receiving 8 cycles of lenalidomide and low-dose dexamethasone until plateau of best response (Arm B).

The secondary objectives are to estimate duration of complete response, objective response rate (complete response rate plus partial response rate), progression free survival, overall survival, time to progression, time to transplant in both arms and toxicity of the two treatments.

Objective response is based on the definitions of complete response, partial response, minimal response, and progression as outlined by the IBMTR/ABMTR (Blade 1998).

Target enrollment for this study is 60 patients. 50 patients have been enrolled at the University of Pittsburg Cancer Institute, and expected enrollment at the Columbia University Medical Center is 10 patients.

Adverse events are evaluated by NCI common toxicity criteria for adverse events (CTCAE) v4.0. Toxicity is defined as any adverse event that is probably, possibly, or definitely attributable to the regimen.

Duration of complete response is calculated as the time interval between the date when a confirmed complete response is first documented and the documented date of disease progression or death. For an alive and progression free patient, duration of complete response is censored by the last follow-up date when patient is documented to be progression free.

Progression free survival (PFS) is calculated as the time interval between the treatment start date and the documented date of disease progression or death. For an alive and progression free patient, PFS is censored by the last follow-up date when patient is documented to be progression free.

Time to progression (TTP) is calculated as the time interval between the treatment start date and the documented date of disease progression. For a progression-free patient, TTP is censored by the date of death or by the last follow-up date when that patient is documented to be progression free.

Overall survival (OS) is calculated as the time interval between the treatment start date and the documented date of death. For a surviving patient, OS is censored by the last follow-up date when that patient is documented to be alive.

Evaluable patients will be used for both efficacy and safety analysis. Evaluable patients are patients who meet the protocol inclusion/exclusion criteria, sign the consent form, and receive at least one dose of lenalidomide or dexamethasone.

10.2 Statistical Analysis

Descriptive statistics will be provided for age, gender, race, disease stage at enrollment etc.

We will estimate the complete response rates in both Arms A and B, and construct exact 95% confidence intervals. We hypothesize that the response rate among patients receiving 8 cycles lenalidomide/dexamethasone (Arm B) is not worse than that that in Arm A. We will use one-sided binomial test at significance level 0.05 to compare the complete response rates between the two arms.

In preliminary results, among 19 patients who assigned to Arm A, none of them had complete response; while 3 out of 20 patients in Arm B achieved complete response. Assuming the actual response rate among patients in Arm A is 1% and actual complete response rate in Arm B is 17%, with total sample size 60 patients and 1:1 randomization scheme, we have 80.8% power to detect such difference at 5% significance level.

The accrual rate is estimated to be 15 patients per year in both centers UPMC and CUMC. The overall duration of accrual is expected to be 2 – 3 years. The remaining duration of accrual is expected to be 12-18 months.

Adverse events will be tabulated by the type, grade, and treatment arm. Fisher exact test or Chi-square test will be used to compare severity of different type of adverse event across two arms. For any observed serious adverse events (SAEs), its attribution to regimen (unrelated,

unlikely, possible, probable, or definite) will be reported. The observed proportion of regiment-related SAEs (number of patients experienced regiment-related SAEs / total number of patients treated), along with a 95% confidence interval will be calculated by treatment arms.

Duration of complete response, progression free survival, time to progression and overall survival curves will be estimated by Kaplan-Meier method. Median PFS, TTP, OS and corresponding 95% confidence interval will be reported by treatment arms. Log rank test will be used to compare the duration of complete response, progression free survival, time to progression and overall survival curves across two treatment arms.

10.3 Interim Analysis

An interim analysis is planned when each treatment arm has at least 25 patients evaluated for objective response (yes or no). The objective response rate and toxicity will be summarized by treatment arms.

The toxicity will be continuously monitored. We expect some toxicity with these two regimens, and have set up some rules for holding doses and dose de-escalation in the events of selected toxicities (section 5.3). Lenalidomide, dexamethasone and autologous stem cell transplant for multiple myeloma are approved by food and drug administration (FDA). If the observed proportion of SAEs for those 25 patients in each arm is much higher than the FDA reported rate of SAE for the corresponding treatment, the enrollment of the study will be suspended pending review by data safety and monitoring committee (DSMC) at the Columbia University Medical Center.

If the underlying complete response rate in the treatment arm (Arm B) is 30%, the probability of observing 3 or less complete responses out of 25 treated patients in arm B is 0.10. Therefore, if there are 3 or less complete responses out of 25 treated patients in arm B, i.e. the observed complete response rate is 10% or less, the trial will be stopped early for lack of efficacy. Table 1 lists the probability of stopping the study early under different underlying but unknown complete response rate in arm B.

Table 1: Probability of stopping the study early due to lack of efficacy

Underlying but unknown complete response rate in arm B	Pr(Early stop)*
30%	0.03
25%	0.10
20%	0.23
15%	0.47
10%	0.76
6%	0.94

*: Stopping rule: 3 or less complete responses out of 25 treated patients in arm B.

11 PREMATURE DISCONTINUATION OF STUDY

The Principal Investigator, institution and Celgene have the right to discontinue this study at

any time for reasonable medical or administrative reasons. 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.

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.).

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Appendix A Subject Medication Diary

Subject Name	
Sequence Number	
Cycle	

Please use this diary to record the medication you take for the protocol. Use the space marked comments to make notes about things you would like to tell the study doctor (including symptoms you experience, and anything else you think would be of interest).

DAY	DATE	LENALIDOMIDE DOSE TAKEN	DEXAMETHASONE DOSE TAKEN	OTHER MEDICATIONS	COMMENTS
Example		*_ mg*	*40 mg*	*Aspirin at least 81 mg, Ranitidine 2 tablets*	*Skin rash*
1					
2					
3					
4					
5					
6					
7					
8					
9					
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11					
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28					

Appendix B 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 C Impaired Renal Function Dosing Schedule

Recommended dose adjustments during lenalidomide therapy in patients with impaired renal function.

Renal function (CL_{Cr})	Lenalidomide dose adjustment
Mild renal impairment ($CL_{Cr} \geq 50$ ml/min)	25 mg once daily
Moderate renal impairment ($30 \leq CL_{Cr} < 50$ ml/min)	10 mg once daily*
Severe renal impairment ($CL_{Cr} < 30$ ml/min, not requiring dialysis	15 mg every other day*
End-stage renal disease ($CL_{Cr} < 30$ ml/min, requiring dialysis	15 m g 3 times per week following each dialysis

*The dose may be escalated to 15 mg once daily after 2 cycles if the patient is not responding to, but is tolerating, the treatment.

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

RISKS ASSOCAITED 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.

Study participants must follow pregnancy testing requirements as outlined in the Revlimid REMS® program material.

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

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

Male Subjects
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 Subjects
FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of lenalidomide treatment, including dose interruptions and then every 28 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 28 following lenalidomide discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days of lenalidomide treatment, including dose interruptions, and then every 14 days throughout the remaining duration of lenalidomide treatment, including dose interruptions, at lenalidomide discontinuation, and at Day 14 and Day 28 following lenalidomide discontinuation.
At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control at each visit during the time that birth control is required.
If pregnancy or a positive pregnancy test does occur in a study 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 Subjects
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
Both female and male subjects should be instructed never to give lenalidomide to another person.
Female subjects should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
Male subejcts 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 Staging of Myeloma: Durie-Salmon System and International Staging System

The staging system most widely used since 1975 has been the Durie-Salmon system, in which clinical stage of disease (stage I, II, or III) is based on four measurements: levels of M protein, the number of lytic bone lesions, hemoglobin values, and serum calcium levels. Stages are further divided according to renal function.
There is somewhat of an overlap between the various myeloma categories and stages. For example, both patients with smoldering myeloma and patients with Stage I disease do not require immediate treatment, and patients with Stage II and III disease have active, symptomatic myeloma. Increasingly, physicians are relying less on the Durie-Salmon staging system and more on biologically relevant markers as prognostic indicators when making treatment choices.
A new, simpler, more cost-effective alternative is the International Staging System (ISS). The ISS is based on the assessment of two blood test results, beta 2-microglobulin (ß2-M) and albumin, which together showed the greatest prognostic power for multiple myeloma. This system has only recently been developed, but has already been proven more sensitive in discriminating between three stages of the disease, which indicate different levels of projected survival and suggest increasingly more aggressive treatment strategies.

The following table summarizes the staging criteria.

Stage	Durie-Salmon Criteria	ISS Criteria
I	All of the following: Hemoglobin value >10 g/dL Serum calcium value normal Bone x-ray, normal bone structure (scale 0) or solitary bone plasmacytoma only Low M-component production rate - IgG value <5 g/dL; IgA value <3 g/dL Bence Jones protein <4 g/24 h	ß2-M 3.5 mg/L and album n ≥3.5 g/ L
II*	Neither stage I nor stage III	*Stage II =(ß2-M <3.5 g/dL & albumin <3.5) OR (ß2-M 3.5 - 5.5 mg/dL,)
III	One or more of the following: Hemoglobin value <8.5 g/dL Serum calcium value >12 mg/dL Advanced lytic bone lesions (scale 3) High M -component production rate - IgG value >7 g/dL; IgA value >5 g/dL - Bence Jones protein >12 g/24 h	ß2-M ≥ 5.5 mg/L
Durie-Salmon sub classifications (either A or B)		

A: Relatively normal renal function (serum creatinine value <2.0 mg/ L B: Abnormal renal function (serum creatinine value =2.0 mg/dL