Phase I/II Study of Lenalidomide (Revlimid®), Thalidomide and Dexamethasone in Patients with Relapsed/Refractory Multiple Myeloma

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1.1 Introduction

1.2 Overview of the Disease

Multiple myeloma (MM), the second most common hematologic malignancy, is an incurable disease that is characterized by the accumulation of clonal plasma cells in the bone marrow (1). It accounts for approximately 11,300 deaths annually in the United States. The primary approach to the treatment of MM is systemic chemotherapy. Prior to the introduction of alkylator agents in the 1960s, the median survival for patients with MM was less than 12 to 17 months from the time of diagnosis(1). Subsequently, conventional chemotherapy has increased median survival to about 3 years. Myeloablative therapy followed by autologous stem cell transplantation is an adjunct to conventional chemotherapy and improves survival in selected patients (1,2). However, MM remains incurable; therefore, innovative approaches are needed (3).

1.3 Relapsed/Refractory Multiple Myeloma

The management of relapsed/refractory multiple myeloma has changed significantly in the last 10 years with the introduction of several new agents/combinations including thalidomide, lenadalidomide/dexamethasone, bortezomib and the combination of bortezomib/pegylated doxorubicin.

There is only one study which combined lenalidomide and thalidomide that has been published. Oral lenalidomide was administered at 10 mg/day on days 1–21, oral melphalan at 0.18 mg/kg on days 1–4, oral prednisone at 2 mg/kg on days 1–4. Thalidomide was administered at 50 mg/day (Arm A) or 100 mg/day (Arm B) on days 1–28. Each course was repeated every 28 days for a total of 6 courses. Aspirin 100 mg/day was given as a prophylaxis for thrombosis. Maintenance therapy included lenalidomide alone at 10 mg/day on days 1–21. Forty-four patients, median age 69 years (range 47–80), with relapsed or refractory MM were enrolled. Twenty-six patients received RMPT as second line of therapy, 18 as third line. Twenty patients received prior autologous transplant, 10 thalidomide-based regimen, 9 bortezomib-based regimen and 3 allogeneic stem cell transplant. After a median of 2 courses, 75.8% of patients achieved at least a partial response (PR), including 30% very good partial response (VGPR). Among patients who received RMPT as second line therapy the PR rate was 81.8%, including VGPR 36.4%.Among patients who received thalidomide 100 mg, the PR rate was 93.3% (including VGPR 46.7%) compared to 64.7% of thalidomide 50 mg. The 1-year-progressionfree survival was 48.6% and the 1-year survival from study entry was 90%. Grade 3–4 hematologic adverse events included: neutropenia (66.6%), thrombocytopenia (36.3%) and anemia (30.2%). Grade 3–4 non hematologic adverse events included: infections (21.2%), neurological toxicity (6%) and fatigue (9%). No thromboembolic events were reported. This was presented as abstract by Palumob et al in ASH Annual Meeting Abstracts 2008 112: 868.

There is also an ongoing phase 1 study of the same combination of lenalidomide/thalidomide/dexamethasone in newly diagnosed patients which is currently ongoing.

1.3.1 Thalidomide - Introduction

The use of thalidomide in the treatment of malignancies is growing. Thalidomide has been shown to have activity in a variety of malignancies including multiple myeloma, myelodysplastic syndromes, renal cell cancer, glioblastoma multiforme, and prostate cancer (4,5,6,7,8).

Thalidomide was initially studied as an anti-cancer agent based on the finding that it inhibits angiogenesis induced by basic fibroblast growth factor (bFGF) (9) and vascular endothelial growth factor (VEGF) (23). Angiogenesis is important in the pathogenesis of tumor growth and metastasis (13). Adequate blood supply must be available to deliver nutrition to the tumor cells, which is accomplished by neo-vascularization. In a phase II trial of thalidomide in patients with recurrent high-grade gliomas serum bFGF declines correlated with response, time to progression and overall survival. No such relationship was found for VEGF. Thalidomide inhibits endothelial cell proliferation *in vitro* in association with a marked decrease in the activity of the nuclear binding factor (12).

Thalidomide has several additional mechanisms of action, which could confer antitumor and antimetastatic effects that may be of equal or greater importance than its antiangiogenic properties. Thalidomide inhibits the production of human monocyte tumor necrosis factor alpha (TNF-alpha) through accelerated degradation of TNF-alpha mRNA (13). Thalidomide alters the expression of various adhesion molecules (12,13). Thalidomide produces free radical-mediated oxidative damage to rabbit DNA, a potential mechanism of thalidomide teratogenicity (14). Thalidomide is a potent co-stimulator of T cell responses, particularly, in the CD8 expressing subset (15). In addition to these effects, thalidomide stimulates T cell proliferation, and IL-2, IL-10 and IFN-gamma production, and inhibits IL-1 beta and IL-6 (15).

Although the exact antitumor mechanism of action of thalidomide in various malignancies is unknown, a number of mechanisms are postulated to be responsible for thalidomide's activity against multiple myeloma. Recently, thalidomide has been shown to increase T cell proliferation, which leads to an increase in IL-2 and IFN-gamma secretion. The increased level of these circulating cytokines augment natural killer cell number and function, and enhance natural killer cell activity to yield an increase in multiple myeloma cell lysis (13,14,15). In addition, thalidomide has direct activity against multiple myeloma and induces apoptosis or G1growth arrest in multiple myeloma cell lines and in multiple myeloma cells of patients resistant to melphalan, doxorubicin and dexamethasone (9).

1.3.2 Thalidomide - Clinical Experience in Multiple Myeloma

Singhal et al were the first to demonstrate activity of thalidomide in patients with relapsed MM (4). Ninety percent of the patients in this study had relapsed after prior ASCT. Responses (at least 25 % reduction in M protein) were seen in 32% of patients using doses of 200-800 mg/d. After 12 months of follow-up, the Kaplan-Meier estimates of the mean (+/-SE) rate of event-free survival was 22 ± 5 %. The activity of single agent thalidomide was found to be a dose-intensity dependent phenomenon. Higher response rates were demonstrated in combination with dexamethasone. Among patients with resistant or relapsing disease treated with a combination of thalidomide and dexamethasone, 47% of patients achieved remission with significant prolongation of survival for responsive patients. Among patients in stable partial remission after intensive therapy who received the same program, myeloma protein was reduced further by greater than 90% in 52% of patients who had not received prior thalidomide/dexamethasone (6).

Higher response rates were observed in the upfront setting. Weber et al treated forty consecutive previously untreated patients with symptomatic myeloma with Thalidomide (maximum dose 400 mg) and pulse dexamethasone. The response rate was 72% including complete remission in 16% of patients (6). A similarly high response rate was seen in fifty newly diagnosed myeloma patients treated at the Mayo clinic with thalidomide at 200 mg/d in combination with pulse dexamethasone where a 64% response rate was observed (7). A phase III study, involving 207 patients, coordinated by the Eastern Cooperative Oncology Group reported a 72% response rate to the combination of thalidomide (200 mg/d) and pulse dexamethasone in newly diagnosed multiple myeloma patients, compared to a 41% response rate with dexamethasone alone (7). This study led to the recent approval by the Unites States Food and Drug administration of the use of combination of dexamethasone and thalidomide for the initial therapy of newly diagnosed multiple myeloma patients.

Thalidomide has been shown to be efficacious in myeloma patients in combination with other agents as well. Notably, Palumbo et. al. treated 255 newly diagnosed multiple myeloma patients either with oral melphalan, prednisone and thalidomide (at 100 mg/day) or melphalan and prednisone alone. Combined response rates were 76.0% for MPT and 47.6% for MP alone.

1.3.3 Thalidomide - Toxicity

Available data from three clinical pharmacology studies sponsored by Celgene Corporation showed that 38 subjects have been exposed to single doses of thalidomide given either on one occasion or three occasions with one to two week washouts between doses. Two studies were conducted in healthy volunteers and the third study was conducted in patients with Hansen's disease. Thalidomide was administered in a 50 to 400 mg single dose range.

Based on the results of the studies, the most frequently reported adverse experiences were dizziness (31 subjects or 82 %), somnolence (29 subjects or 76%), headache (15 subjects or 39%), and asthenia (12 subjects or 32%). Somnolence and dizziness were reported to occur more frequently at doses of 200 mg and 400 mg than they did at a dose of 50 mg. There was no dose relationship evident for the remaining adverse experiences.

There was no reported severity in intensity of all adverse experiences. All events were mild with the exception of moderate somnolence in 13 subjects, moderate dizziness in 6 subjects, moderate headache in 4 subjects, moderate hypotension in 2 subjects and moderate constipation and moderate pallor in 2 subjects, and a single report of moderate asthenia, diarrhea, leg cramps, nausea and rhinitis. There have been reports of a slowing of the heart rate.

Thalidomide is known to cause nerve damage that may be permanent. Peripheral neuropathy is a common, potentially severe, side effect of treatment with thalidomide that may be irreversible. Peripheral neuropathy generally occurs following chronic use over a period of months, however, reports following short-term use also exist. The correlation with cumulative dose is unclear. Patients should be examined at monthly intervals for the first three months of thalidomide therapy to enable the clinician to detect early signs of neuropathy, which include numbness, tingling or pain in the hands and feet. Patients should be evaluated periodically thereafter during treatment. If symptoms of drug-induced neuropathy develop, thalidomide should be discontinued immediately to limit further damage, if clinically appropriate. Usually treatment with thalidomide should only be reinitiated if the neuropathy returns to baseline status.

Serious dermatologic reactions including toxic epidermal necrolysis and Stevens-Johnson syndrome, which may be fatal, have been reported in association with thalidomide therapy. THALOMID®® should be discontinued, if a skin rash occurs and only resumed following appropriate clinical evaluation. If the rash is purpuric, vasculitic, exfoliative, or bullous or if Stevens-Johnson syndrome or toxic epidermal necrolysis is suspected, use of THALOMID®® should not be resumed.

The use in Thalidomide in Multiple Myeloma results in an increased risk of venous thromboembolytic events, such as deep vein thrombosis and pulmonary embolus. The risk increases significantly when thalidomide is used in combination with standard chemotherapeutic agents including dexamethasone. In one controlled trial the rate of veinous thromboembolic events was 22.5% in patients receiving thalidomide in combination with dexamethasone compared to 4.9% receiving dexamethasone alone. Patients and physicians are advised to be observant for signs of thromboembolism. Patients should seek medical attention should they develop symptoms such as shortness of breath, chest pain or leg or arm swelling. Preliminary reports suggest that patients who are appropriate candidates may benefit from concurrent prophylactic anticoagulation or aspirin treatment.

Although not reported from pre-marketing controlled clinical trials, seizures, including grand mal convulsions, have been reported during post-approval use of THALOMID®® (thalidomide) in clinical practice. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made. Most patients had disorders that may have predisposed them to seizure activity, and it is not currently known whether thalidomide has any epileptogenic influence. During therapy with thalidomide, patients with a history of seizures or with other risk factors for the development of seizures should be monitored closely for clinical changes that could precipitate acute seizure activity.

THALOMID®(thalidomide) can cause severe birth defects in humans. Women and men taking thalidomide must take special precautions and be willing and able to comply with all aspects of the FDA-mandated S.T.E.P.S.® program. (see Appendix A: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods)

This medicine is for subject use ONLY. IT SHOULD NOT BE SHARED WITH ANYONE. It should be safely stored. It must be kept out of the reach of children and should never be given to women who are able to have children, and used only as directed by the physician.

Subjects should not drink alcohol or take any other medicine that has not been prescribed by the doctor, especially nonprescription drugs that makes the subject sleepy.

1.3.4 Lenalidomide – Introduction

Lenalidomide is a proprietary IMiD™ compound of Celgene Corporation. IMiD™ compounds have both immunomodulatory and anti-angiogenic properties which could confer antitumor and antimetastatic effects. Lenalidomide has been demonstrated to possess anti-angiogenic activity through inhibition of bFGF, VEGF and TNF-alpha induced endothelial cell migration, due at least in part to inhibition of Akt phosphorylation response to bFGF. In addition, lenalidomide has a variety of immunomodulatory effects. Lenalidomide stimulates T cell proliferation, and the production of IL-2, IL-10 and IFN-gamma, inhibits IL-1 beta and IL-6 and modulates IL-12 production . Upregulation of T cell derived IL-2 production is achieved at least in part through increased AP-1 activity (12,13,14,15).

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

1.3.5 Lenalidomide - Clinical experience in Multiple Myeloma

In 2 phase I studies in multiple myeloma, a total of 41 patients have been treated with lenalidomide. In one study at the University of Arkansas, 15 patients who relapsed or were refractory to high dose melphalan therapy with stem cell transplant were treated for 4 weeks in an open-label safety study and were permitted to continue therapy in an extension phase of the trial. Patient cohorts were treated at the following daily doses: 5mg, 10mg, 25mg, and 50mg (16). In a similar study at the Dana Farber Cancer Institute, 27 patients with rapidly advancing refractory multiple myeloma were enrolled (17).

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

Pharmacokinetic analyses were performed on 15 multiple myeloma patients treated in the phase I studies. Absorption was found to be rapid on both Day 1 and Day 28 with time to maximum blood levels ranging from 0.7 to 2.0 hours at all dose levels (5mg, 10mg, 25mg, and 50mg). Plasma lenalidomide declined in a monophasic manner with elimination half-life ranging from 2.8 to 6.1 hours on both Day 1 and 28 at all 4 doses. No plasma accumulation was observed with multiple daily dosing. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg (18).

A multicenter, randomized, phase II trial compared 2 syncopated dose schedules of lenalidomide used alone or in combination with dexamethasone in the treatment of relapsed or refractory multiple myeloma. All patients were treated on Days 1-21 of a 28-day cycle. Patients treated with 15mg BID experienced more myelosuppression and dose reductions compared with patients treated with 30mg daily. Anti-myeloma activity was observed with each dose and schedule of single agent lenalidomide. The addition of dexamethasone to lenalidomide yielded responses in some patients who had not responded to lenalidomide alone (19).

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

A phase I/II trial of Liposomal doxorubicin (Doxil®), vincristine, dexamethasone (DVd) and lenalidomide in heavily pretreated relapsed/refractory multiple myeloma patients is ongoing. The MTD of lenalidomide was 10mg on Days 1-21 in combination with Doxil® 40mg/m2 IVPB on Day 1, vincristine 2mg IVP on Day 1 and dexamethasone 40mg PO on Days 1-4 cycled every 28 days. All patients received amoxicillin, acyclovir and aspirin 81mg prophylactically. The dose limiting toxicity with lenalidomide 15mg on Days 1-21 in combination with DVd was sepsis/septic shock(21).

2 multicenter, randomized, double-blinded, placebo-controlled phase III trials [1 U.S. (MM-009) led by Donna Weber at MDACC and 1 international (MM-010)] evaluated the combination of lenalidomide and dexamthesone in patients with relapsed or refractory multiple myeloma (22). More than 350 patients were enrolled into each of these studies. All patients had to be considered sensitive to dexamethasone and were treated with dexamethasone 40mg daily on Days 1-4, 9-12 and 17-20. In addition to receiving dexamethasone, patients were randomized to lenalidomide 25mg or placebo each given daily on Days 1-21. Cycles were repeated every 28 days. After 4 cycles, there was a predetermined reduction of the dexamethasone dose to 40mg daily on Days 1-4 repeated every 28 days. In both studies, a pre-specified interim analysis conducted by an Independent Data Monitoring Committee demonstrated that subjects receiving the combination of lenalidomide (Len) plus dexamethasone (Dex) had significantly longer times to progression and higher response rates than those treated with single-agent dexamethasone. These studies led to the FDA approval of lenalidomide in combination with dexamethasone for the treatment of multiple myeloma in patients that have received at least one prior therapy. The follow up of these trials was recently published in the New England Journal of Medicine in November, 2007. Both trials had similar results. In the American trial with a median follow up of 17.6 months, complete, near-complete, or partial responses occurred in 61 % in the lenalidomide group and in 19.9% in the placebo group ($P<0.001$); complete responses occurred in 14.1% and 0.6%, respectively ($P<0.001$). The median time to progression was 11.1 months in the lenalidomide group and 4.7 months in the placebo group ($P<0.001$). Median overall survival times in the two groups were 29.6 months and 20.2 months, respectively ($P<0.001$) (22).

1.2.6 Lenalidomide Toxicity

This drug has demonstrated a significantly increased risk of DVT and PE in patients with multiple myeloma who were treated with REVLIMID® (lenalidomide) combination therapy. Patients and physicians are advised to be observant for the signs and symptoms of thromboembolism. Patients should be instructed to seek medical care if they develop symptoms such as shortness of breath, chest pain, or arm or leg swelling. Prophylactic anticoagulation or antiplatelet therapy prescribed in conjunction with REVLIMID® (lenalidomide) is required for patients enrolled in this current trial.

Most frequently reported adverse events reported during clinical studies with lenalidomide in oncologic and non-oncologic indications, regardless of presumed relationship to study medication include: anemia, neutropenia, thrombocytopenia and pancytopenia, abdominal pain, nausea, vomiting and diarrhea, dehydration, rash, itching,

infections, sepsis, pneumonia, UTI, Upper respiratory infection, cellulites, atrial fibrillation, congestive heart failure, myocardial infarction, chest pain, weakness, hypotension, hypercalcemia, hyperglycemia, back pain, bone pain, generalized pain, dizziness, mental status changes, syncope, renal failure, dyspnea, pleural effusion, pulmonary embolism, deep vein thrombosis, CVA, convulsions, dizziness, spinal cord compression, syncope, disease progression, death not specified and fractures.

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

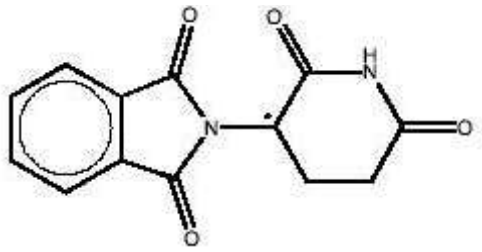
2.1 Background Drug Information

2.2 Thalidomide

2.2.1 Description of Thalidomide

THALOMID® (thalidomide), α-(N-phthalimido)glutarimide, is an immunomodulatory agent. The empirical formula for thalidomide is C13H10N2O4 and the gram molecular weight is 258.2.

Chemical Structure of thalidomide



Note: • = asymmetric carbon atom

THALOMID®(thalidomide), α-(N-phthalimido) glutarimide, is an immunomodulatory agent. The empirical formula for thalidomide $C_{13}H_{10}N_2O_4$ and the gram molecular weight is 258.2. The CAS number of thalidomide is 50-35-1. Thalidomide is off-white to white, nearly odorless, crystalline powder that is soluble at 25°C in dimethyl sulfoxide and sparingly soluble in water and ethanol. The glutarimide moiety contains a single asymmetric center and, therefore, may exist in either of two optically active forms designated S (-) or R (+). THALOMID® (thalidomide) is an equal mixture of the S (-) and R (+) forms and, therefore, has net optical rotation of zero.

Active ingredient: thalidomide. Inactive ingredients: anhydrous lactose, microcrystalline cellulose, polyvinylpyrrolidone, stearic acid, colloidal anhydrous silica, and gelatin.

2.2.2 linical Pharmacology

Mechanism of Action

Thalidomide is an immunomodulatory agent with a spectrum of activity that is not fully characterized. In patients with erythema nodosum leprosum (ENL) the mechanism of action is not fully understood. Available data from *in vitro* studies and preliminary clinical trials suggest that the immunologic effects of this compound can vary substantially under different conditions, but may be related to suppression of excessive tumor necrosis factor-alpha (TNF-α) production and down-modulation of selected cell surface adhesion molecules involved in leukocyte migration.3-6 For example, administration of thalidomide has been reported to decrease circulating levels of TNF-α in patients with ENL, 3 however, it has also been shown to increase plasma TNF-α levels in HIV-seropositive patients.

2.2.3 harmacokinetics and Drug Metabolism

Clinical pharmacokinetics studies have shown that thalidomide when administered as a single 200-mg dose, the mean peak plasma concentration is 1.9 μg/ml ± 0.5, occurring 3.3 hours ± 1.7 after dosing. Mean half-life of elimination is 5.9 hours ± 2.1. Single dose, dose proportionality was evaluated over the clinical dose range, i.e., from 50 to 400 mg. The extent of absorption is proportional to dose, however, as the dose increases beyond 200 mg, a flattening of the peak concentration is seen with a delay in the time to the peak concentration. The mean peak plasma concentration following a single 400 mg dose administration was 2.82 μg/ml ± 0.80 occurring by 4.3 ± 1.6 hours after the dose; mean half-life of elimination was 7.29 hours ± 2.62. The rate of absorption was also slower at the highest dose as evidenced by a rate constant of absorption that was approximately one-half that observed at the lower doses.

Distribution
In human blood plasma, the geometric mean plasma protein binding was 55% and 66%, respectively, for (+)-(R)- and (-)-(S)-thalidomide.8.

Metabolism
At the present time, the exact metabolic route and fate of thalidomide is not known in humans. Thalidomide itself does not appear to be hepatically metabolized to any large extent, but appears to undergo non-enzymatic hydrolysis in plasma to multiple metabolites. In a repeat dose study in which THALOMID® (thalidomide) 200 mg was administered to 10 healthy females for 18 days, thalidomide displayed similar pharmacokinetic profiles on the first and last day of dosing.

Elimination
The mean half-life of elimination ranges from approximately 5 to 7 hours following a single dose and is not altered upon multiple dosing. As noted in the metabolism subsection, the precise metabolic fate and route of elimination of thalidomide in humans is not known at this time. Thalidomide itself has a renal clearance of 1.15 mL/minute with less than 0.7% of the dose excreted in the urine as unchanged drug. Following a single dose, urinary levels of thalidomide were undetectable 48 hrs after dosing. Although thalidomide is thought to be hydrolyzed to a number of metabolites, only a very small amount (0.02% of the administered dose) of 4-OH-thalidomide was identified in the urine of subjects 12 to 24 hours after dosing.

Supplied
Thalidomide is commercially available. Patients, prescribers and dispensing pharmacies must be registered in the FDA-mandated S.T.E.P.S.® program. Celgene will provide Thalomid® (thalidomide) study participants at no charge through the Protocol Therapy Assistance Program (P-TAP).

Prescribing Information

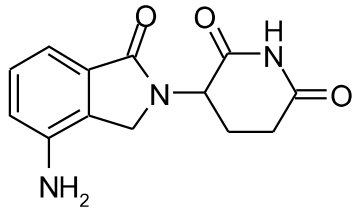
Thalidomide (Thalomid®) will be provided in accordance with the S.T.E.P.S.® program. All physicians who prescribe thalidomide for research subjects enrolled into this trial and all research subjects enrolled into this trial must be registered in and must comply with all requirements of the S.T.E.P.S® program of Celgene Corporation. Only enough thalidomide for 28 days can be prescribed at one time. Prescriptions must be filled within 7 days.

Dosage form
Thalidomide will be supplied as capsules for oral administration.

2.2 Lenalidomide

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

- *Chemical Structure of Lenalidomide*



3-(4-amino-1-oxo 1,3-dihydro-2*H*-isoindol-2-yl) piperidine-2,6-dione
The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.
Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

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

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

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

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

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

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

Dosage form
Lenalidomide will be supplied as capsules for oral administration.

Packaging
Lenalidomide will be shipped directly to patients. 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.

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

2.3 Dexamethasone

2.3.1 Description of Dexamethasone
Dexamethasone is a potent synthetic glucocorticoid that affects almost every body system. It has anti-inflammatory, immunosuppressant, antineoplastic and antiemetic properties. Dexamethasone is well established in the treatment of myeloma and is part of many, usually pulsed, regimens. Alexanian et al.(30) treated 112 newly diagnosed, chemo naïve myeloma patients with dexamethasone. Using criteria based on a 75% or greater reduction of calculated tumor mass, the overall response rates were approximately 43%.

2.3.2 Mechanism of Action:

The mechanism of control with dexamethasone remains unclear. As an antineoplastic agent, it may bind to specific protein (receptors) within the cell forming a steroid-receptor complex. Binding of the receptor-steroid complex with nuclear chromatic alters message RNA (mRNA) and protein synthesis within the cell. It also inhibits the expression of interleukin- 6 (IL-6) in myeloma cells, a growth factor considered to be a major mediator of plasma cell proliferation. In view of the probably dominant role of bond marrow stromal cells in the production of IL-6, dexamethasone may induce a plasma cell apoptosis by blocking the IL-6 support network.

2.3.3 Adverse events:
The commons side effects related to dexamethasone include: nausea, vomiting, hyperphagia, weight gain, gastro-intestinal bleeding or ulcer, euphoria, headache, psychosis, depression, seizures, muscle weakness, insomnia, thrombophlebitis, menstrual irregularities, infection, cataracts or glaucoma, osteoporosis, fluid and electrolyte disturbances, edema, hypertension, hyperglycemia, thrush, pancreatitis, echymoisis, acne, delayed wound healing and rash.

2.3.4 Distribution:
Dexamethasone is manufactured by several pharmaceutical companies and the use of any generic dexamethasone is acceptable in this study. Since package inserts are periodically updated to reflect more current safety and other information, please refer to the FDA website: www.accessdata.fda.gov/scripts/cder/dregsaftda for the most recent version.

3.0 Rationale

Multiple myeloma (MM) is an incurable disease that is characterized by the proliferation of clonal plasma cells in the bone marrow. Conventional chemotherapy and autologous stem cell transplantation have improved survival. However, because MM remains an incurable disease, innovative approaches are needed. The immunomodulatory drug thalidomide and the combination of thalidomide/dexamethasone have been approved for both relapsed/refractory disease and front line MM therapy. Lenalidomide is an immunomodulatory derivative that has demonstrated significant activity with acceptable toxicity in patients with refractory and relapsed MM. Lenalidomide has demonstrated activity in patients who have both responded to prior thalidomide as well as patients who are refractory to prior thalidomide, suggesting a different mechanism of action for the immunomodulatory drugs.

However despite the recent advancements in MM with several new agents recently approved, including bortezomib, lenalidomide and pegylated doxorubicin, the disease remains incurable and attempts to increase the response rates in the relapsed/refractory setting are warranted. The aim of this study is to evaluate in a phase I/II clinical trial the safety, tolerability, and efficacy of the combination of lenalidomide, thalidomide and dexamethasone in relapsed or refractory MM patients.

4.0 Objectives

Phase 1:
Primary Objectives
1. To determine the maximum tolerated dose (MTD) of the combination of lenalidomide and thalidomide and dexamethasone (LTD) in patients with relapsed/refractory multiple myeloma (RRMM).

Secondary Objectives
1. To determine the Overall response rate (ORR)
2. To determine the Time to progression (TTP)
3. To determine the Progression free survival (PFS)
4. To determine the Time to best response

Phase 2:
Primary objective:
1. To determine the overall (CR + VGPR+ PR) response rate of the combination after 4 cycles of therapy.

Secondary Objectives
1. To determine the CR, VGPR
2. To determine the Time to progression (TTP)
3. To determine the Progression free survival (PFS)
4. To determine the Time to best response
5. To assess the safety of the combination of LTD in patients with RRMM.
6. Time to next therapy
7. Symptom measurement - Multiple-symptom assessment tool

5.1 Selection of Patients

5.2 Inclusion Criteria

1. Understand and voluntarily sign an informed consent form.

2. Age ≥ 18 years at the time of signing the informed consent form.

3. Relapsed/refractory MMM with measurable levels of myeloma paraprotein in serum (≥ 0.5 g/dl), urine (≥ 0.2 g excreted in a 24-hour collection sample), or abnormal free light chain (FLC) ratio.

4. Serum Creatnine ≤ 2.5 mg/dl

5. Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mlU/mL within 10-14 days prior to and again within 24 hours of starting lenalidomide 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 affective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a female of childbearing potential even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix A: risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control methods.

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

6. Laboratory test results within these ranges:
   Absolute neutrophil count > 1000 cells/mm^3
   Platelet count > 50,000 cells/mm^3 for patients with < 50% of bone marrow plasma cells and platelet count > 25,000 cells/mm^3 for patients in whom > 50% of the bone marrow nucleated cells were plasma cells
   Total bilirubin </= 2.0 mg/dL
   AST (SGOT) and ALT (AGPT) < 3 x ULN

7. Able to take prophylactic anticoagulation, warfarin or equivalent agent.

8. Patient is able to understand and comply with the terms and conditions of the Lenalidomide and Thalidomide Counseling Program.

9. All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®, AND the S.T.E.P.S.® program.

5.3 Exclusion Criteria

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

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

3. Use of any cancer therapy within 21 days prior to beginning cycle 1 day 1 of therapy (radiation therapy allowed within 5 days of completion of radiation therapy).

4. Known hypersensitivity to thalidomide, lenalidomide and dexamethasone.

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

6.1 Treatment Plan

This is an open-label, phase I/II, single center study, which will enroll up to ~~54~~ 64 patients with relapsed/refractory multiple myeloma.

6.2 Phase I Portion

To determine the MTD of the combination of thalidomide, lenalidomide and dexamethasone (LTD), with 4 dose levels planned. Dosing will start at doses of LTD that are intermediate intensity because of overlapping side effect profile of lenalidomide and thalidomide to determine the MTD and maximize the overall response rate of the regimen.

Table 6-1 Dose Levels to be studied

Dose Level	Assigned Therapy
Level -1	15 mg Lenalidomide daily on days 1-21 followed by 7-day rest every 28 days 50 mg Thalidomide daily 40 mg dexamethasone *
Level 1	15 mg Lenalidomide daily on days 1-21 followed by 7-day rest every 28 days 100 mg Thalidomide daily 40 mg dexamethasone*
Level 2	25 mg Lenalidomide daily on days 1-21 followed by 7-day rest every 28 days 100 mg Thalidomide daily 40 mg dexamethasone*
Level 3	25 mg Lenalidomide daily on days 1-21 followed by 7-day rest every 28 days 200 mg Thalidomide daily 40 mg dexamethasone

* Dexamethasone dosing for cycle 1-2: 40 mg days 1-4, 9-12, and 17-20; all subsequent cycles: 40 mg days 1,8, 15, 21

Dose Escalation
The first cohort of three patients enrolled into the study will receive dose level 1. A full safety evaluation will be conducted when these subjects have completed one cycle (28 days) of combination therapy.

Definition of DLT

A DLT will be defined as follows:

- Hematologic dose-limiting toxicity will be defined as either Grade 4 neutropenia lasting for ≥ 7 days in duration, any Grade 4 thrombocytopenia, or any Grade 5 hematologic toxicity. At least three patients in each cohort must be evaluable for hematologic toxicity.
- Non-hematologic dose-limiting toxicity will be defined as any Grade 3, 4 or 5 non-hematologic toxicity, with the specific exception of:
    - Isolated Grade 3 elevation of liver function tests (LFTs) without associated clinical symptoms, lasting for ≤ 7 days in duration.
    - Isolated Grade 3 elevation of amylase without associated clinical symptoms
    - Grade 3 hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, or hyphosphatemia which responds to medical intervention.

Definition of Maximum Tolerated Dose:

The MTD of the combination of lenalidomide, thalidomide and dexamethasone in multiple myeloma subjects shall be defined at the end of the trial, the dose with the smallest absolute value of (*posterior mean of pi-pT*) among all the tried doses *i* for which *Ti*=0 will be selected as the MTD.

The dose will be escalated either until an MTD is identified or the maximum planned dose is achieved.

6.3 Phase II

Patients will be enrolled in the phase II portion of this study at the dosing regimen established in the phase 1 portion. Patients will be assessed for response each cycle of therapy.

An additional cohort of 10 patients with myeloma refractory to lenalidomde will be enrolled. This cohort of patients will be treated at the MTD regimen, with lenalidomide 25 mg po days 1-21 on a 28 day cycles and thalidomide 100 mg po daily. The dose of dexamethasone will be 40 mg po weekly.

6.3.1 tudy Duration

Patients who attain a CR/VGPR/PR may elect to stop treatment at any point after cycle 2 and proceed to stem cell mobilization and transplantation. Patients who achieve less than a CR/nCR or patients, or who do not proceed to SCT, may receive upto 8 cycles of the combination therapy. Patients who progress will be removed from therapy. If a patient in CR/nCR/VGPR then patients receive upto 2 cycles beyond best response or up to 8 cycles at physician discretion and then proceed to maintenance therapy.

After 8 cycles, patients who have stable or responding disease to treatment and have an acceptable toxicity profile will be allowed to continue treatment on a maintenance schedule described below until disease relapse, unacceptable toxicity, withdrawal of consent or no further clinical benefit is experienced. Doses of thalidomide, lenalidomide, or dexamethasone may be interrupted or reduced in an attempt to manage toxicity at physician discretion

6.3.2 Dose Delays

Therapy may be held at physician discretion and can continue on study drug when recovered from toxicity as long as they are benefitting from the trial.

6.3.3 Retreatment Criteria

Subsequent cycle of therapy will be initated when non hematology toxicity have recovered to Grade 1 or baseline. Hematology parameters to redose:

- ANC > 500.
- ***Platelet count > 50,000 cells/mm^3 for patients with < 50% of bone marrow plasma cells and platelet count > 25,000 cells/mm^3 for patients in whom > 50% of the bone marrow nucleated cells were plasma cells.***

6.4 Maintenance Therapy

Maintenance therapy consists of lenalidomide at the dose level tolerated at the completion of cycle 8 and thalidomide at 50 mg daily. Dexamethasone may be continued in the maintenance phase at physician discretion. Patients unable to tolerate either lenalidomide or thalidomide in combination during the maintenance phase may continue on either agent at the investigators discretion.

6.5 Screening

The following screening procedures must be performed within 28 days prior to study entry:

- Subjects who are potentially eligible for study participation must sign an informed consent form prior to the undertaking of screening procedures for this study.
- Inclusion and exclusion criteria are reviewed and documented .
- Multiple myeloma diagnosis will be confirmed and the stage at original diagnosis according to the International Staging System (ISS) and current disease status will be documented if data is available.
- Complete medical history will be obtained to include documentation of all treatments given for multiple myeloma and all concomitant medications used in the prior 4 weeks.
- Physical examination to include measurement of vital signs, height, weight.
- 12-lead ECG
- Directed neurologic examination will be performed, and questioning for symptoms of paresthesia and numbness.
- Clinical laboratory tests: Blood chemistry [sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, aspartate transaminase (SGOT/AST), glutamic pyruvic transaminase (SGPT/ALT), lactate dehydrogenase (LDH), B2-microglobulin
- Hematology: hemoglobin, hematocrit, white blood cell (WBC) count and differential, and platelet count.
- Serum or urine pregnancy tests (sensitivity of at least 50 mIU/mL), for females of childbearing potential (WCBP) must be completed. The first test should be performed within 10 – 14 days, and the second test within 24 hours prior to initiation of lenalidomide. Appendix A for more details and for the definition of females of childbearing potential in use for this trial.
- Serum sample for FreeLite™ Testing.
- M component quantification by immunoelectrofixation from serum (SPEP) and 24 hour urine collection for paraprotein measurement (UPEP), SIFE, and UIFE
- Bone marrow aspiration and biopsy to be evaluated for morphology and for cytogenetics by standard banding and FISH (suggested probes include, at a minimum del 13q14, t(4,14), t(14,16), and del 17p).
- Skeletal survey by roentgenograph for quantification of bone lesions with magnetic resonance imaging (MRI) and CT scans as clinically indicated.
- Multiple-symptom assessment tool.
- Serum Cytokines

6.6 Patient enrollment and Registration

Patients are to be registered by the research coordinator. The checklist will be verified and a subject number will be assigned.

6.7 On-study evaluations

Subjects who meet eligibility criteria will be enrolled into the study, and will be assigned a patient number.

Cycle one patients will be followed weekly on Cycle 1, Day 8, 15, 22 (+/- 3 days):

- Clinical laboratory tests: Blood chemistry [sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, aspartate transaminase (SGOT/AST), glutamic pyruvic transaminase (SGPT/ALT), lactate dehydrogenase (LDH)
- Hematology: hemoglobin, hematocrit, white blood cell (WBC) count and differential, and platelet count.
- Symptom directed physical examination/vitals

Day 1+/- 7 days of each cycle of therapy (starting with cycle 2):

- Standard myeloma restaging studies including SPEP, UPEP, Free Light Chain measurements (SIFE, UIFE and Bone Marrow biopsy will be done at time of suspected complete remission to document complete remission). MRI and skeletal surveys will be done as clinically indicated to follow the disease.
- Directed neurologic examination will be performed,and questioning for symptoms of paresthesia and numbness.
- Physical Examination
- Clinical laboratory tests: Blood chemistry [sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, aspartate transaminase (SGOT/AST), glutamic pyruvic transaminase (SGPT/ALT), lactate dehydrogenase (LDH)
- Hematology: hemoglobin, hematocrit, white blood cell (WBC) count and differential, and platelet count.
- 12 lead EKG
- Patients will be evaluated for AEs at each visit with the NCI CTCAE v3.0 used as a guide for the grading of severity.
- Multiple-symptom assessment tool (also known as the MDASI).
- Blood sample for Serum Cytokines every even cycle.

An unscheduled visit can occur at any time during the study. Source must be maintained for these unscheduled visits.

Multiple-symptom assessment tool.(Also known as MDASI)

Symptoms will be measured by the MM module of the MDASI (MDASI-MM). The MDASI is a multiple-symptom measure of cancer-related symptoms (Cleeland et al., 2000) that is sensitive to disease and treatment changes (Cleeland et al., 2004). This instrument is brief, easily understood, and validated in the cancer population. Patients rate the intensity of physical, affective, and cognitive symptoms on 0–10 numeric scales, ranging from "not present" to "as bad as you can imagine." Patients also rate the amount of interference with daily activities caused by symptoms on 0–10 numeric scales, ranging from "did not interfere" to "interfered completely." The MDASI-MM has 6 additional items known to be important in assessing patients with MM or MM therapies (constipation, diarrhea, rash, muscle weakness, mouth or throat sores, and poor concentration). The MDASI-MM takes less than 5 minutes to complete. Symptom severity and interference will be the variables of primary interest.

Serum Cytokines

Serum will be obtained on day 1 of each even cycle for measurements of proinflammatory and anti-inflammatory cytokines to correlate to symptom measurements using the MDASI.

Five milliliters of blood will be drawn by vacutainer system into red-top tubes without anticoagulant. Next, the tube will be removed from the refrigerator, and spun at 2000 rpm for 10 minutes at room temperature. The serum is aspirated with a sterile disposable Pasteur pipet and 0.5-mL aliquots are dispensed into each of 3 Nunc (or equivalent) 1-mL cryopreservation tubes. The tubes are labeled with subject's study number, date of phlebotomy, volume of serum in tube, initials of phlebotomist, and date. The location of the tube in the freezer will be recorded.

Cytokines to be measured include proinflammatory and anti-inflammatory cytokines including IL-1ra, IL-2, IL-6, TNF-a, sTNF-R1, and sTNF-R2 (Lee et al., 2004), the acute-phase response protein CRP, and a transcriptional factor (p50/p65 of NF-kB) that has been appreciated as a factor regulating IL-6 expression *in vivo* in an MM cell line study (Chiang & Stadtmauer, 2004).

The most commonly used assay to measure cytokines is the enzyme-linked immunosorbent assay (ELISA). However, this assay requires a significant volume of sample that may not always be available due to clinical

concerns and institutional guidelines for the maximum volume of blood that can be drawn for research purposes from a patient over a defined period of time. To address this issue, we have implemented another assay system, the flow cytometry-based Luminex Multiplex Cytometric Bead Array (Multiplex) assay, which requires little serum. In addition, the advantage that the Multiplex has over the ELISA is its ability to measure up to 25 cytokines in one run using a single sample, thereby providing relative concentrations among 25 cytokines and also minimizing the variance of the data. However, in some instances, the Multiplex assay may not be as sensitive as a high-sensitivity ELISA, which requires twice the volume of sample as routine ELISA.

Cellular studies for NFk-B expression: synthesis of cytokines and/or NF-kB expression by individual peripheral blood leukocytes (lymphocytes and monocytes) will be measured by flow cytometry. Specifically, we will measure the synthesis of IL-6, IL-10, IL-1β, and normal leukocytes using 3- or 4-color flow cytometry methods. Leukocytes from peripheral blood specimens will be cryopreserved for batch analysis at a later date.

Peripheral blood mononuclear cells (PBMC). At baseline and at the beginning of every even cycle PBMC will be isolated from 10 mL of peripheral blood drawn into a green-top tube using density gradient centrifugation (Ficoll-Hypaque) separation. Next, the PBMC pellet will be lysed for determination of active NFkB using the ELISA-based assay for NFkB p50 and p65 (Strassgen, Ann Arbor, MI). The assay is developed with a chemiluminescent substrate and the manufacturer-recommended procedure will be followed to obtain reliable assay results.

Maintenance Therapy Study Visits

Once a month during Maintenance Therapy, the following tests and procedures will be performed:

- Standard myeloma restaging studies including SPEP, UPEP, Free Light Chain measurements (SIFE, UIFE and Bone Marrow biopsy will be done at time of suspected complete remission to document complete remission)
- Clinical laboratory tests: Blood chemistry [sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, aspartate transaminase (SGOT/AST), glutamic pyruvic transaminase (SGPT/ALT), lactate dehydrogenase (LDH)
- Hematology: hemoglobin, hematocrit, white blood cell (WBC) count and differential, and platelet count.

End-of-Study Visit

If you go off study for any reason, you will have an end-of-study visit. This is usually done about 30 days after the last dose of the study drugs. At this visit, the following tests and procedures will be performed:

You will have a physical exam, including measurement of your vital signs and weight.

- Standard myeloma restaging studies including SPEP, UPEP, Free Light Chain measurements (SIFE, UIFE and Bone Marrow biopsy will be done at time of suspected complete remission to document complete remission)
- Clinical laboratory tests: Blood chemistry [sodium, potassium, chloride, CO_2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, aspartate transaminase (SGOT/AST), glutamic pyruvic transaminase (SGPT/ALT), lactate dehydrogenase (LDH)
- Hematology: hemoglobin, hematocrit, white blood cell (WBC) count and differential, and platelet count.

Follow-Up

Subjects who discontinue treatment for any reason, will be followed for 30 days. At treatment discontinuation, subjects will undergo a safety assessment approximately 30 days post the last dose of study drug.

Treatment is to be continued and patients will be followed until progression of disease. Patients eligible for and wishing to pursue stem cell transplant will receive at least 2 courses of therapy and will be followed until stem cell transplant, progression of disease, or treatment failure.

Treatment failure will be defined by progression of disease.

Response and progression will be evaluated in this study using the International uniform response criteria for multiple myeloma (Appendix D).

6.8 Drug Administration

6.8.1 Lenalidomide Administration

For all cycles, lenalidomide will be given as a single daily oral dose on Days 1-21 followed by 7-day rest period. The dose will be specified for each cohort in phase 1 portion. Lenalidomide is an oral drug supplied in capsules. Administration of Lenalidomide will be in the evening at approximately the same time each day (Days 1-21 followed by 7-day rest). If a dose of lenalidomide is missed or vomited, the patient should continue with the regular schedule of the drug at the next dose, and a missed dose should NOT be made up.

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

6.8.2 Dexamethasone Administration

For cycles 1-2 Dexamethasone will be given as a single daily oral dose of 40mg/day on Days 1-4, 9-12, and 17-20. If a dose of dexamethasone is missed or vomited, the patient should continue with the regular schedule of the drug at the next dose.

For cycles beyond 2, dexamethasone 40 mg/day will be given on days 1, 8, 15, and 22.

In the last cohort of 10 patients enrolled in the phase II, who were lenalidomide refractory, dexamethasone will be dosed weekly starting from cycle 1.

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Dexamethasone should be taken at approximately the same time each day. Each dose of dexamethasone should be taken with food.

6.8.3 Thalidomide Administration

Thalidomide will be administered orally daily each 28-days cycle. The dose of thalidomide will be specified by each dose level. The dose may be reduced for individual patients in subsequent cycles depending on toxicity. Treatment will be administered on an outpatient basis.

6.8 Concomitant therapy

Lenalidomide and thalidomide both increase the risk of thrombotic events in patients especially in patients who are at high risk or with a history of thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide and thalidomide is combined with other agents such as steroids (e.g.

dexamethasone, prednisone), anthracyclines (doxil, adriamycin) and erythropoeitin the risk of thrombosis is increased.

1. All patients will receive anticoagulation with either low molecular weight heparin (LMWH) (dose adjusted) or warfarin (INR 2-3) if platelets > 50,000. If the platelet count is less than 50,000, and full dose anticoagulation is contraindicated, prophylactic dose of LMWG or aspirin 325 mg po daily may be substituted. For patients who are no longer taking dexamethasone and on maintenance with only single agent therapy may discontinue anticoagulation and use only aspirin.

2. All patients will be given a proton pump inhibitor or H2-blocker for gastric prophylaxis.

6.9 Treatment Compliance
To monitor treatment compliance, reconciliation of lenalidomide and thalidomide capsules will be done at each visit.

6.10 Prohibited concomitant therapy
Concomitant use of other anti-cancer therapies, is not permitted while subjects are receiving study drug during the treatment phase of the study.

6.11 Instructions for dose modifications or interruption during a cycle

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v3.0 used as a guide for the grading of severity. The following tables in Appendix C are suggested modification criteria but not required and dose modification will be physician discretion.

6.12 Discontinuation of Study Treatment

Treatment will continue until the occurrence of any of the following events.

- Disease progression
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death
- Suspected pregnancy

Any patient who receives at least one cycle of therapy will be included in the safety analysis.

7.0 Statistical Consideration

This is an open label, phase I/II clinical trial to evaluate the safety and efficacy of lenalidomide, thalidomide, and dexamethasone in patients with relapsed/refractory multiple myeloma. The maximum number of patients that will be recruited for the study is 64.

Phase I design:

The objective of the phase I portion is to determine the maximum tolerated dose (MTD) of the combination regimen of lenalidomide, thalidomide, and dexamethasone. There are four predefined dose levels for lenalidomide, thalidomide, and dexamethasone, and the first cohort of patients will be treated at the second dose (Dose Level 1).

Dose Level	Assigned Therapy
Level -1	15 mg Lenalidomide daily on days 1-21 followed by 7-day rest every 28 days 50 mg Thalidomide daily 40 mg dexamethasone *
Level 1	15 mg Lenalidomide daily on days 1-21 followed by 7-day rest every 28 days 100 mg Thalidomide daily 40 mg dexamethasone*
Level 2	25 mg Lenalidomide daily on days 1-21 followed by 7-day rest every 28 days 100 mg Thalidomide daily 40 mg dexamethasone*
Level 3	25 mg Lenalidomide daily on days 1-21 followed by 7-day rest every 28 days 200 mg Thalidomide daily 40 mg dexamethasone

Dose limiting toxicity (DLT) is defined as in the treatment plan. To find the MTD, a statistical design based on a Bayesian model described in Ji, Li, and Bekele (2006) will be used. The details of the design are described below.

Let p_i denote the toxicity probabilities for dose *i=1, 2, 3, and 4*. The goal is to accurately estimate the probability of toxicity at the current tried dose level. Assuming a vague independent beta prior B(0.005, 0.005) for each p_i, with observed data(n_i, x_i), where n_i represents the number of patients treated at current dose and x_i represents the number of patients experienced DLTs, the posterior of p_i follows an independent B(0.005+ x_i, 0.005+ n_i - x_i) for *i=1, 2, 3, and 4*. Let

$$T_i = 1\{P(p_i > p_T \mid data) > \xi\}$$

We define the posterior probabilities of three possible actions as

$$q(D, i) = P(p_i > p_T + K_1\sigma_i \mid data)$$

$$q(S, i) = P(p_T - K_2\sigma_i \leq p_i \leq p_T + K_1\sigma_i \mid data)$$

$$q(E, i) = P(p_i < p_T - K_2\sigma_i \mid data) * (1 - T_i)$$

where D represents the action of de-escalating to next lower level, S represents staying at current dose and E represents escalating to next higher level, and σ_i is the posterior deviation of p_i. The dose-assignment rule Bi is defined as $Bi^{(e)} = arg\ max_{m \in (D,S,E)}\ q(m, i)$.

Based on dose-assignment rule $Bi^{(e)}$, a dose-finding algorithm is proposed as follows:

1) Suppose that Dose 1 is a dose that has been tried previously. If $T_i = 1$, terminate the trial due to excessive toxicity. Otherwise, terminate the trial when the maximum sample size is reached.

2) At current tried dose i, the decision to select the dose for next cohort are among $\{(i-1), i, (i+1)\}$ based on the assignment rule. There are two exceptions, however: if i=1, the next available doses are {1, 2}; if i=4, the next available doses are {3, 4}.

3) At the end of the trial, the dose with the smallest absolute value of (*posterior mean of pi-pT*) among all the tried doses i for which Ti=0 will be selected as the MTD.

Let ξ =0.95, K_1=1 and K_2=1.5. Starting at Dose Level 1 (the second dose), the trial will enrol patients in a cohort size of three. The maximum sample size is 18 and the MTD has a probability of toxicity p_T=0.4. Table 1 presents the monitoring rules for each dose and Table 2 presents the operating characteristics of the proposed design under six toxicity scenarios. When MTD is among the doses studied (Scenarios 1, 2, and 3), this dose will be selected with the highest probability and the number of patients treated at this dose will be the largest among all doses. If all the Dose levels turn out to be too toxic (Scenario 6), the chances of these doses being selected are very low and most of the few patients treated will be at the lowest dose level. On the other hand, if all the Dose levels are below the MTD (Scenario 5), the highest dose will be chosen with the highest probability and most patients will be treated at the highest dose.

Table 1. Dose-finding trail-monitoring chart

Number of toxicities	Number of patients treated at current dose																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
0	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E	E
	D																	
1	U	S	S	S	E	E	E	E	E	E	E	E	E	E	E	E	E	E
		D																
2		U	D	S	S	S	S	S	E	E	E	E	E	E	E	E	E	E
			D															
3			U	D	D	S	S	S	S	S	S	S	E	E	E	E	E	E
				D	D													
4				U	U	D	D	S	S	S	S	S	S	S	S	E	E	E
					D	D	D											
	5				U	U	U	D	D	S	S	S	S	S	S	S	S	S
						D	D	D	D									
	6					U	U	U	U	D	D	S	S	S	S	S	S	S
							D	D	D	D								
	7						U	U	U	U	D	D	D	S	S	S	S	S
								D	D	D	D	D						
	8							U	U	U	U	U	D	D	D	S	S	S
									D	D	D	D	D	D				
	9								U	U	U	U	U	U	D	D	D	S
										D	D	D	D	D	D	D		
	10									U	U	U	U	U	U	U	D	D
											D	D	D	D	D	D	D	D
11											U	U	U	U	U	U	U	U
												D	D	D	D	D	D	D
12												U	U	U	U	U	U	U
													D	D	D	D	D	D
13													U	U	U	U	U	U
														D	D	D	D	D
14														U	U	U	U	U
															D	D	D	D
15															U	U	U	U
																D	D	D
16																U	U	U
																	D	D
17																	U	U
																		D
18																		U

E = Escalate to next higher dose

S = Stay at current dose

D = De-escalate to next lower dose

U = Current dose is unacceptable

Table 2. Operating characteristics

Scenario		Dose -1	Dose 1	Dose 2	Dose 3	Total # of Pts	Overall Toxicity
1	**Toxicity Rate**	***0.4***	0.55	0.65	0.65	17.568	0.535121
	Chance Selected	0.507	0.313	0.08	0.015		
	# of Pts Treated	5.799	6.069	5.322	0.378		
2	**Toxicity Rate**	0.05	0.1	***0.4***	0.6	18	0.366222
	Chance Selected	0.002	0.17	0.703	0.125		
	# of Pts Treated	0.432	3.321	11.718	2.529		
3	**Toxicity Rate**	0.05	0.1	0.15	***0.4***	18	0.287222
	Chance Selected	0	0.003	0.232	0.765		
	# of Pts Treated	0.012	0.48	7.164	10.344		
4	**Toxicity Rate**	0.2	0.35	0.55	0.6	17.979	0.435675
	Chance Selected	0.12	0.53	0.322	0.025		
	# of Pts Treated	2.073	7.074	7.941	0.891		
5	**Toxicity Rate**	0.05	0.1	0.15	0.2	18	0.184056
	Chance Selected	0	0.005	0.114	0.881		
	# of Pts Treated	0.03	0.315	5.991	11.664		
6	**Toxicity Rate**	0.5	0.6	0.65	0.7	17.16	0.574242
	Chance Selected	0.492	0.233	0.078	0.004		
	# of Pts Treated	6.216	5.283	5.388	0.273		

Phase II design:

During the phase II portion of the study, patients will be treated with lenalidomide, thalidomide, and dexamethasone in combination at the MTD established in the phase I portion. Furthermore, the patients treated at the MTD in the phase I portion of the study will be considered the first patients of the phase II portion. It is anticipated that at least 6 patients will be treated at the MTD in the phase I and will be later included in the analysis of the phase II portion.

Response will be assessed after 4 cycles of therapy.

The overall response and toxicity will be monitored simultaneously using the Bayesian approach of Thall, Simon, Estey (1995, 1996) as extended by Thall and Sung (1998). Historical data on similar patients show an overall response rate (ORR) of 30% and toxicity rate of 30%. However, the information was down-weighted to reflect the same marginal ORR and toxicity rates in 2 patients. Independence was assumed between OR and toxicity. It is expected for the current trial that the three-drug combination will improve the ORR to 50% while the toxicity rate is maintained at 40%. A sample size of 36 ensures that, if the trial is not terminated early, a posterior 90% credibility interval for overall response rate will have width of 0.26 at most, under the assumption of a 50% of ORR. The probabilities of OR and toxicity for the historical data are modeled by beta distributions (*Beta*(3, 7) and *Beta*(3, 7), respectively). The prior probabilities of OR and toxicity for the experimental regimen are also modeled by beta distributions (*Beta*(0.6, 1.4) and *Beta*(0.6, 1.4), respectively), which have the same *a/b* (*a* and *b* denote the parameters for a *Beta* distribution) ratio as the beta distributions for the historical data. Denoting the historical probabilities of overall response rate and toxicity rate by {p(OR,H) , p(TOX,H)}, the following decision criteria will be applied:

1) Let E correspond to the experimental treatment, stop if
   Prob{p(OR,H) $+ \delta_{OR}$ > p(OR,E) | data} > 0.90, where δ_{OR} =0.20
2) Stop if Prob{p(TOX,H) $+ \delta_{TOX}$ < p(TOX,E)| data}>0.85, where δ_{TOX} =0.10

Patients will be monitored according to the following stopping boundaries for overall response.

Number of patients evaluated	Recommend stopping if ≤ OR observed
12	3
24	7
36	11

At the same time, patients will be monitored according to the following stopping boundaries for toxicity.

Among these number of patients	Recommend stopping if ≥ toxicity observed
12	8
24	15
36	22

The operating characteristics are summarized in the following table (based on simulations from 10,000 trials).

True Toxicity Rate	True OR Rate	Prob(stop the trial early)
0.1	0.3	0.654
	0.4	0.296
	0.5	0.086

	0.6	0.016
	0.7	0.002
0.25	0.3	0.655
	0.4	0.298
	0.5	0.089
	0.6	0.019
	0.7	0.005
0.4	0.3	0.677
	0.4	0.343
	0.5	0.147
	0.6	0.082
	0.7	0.068
0.55	0.3	0.795
	0.4	0.583
	0.5	0.225
	0.6	0.417
	0.7	0.409

Analysis Plan

Summary statistics will be provided for continuous variables. Frequency tables will be used to summarize categorical variables. Logistic regression will be utilized to assess the effect of patient prognostic factors on the response rate and the toxicity rate. The distribution of time-to-event endpoints will be estimated using the method of Kaplan and Meier. Comparison of time-to-event endpoints by important subgroups will be made using the log-rank test. Cox proportional hazard regression will be employed for multivariate analysis on time-to-event outcomes.

8.0 Standard Monitoring Plan

Safety
The primary study objective is to determine the MTD of the combination of lenalidomide, thalidomide and dexamethasone in relapsed/refractory MM patients. The type, frequency, severity, and relationship of adverse events to combination therapy will be ranked. Dose limiting toxicity (DLT) is defined previously and toxicity graded according to the NCI Common Terminology Criteria for Adverse Events v3.0. Dose adjustments will be made as described in the study design. The trial will be monitored by the PI with weekly meetings with the research nurse and data coordinator.

Safety Assessments
Safety assessments will consist of monitoring and recording all adverse events and serious adverse events, the regular monitoring of hematology, blood chemistry and urine values, regular measurement of vital signs and the performance of physical examinations.

9.1 Adverse Events

9.2 Serious Adverse Event (SAE) Definition

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

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

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

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

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

9.3 Adverse Drug Reaction Reporting

Toxicity will be scored using CTCAE Version 3.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 3.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas have access to a copy of the CTCAE Version 3.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

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

9.4 Pregnancies

Pregnancies occurring while the subject is on lenalidomide or within 4 weeks after the subject's last dose of lenalidomide are considered expedited reportable events. If the subject is on lenalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of the study 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 the study drug should also be reported.

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

9.3.1 Celgene Drug Safety Contact Information:

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

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

9.4 Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements.

IND Annual Reports
If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in

the report. The Annual Report should be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

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

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

9.4.1 Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using any of the following forms, Celgene SAE form, MD Anderson SAE form, FDA 3500A or MEDWATCH form. of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. This must be documented on The written report must be completed and supplied to Celgene 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 protocol number (RV-MM-PI -0199) as well as the institutional protocol number (2008-0462) should be included on SAE reports (or on the fax cover letter) 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.

9.4.2 Report of Adverse Events to the Institutional Review Board

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

9.4.3 Investigator Reporting to the FDA

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

9.4.4 Adverse event updates/IND safety reports

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

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

- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

The Investigator shall notify his/her IRB/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.

10 Protocol Amendments/Deviations

10.1 Protocol amendments

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

10.2 Protocol deviations

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

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

10.3 Investigator responsibilities

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 monitoring visits and 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 monitoring visits to review data and resolve any queries and to allow direct access to the subject's records (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification. The data collection must be completed prior to each visit and be made available to the Celgene representative so that the accuracy and completeness may be checked.

11.1 Regulatory Considerations

11.2 Institutional Review Board/Ethics Committee approval

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

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

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

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

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

11.3 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.

11.4 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 Celgene's representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

Should direct access to medical records require a waiver or authorization separate from the subject's statement of informed consent, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

11.5 Study records requirements

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

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

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. The risks to a fetus are not known. However, because lenalidomide is related to thalidomide, and thalidomide is known to cause severe birth defects, the following requirements must be observed.

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

Females of childbearing potential (FCBP)[†] must agree to use two reliable forms of contraception simultaneously or to practice complete abstinence from heterosexual intercourse during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; and 3) for at least 28 days after discontinuation from the study. The two methods of reliable contraception must include one highly effective method (i.e. intrauterine device (IUD), hormonal [birth control pills, injections, or implants], tubal ligation, partner's vasectomy) and one additional effective (barrier) method (i.e. latex condom, diaphragm, cervical cap). FCBP must be referred to a qualified provider of contraceptive methods if needed.

Before starting study drug:

Female Subjects:

- FCBP must have two negative pregnancy tests (sensitivity of at least 50 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

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

Male Subjects:

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

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

All Subjects:

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

Female Subjects:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for

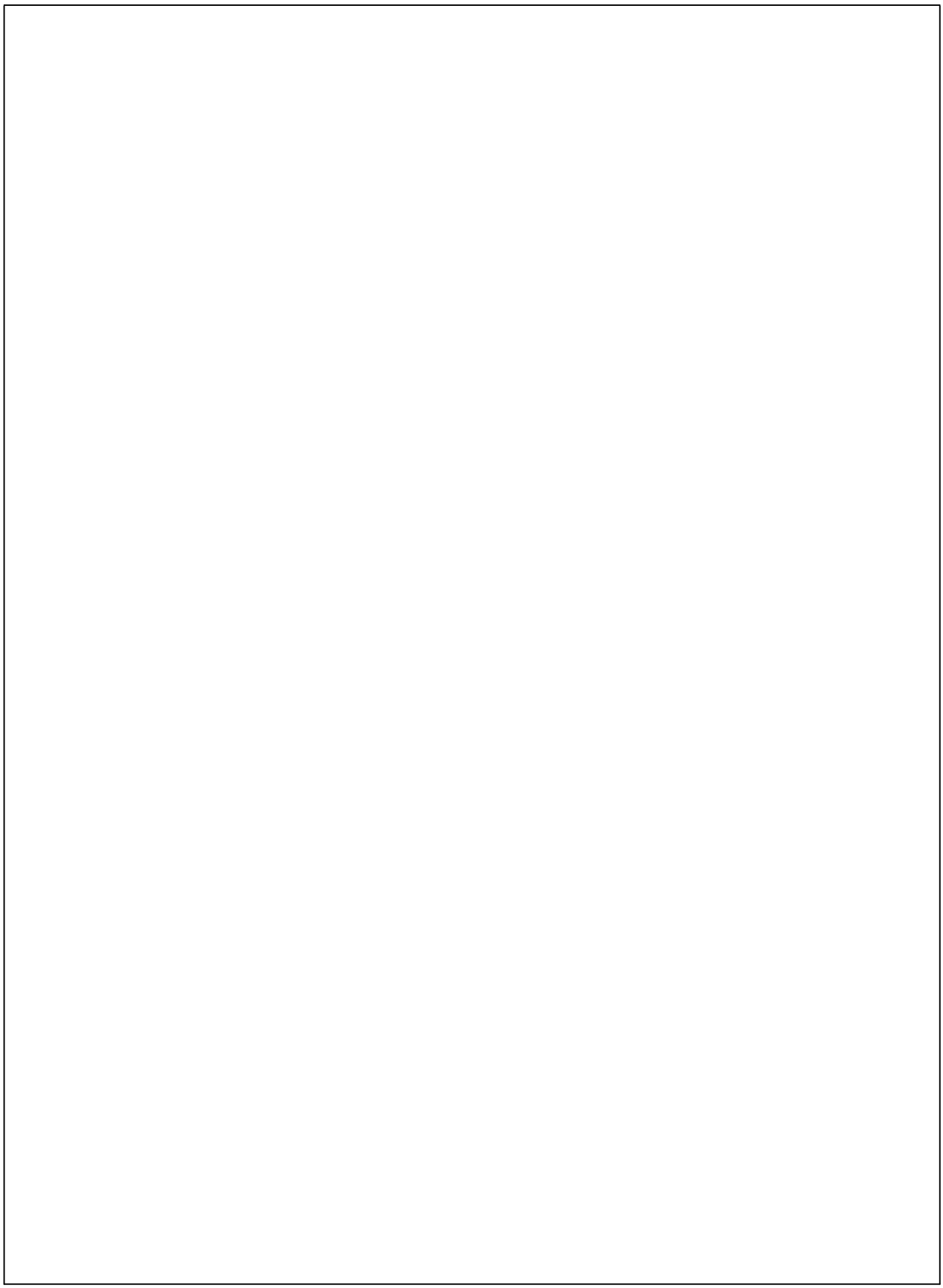
the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study.

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

Male Subjects:

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

Appendix B: Suggested Dose Modification Guidelines



NCI CTC Toxicity Grade	Day 2-14 of Cycle	≥Day 15 of Cycle
Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia	• Hold (interrupt dose). • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remainder of cycle If neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the dose maintained for the next cycle at the investigators discretion.
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³) *If patient starts at a platelet count of 50,000/mm^3 then follow these guidelines if platelets drop < 30,000 mm^3	• Hold (interrupt dose). • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remainder of cycle
Non-blistering rash Grade 3 Grade 4	• If Grade 3 hold (interrupt) dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. • Discontinue lenalidomide study drug.	• Omit lenalidomide for remainder of cycle. • Discontinue lenalidomide study drug.
Desquamating (blistering) rash- any Grade	• Discontinue lenalidomide study drug.	• Discontinue lenalidomide study drug.
Erythema multiforme ≥ Grade 3	• Discontinue lenalidomide study drug.	• Discontinue lenalidomide study drug.
Sinus bradycardia/ other cardiac arrhythmia Grade 2 ≥ Grade 3	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. • Discontinue lenalidomide study drug.	• Omit lenalidomide for the remainder of the cycle. • Discontinue lenalidomide study drug.
Allergic reaction or hypersensitivity Grade 2-3 Grade 4	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21. • Discontinue lenalidomide study drug.	• Omit lenalidomide for the remainder of the cycle. • Discontinue lenalidomide study drug
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) dose and start anticoagulation; restart at investigator's discretion (maintain dose level).	• Omit lenalidomide for remainder of cycle and start anticoagulation.

other non-hematologic toxicity assessed as LENALIDOMIDE-related ≥ Grade 3	• Hold (interrupt) dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21 restart at next lower dose level and continue the cycle until Day 21.	• Omit lenalidomide for remainder of cycle.
Hyperthyroidism or hypothyroidism	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).	• Omit lenalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart lenalidomide next cycle (decrease dose by one dose level).

Dose modifications for Dexamethasone

Table 3: Dexamethasone Dose Modification

NCI Toxicity Grade	Toxicity	Action
Grade 1/2	Dyspepsia, gastric or duodenal ulcer or gastritis	▪ Treat with H2 blockers, sucralfate or omeprazole ▪ If symptoms persist decrease dose by 1 dose level as needed
≥ Grade 3	Dyspepsia, gastric or duodenal ulcer or gastritis	▪ Hold until symptoms controlled ▪ Restart by decreasing dose by 1 dose level and add H2 blockers, sucralfate or omeprazole
≥ Grade 3	Edema	▪ Decrease dose by one dose level ▪ Use diuretics as needed
≥ Grade 2	Confusion or mood alterations	▪ Hold until symptoms resolved ▪ Restart dosing by decreasing dose down1 dose level
≥ Grade 2	Muscle weakness	▪ Decrease dose by 1 dose level ▪ If symptoms persist then decrease by dosing by 1 dose level as needed
≥ Grade 3	Hyperglycemia	▪ Decrease dose by 1 dose level ▪ Treat with insulin or oral hypoglycemics as needed
≥ Grade 3	Acute pancreatitis	▪ Discontinue subject from dexamethasone

Side effects associated with high-dose dexamethasone therapy include the following:

- Gastrointestinal: nausea, vomiting, anorexia, increased appetite, weight gain, aggravation of peptic ulcers
- Dermatologic: rash, skin atrophy, facial hair growth, acne, facial erythema, ecchymoses
- Genitourinary: menstrual irregularities, amenorrhea
- Neurologic: insomnia, euphora, psychosis, headache, vertigo, depression, seizures, muscle weakness
- Cardiovascular: fluid retention, edema, hypertension, thrombophlebitis
- Ocular: cataracts, increased intraocular pressure, exophthalmos
- Metabolic: hyperglycemia, aggravation or precipitation of diabetes mellitus, adrenal suppression (with Cushingoid features), hypokalemia
- Hematologic: leukocytosis
- Other: osteoporosis, infection (including herpes zoster, varicella zoster, fungal infections, pneumocystis carinii, tuberculosis), muscle wasting, delayed wound healing, and suppression of reactions to skin tests.

Dexamethasone may be dose modified due to toxicity at the discretion of the treating physician as follows:

- Starting dose: dexamethasone 40 mg by mouth on days 1-4, 9-12 and 17-20 of each 28 day treatment cycle for cycle 1.

- During Cycle 2, 20 mg by mouth on days 1-4, 9-12, and 17-20.
  For all cycles beyond 2:
- Dose level -1: dexamethasone 20 mg/m^2 po on Days 1, 8, 15 and 22.
- Dose level -2: dexamethasone 20 mg po on Days 1, 8, 15, and 22.
- Dose level -3: dexamethasone 20 mg po on Days 1 and 15.

Dose Modification Guidelines for Thalidomide:

1. Grade 1-2 AE the dose will be continued at the investigators discretion.
2. Grade 3 or higher AEs related to study drug, dose will be held until AE returns to grade 2 or less. If grade 3 AE occurs a second time the dose will be held until the AE decreases to grade 2 or less. Thalidomide will be restarted at 50% of previous dose. If grade 3 AE occurs a third time drug will be discontinued and the pt followed until the AE resolves or stabilizes.
3. For neurotoxicity for grade 2 toxicity or higher, hold drug until symptoms subside to baseline, grade 1 or less and then Thal may be restarted at 50% of previous dose. If neuropathy develops again with either Thal another 50% reduction can occur after symptoms resolve to 50 mg every day or every other day.
4. For grade 2 constipation Senna will be added to sodium docusate.
5. For somnolence the dose of Thalidomide should be held until sympotoms resolve and then will be reduced 50%.

International Myeloma Working Group uniform response criteria:

Response Subcategory	*Response criteria*
sCR	CR as defined below plus Normal FLC ratio and Absence of clonal cells in bone marrow[b] by immunohistochemistry or immunofluorescence[c]
CR	Negative immunofixation on the serum and urine and Disappearance of any soft tissue plasmacytomas and ≤ 5% plasma cells in bone marrow[b]
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis of 90% or greater reduction in serum M-protein plus urine M-protein level < 100 mg per 24 h
PR	≥ 50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to < 200 mg per 24h If the serum and urine M-protein are unmeasurable,[d] 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 assay is also unmeasurable, ≥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 listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR or progressive disease

Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.

[a] All response categories require two consecutive assessments made at anytime before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.

[b] Confirmation with repeat bone marrow biopsy not needed.

[c] Presence/absence of clonal cells is based upon the < /< ration. An abnormal < << ration by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ration reflecting presence of an abnormal clone is << < of >4:1 or <1:2.

[d] Refer to Table_____for definitions of measurable disease.

International Myeloma Working Group uniform response criteria: disease progression and relapse

Relapse subcategory	*Relapse criteria*
Progressive disease[a] To be used for calculation of time to progression and progression-free survival end points for all patients including those in CR (includes primary progressive disease and disease progression on or off therapy)	Progressive Disease: requires any one 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)[b] Urine M-component and/or (the absolute increase must be ≥200 mg/24h 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%[c] 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[a]	Clinical relapse requires one or more of: Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)[b] It is not used in calculation of time to progression of progression-free survival but is listed here as something that can be reported optionally or 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 a 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 of > 2 g/dl [1.25 mmol/l] (see Table 3 for further detials) Rise in serum creatinine by 2 mg/dl or more [177 < mol/l or more]
Relapse from CR[a]	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[c] Appearance of any other sign of progression (i.e.,new plasmacytoma, lytic bone lesion, or hypercalcemia see below)

Abbreviations: CR, complete response; DFS, disease-free survival.

[a] All relapse categories require tow consecutive assessments made at anytime before classification as relapse or disease progression and/or the institution of any new therapy.

[b] for progressive disease, serum M-component increases of ≥1 gm/dl are sufficient to define relapse if starting M-component is ≥5 g/dl.

[c] Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.

[d] For purposes of calculating time to progression and progression-free survival, CR patients should also be evaluated using criteria listed above for progressive disease.