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A Phase II Clinical Trial of Lenalidomide Intensification in Patients with Serologic/Asymptomatic Progression of Multiple Myeloma While on Lenalidomide Maintenance

PROTOCOL FACE PAGE FOR MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

1.1 Background and Rational

The standard first line therapy for patients with multiple myeloma includes 2 phases: An *initial* treatment, which usually consists of a combination of several drugs given for 3 to 6 cycles, followed by *consolidation* with autologous stem cell transplantation using high dose melphalan (HDM/ASCT). In recent years, the HDM/ASCT consolidation phase has often been replaced by a continuous phase, in which some or all the drugs used as initial treatment are continued beyond the initial 3-6 cycles. Lenalidomide is often chosen for this continuous phase, due to its convenient oral administration, becoming a continuous/maintenance treatment. In additions, two major large studies recently presented at the ASCO and ASH meetings in 2010, have emphasized the role of maintenance therapy with low dose lenalidomide after HDM/ASCT. Both studies have shown a statistically significant improvement in the progression free survival for patients receiving maintenance therapy with low dose lenalidomide after HDM/ASCT. Although the improvement in overall survival is currently not fully established (there is a trend toward increased OS), it is clear at this time that maintenance therapy post HDM/ASCT has been widely adopted by myeloma experts. Therefore, most patients who initiate therapy for multiple myeloma will remain on maintenance therapy with low dose lenalidomide as part of their initial treatment.

However, most of these patients will eventually progress while on lenalidomide therapy. Patients with “symptomatic progression of disease (POD)” defined by new symptomatic bone lesions, progressive anemia, hypercalcemia, or progressive renal failure attributable to the multiple myeloma, usually in association with a rise in the serum or urine paraprotein, will require re-induction therapy with combination chemotherapy to prevent further organ deterioration. However, the subset of patients with “serologic or asymptomatic POD”, i.e. whose only evidence of disease progression is an increase in the paraprotein level by $\geq$ 25% above plateau baseline, have a variable natural history with many patients not showing symptomatic progression for months. Based on the results of the initial phase I trial of lenalidomide in which higher responses were seen with higher doses of lenalidomide, we hypothesize that in patients relapsing on lenalidomide maintenance doses of 5-15 mg orally daily, the disease could be brought under control by increasing the dose of lenalidomide (intensification) to 25 mg. However, the response rates and tolerance of lenalidomide dose intensification in the setting of lenalidomide maintenance is unknown, which is the basis for the proposed clinical trial.

For the purpose of clarity, the term asymptomatic POD will be used henceforward to designate serologic only POD, while symptomatic POD will be used to designate POD associated with progression of organ damage.

1.2 Study Design and Objectives

The proposed study is designed as a Phase II, multi-center trial of lenalidomide intensification in patients with asymptomatic POD while on low dose lenalidomide maintenance after HDM/ASCT or as continuous/maintenance therapy after initial treatment. The primary objective of this trial is to determine the overall response rate (ORR) at 6 months and the toxicity of lenalidomide administered at a dose of 25 mg orally, days 1 to 21 of a 28 day-cycle, without or with dexamethasone added after 2 cycles, in patients with multiple myeloma found to have asymptomatic POD while on a maintenance lenalidomide dose of 15 mg daily or less.

1.3 Patients Eligibility

Patients with multiple myeloma with evidence of *asymptomatic POD* while on lenalidomide maintenance post HDT/ASCT or on continuous/maintenance therapy as part of first line therapy will be eligible to participate in this trial. Patients will need to have progression of disease documented as defined by modified IMWG criteria and will have no evidence of progression of organ damage (progression of severe anemia, renal failure, hypercalcemia, bone disease).

1.4 Treatment Intervention

After registration patients will begin therapy with lenalidomide 25 mg daily, 21 days out of a 28 day schedule. All patients will be evaluated monthly after every cycle. The dose will be adjusted downward in response to side effects and according to specific guidelines. Symptomatic POD occurring at any time during the study will result in removal of the patient from the study. After 2 cycles of lenalidomide, patients with at least stable disease (SD) will continue lenalidomide indefinitely until asymptomatic POD, at which time dexamethasone will be added at a dose of 40mg weekly. On the other hand, patient with asymptomatic POD after 2 cycles of lenalidomide will have dexamethasone added at a dose of 40 mg weekly. Patients with any type of POD after any cycle that includes dexamethasone will be taken off study. Patients can remain on study on lenalidomide or lenalidomide/dexamethasone indefinitely as long as they do not have POD as stated above and they tolerate the treatment.

1.5 Outcome Measurements

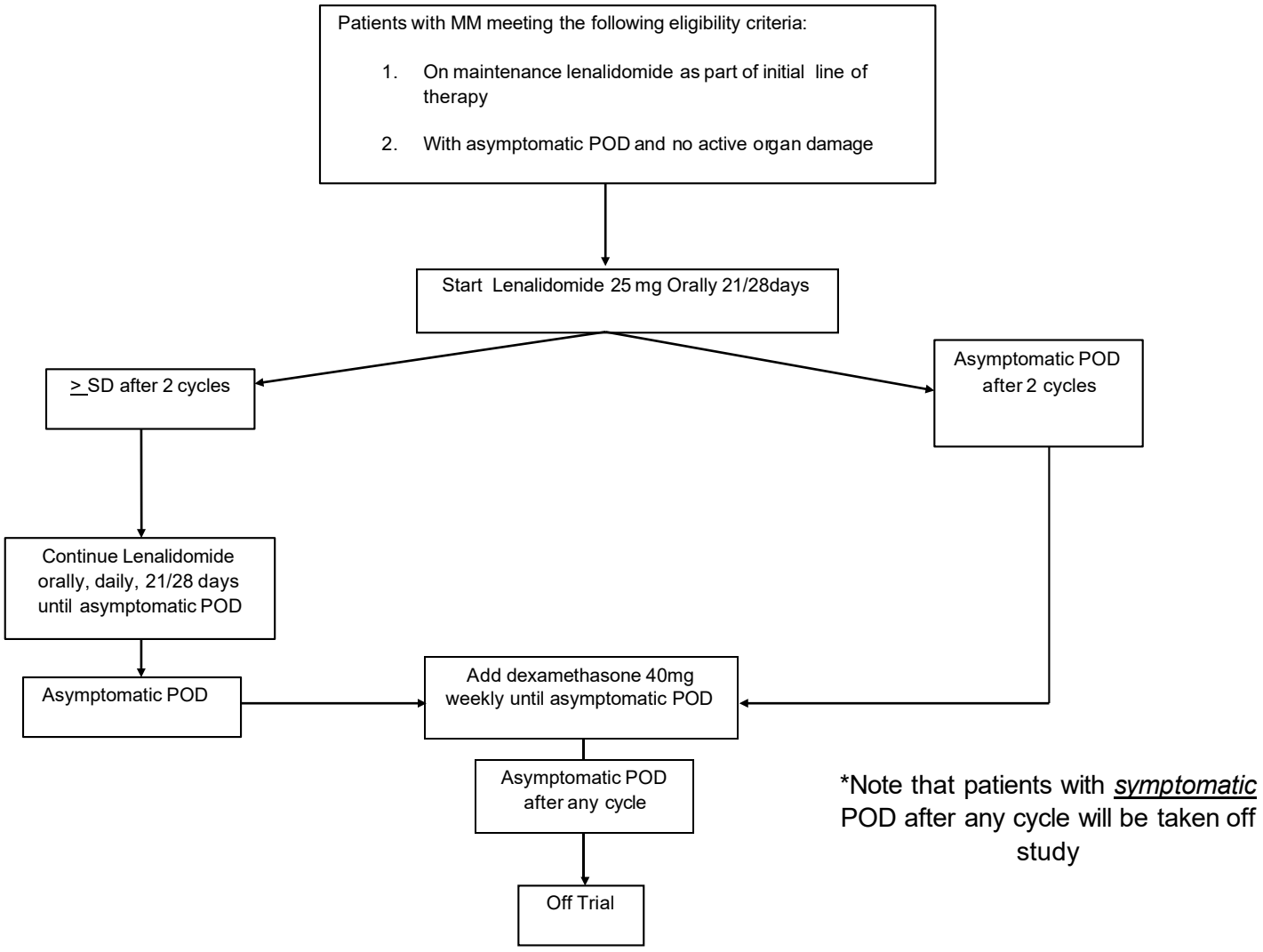
The response to treatment intervention will be measured using a modified version of the widely accepted Uniform International Response Criteria in multiple myeloma. To determine response, patients' disease will be assessed at the beginning of every cycle and compared to the new baseline established within two weeks prior to initiation of lenalidomide intensification.

1.6 Statistical Considerations

The focus of this study is to estimate the overall response rate (≥PR) to lenalidomide

intensification with or without dexamethasone at 6 months. A single stage design that differentiates between response rates of 15% and 30% will be used to assess efficacy of lenalidomide intensification with or without dexamethasone. The probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set to 0.10 and 0.10, respectively. The null hypothesis response rate is based on the response rate to the standard of care therapy in patients previously exposed to thalidomide who have relapsed or refractory disease. A total of 53 patients will be accrued. At the conclusion of the study, if a least 12 of the 53 patients respond by 6 months the treatment will be declared a success.

1.7 Study Schema



*Note that patients with ***symptomatic*** POD after any cycle will be taken off study

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary objective:

- To determine the overall response rate (CR, VGPR, PR, and MR) after 6 months of lenalidomide intensification administered initially at a dose of 25 mg orally days 1 to 21 of a 28 day-cycle, with or without the addition of dexamethasone, in patients with multiple myeloma found to have *asymptomatic* progression of their disease while on maintenance lenalidomide dose of 15mg mg daily or less.

Secondary objectives:

- To determine rates of ≥ Grade 2 toxicity according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0
- To determine the overall response rate (CR, VGPR, and PR) at 6 months from initiation of lenalidomide intensification therapy of lenalidomide given as a single agent.
- To determine progression free survival: The PFS is defined as the time from registration to relapse/progression, death, initiation of non-protocol anti myeloma therapy, loss to follow up or end of study whichever comes first.
- To determine OS: The OS is defined as the time from registration to death, loss to follow-up or the end of the study, whichever comes first. Patients alive at the time of last observation are considered censored.

3.0 BACKGROUND AND RATIONALE

3.1 Overview on Upfront Treatment of Multiple Myeloma

Multiple myeloma (MM) is a disease characterized by a malignant plasma cell proliferation, bone destruction and immunodeficiency. Median age at diagnosis is approximately 70 years. It is responsible for about 1 percent of all cancer-related deaths in Western Countries.[1-3] The disease accounts for an estimated 15,000 new cancer cases per year in the United States, as well as approximately 11,000 deaths[2]. Based on the United Kingdom (UK) Myeloma Forum and the Nordic Myeloma Study Group recommendations[1] and National Comprehensive Cancer Network (NCCN) Practice Guidelines[4], chemotherapy is indicated for the management of myeloma presenting with myeloma-related organ damage (referred to as *symptomatic* myeloma as opposed to *asymptomatic* myeloma). Standard first line treatment for patients with symptomatic multiple myeloma deemed eligible for transplantation, consists of 2 phases of treatment: The first is referred to as the *initial* therapy and consists of various combinations of therapeutic agents. The second consists of high dose melphalan followed by autologous stem cell transplant (HDM/ASCT)[5,6]. Attempts to *cure* myeloma through high-dose therapy followed by autografting or even allografting have largely failed due to both relapsed disease and treatment-related mortality (TRM).Although high-dose therapy with autologous transplantation is safe and has low TRM (< 5%), it is associated with a continuing and nearly universal risk of disease relapse and progression. Therefore, despite the potential benefits of newer treatments, multiple myeloma

remains an incurable disease and relapse occurs in almost all patients, with a median survival period of 5 to 7 years[5,6].

3.1.1 Initial therapy

The regimens currently recommended in the NCCN guidelines for initial therapy of MM in patients who are candidates for HDM/ASCT include dexamethasone, thalidomide and dexamethasone, Lenalidomide and dexamethasone, liposomal doxorubicin. Vincristine and dexamethasone (DVD), as well as several bortezomib based regimens[4]. In previously untreated patients, bortezomib has shown activity as a single agent[7-9] and also in combination with dexamethasone[7,10], thalidomide/dexamethasone[11,12], melphalan/prednisone (MP)[13,14], dexamethasone and adriamycin[15,16] as well as Lenalidomide and dexamethasone. It is widely accepted that in patients who will undergo HDM/ASCT, melphalan-containing regimens should be avoided since stem cell collection may be subsequently hampered.

3.1.2 Autologous Stem Cell Transplantation

There have been two large prospective trials in France (IFM 90) and in UK (MRC 9), and one large retrospective study of myeloma patients in Nordic countries, showing a survival benefit for HDM/ASCT compared to conventional chemotherapy[17-19]. In the larger study, IFM 90, newly diagnosed untreated patients less than 65 years of age with DS stage II or III MM were randomized to either SCT after up to 6 cycles of VMCP alternating with BCNU, vincristine, doxorubicin and prednisone (BVAP) or conventional chemotherapy with 18 cycles of VMCP alternating with BVAP. The SCT regimen was MEL 140 mg/m2 and TBI, and recombinant interferon alpha (IFNα) was administered to patients in both groups until relapse. By intent-to-treat, SCT patients had a significantly higher response rate (CR+VGPR 38% versus 14%) than those receiving conventional chemotherapy. At a median follow-up of 37 months in the chemotherapy group and 41 months in the SCT group, the latter had significantly longer PFS and OS. The other two studies have confirmed these results although the dose of melphalan given was 200 mg/m^2 and radiation therapy was not used. Based on these trials, autologous stem cell transplantation using melphalan 200 mg/m^2 has become part of the standard treatment of symptomatic multiple myeloma. Smaller studies have reached similar conclusions[6,20].

Although HDM/ASCT has improved response rate[6,17,18,20] and overall survival[17,18,20,21] rate in patients with MM, all patients eventually relapse. Clinical trials have investigated the use of consolidation[22] and maintenance[23-26] therapy post-transplant to extend the duration of response.

3.1.3 Post Transplant Maintenance Therapy

One approach to improving disease control after HDM/ASCT is the use of post-transplant interventions, such as interferon and, more recently, anti-angiogenic agents such as thalidomide and lenalidomide. The use of thalidomide as post-transplant maintenance has been studied in several randomized trials[24,25,27]. The IFM 99-02 trial randomized patients after tandem autologous transplantation (using melphalan 140mg/m^2 for the first and melphalan 200mg/m^2 for

the second transplant) to either no maintenance, maintenance with pamidronate or maintenance with thalidomide and pamidronate. Patients received thalidomide for a median of 15 months. The major treatment-related side effect was neuropathy (68% of patients). Patients who received thalidomide had improved EFS and OS. Of note, patients who achieved a VGPR after transplantation did not benefit from thalidomide maintenance[27]. This suggests that the benefit of post-transplant thalidomide might result from upgrading responses.

New immunomodulatory drugs (IMiDs®) such as lenalidomide are now commonly used in clinical practice. The side effect profile of lenalidomide is superior to that of thalidomide. In normal volunteers the most common adverse events with lenalidomide are rash and pruritus. Phase II trials of lenalidomide plus dexamethasone for upfront therapy of myeloma demonstrate high response rates[11]. Lenalidomide, a member of the new immunomodulatory class of drugs has recently demonstrated high-response rates and favorable side effect profile in upfront and salvage trials[28,29]. A Phase II trial at the Mayo Clinic used lenalidomide and dexamethasone as induction therapy. The overall response rate was 91%. The Phase III MM009 trial of lenalidomide and dexamethasone versus dexamethasone alone for relapsed/refractory MM reported response rates of 61% with combination therapy compared to 22% with dexamethasone alone.[29] Hence, based on both a more favorable side effect profile and higher CR rates, lenalidomide appears to be a superior drug for maintenance therapy.

In 2010 two large randomized trials were presented both in the meeting of the American Society of Clinical Oncology in Chicago and the meeting of the American Society of Hematology in Orlando exploring the use of single agent lenalidomide as post transplant maintenance therapies.

McCarthy et al. presented the results of CALGB 100104 whose primary endpoint was to investigate the role of maintenance lenalidomide in prolonging time to progression (TTP) following single autologous SCT.[30] Patients with chemosensitive disease after an initial autologous SCT were randomized at day 100-110 post-ASCT to lenalidomide 10 mg/day or placebo until disease progression. A total of 554 patients were registered during the third interim analysis, and 33% of the required number of events (progression or death before progression) had been observed. The median follow-up is 17.5 months. The number of events among 231 pts randomized to lenalidomide was 37 compared to 84 among 229 pts randomized to placebo. The one-sided unadjusted P-value was < 0.0001. The estimated hazard ratio was 0.35 (95% CI=0.24, 0.53) corresponding to a 65% reduction in event risk (progression or death) in the lenalidomide arm. The estimated median TTP was 22.5 months for the placebo arm. The preliminary estimated median TTP was 45.5 months for the study arm. Benefits were seen regardless of whether patients received lenalidomide or thalidomide as induction therapy. Comparing lenalidomide versus placebo, post-randomization, pooled Gr 3-5 AEs, there were significantly more episodes of thrombocytopenia (11% versus 3%, p=0.01), neutropenia (44% vs 8%, p<0.0001) and anemia (5% vs 1%, p=0 .0082) with lenalidomide. No significant differences in incidence of febrile neutropenia, infection, fatigue, neuropathy, rash, thromboembolic events were seen. Lenalidomide patients discontinued therapy due to AEs more frequently than placebo (13% vs 2%). Attal et al. presented the results of a similar trial performed by the Intergroup Francophone du Myelome that enrolled 614 patients who had undergone autologous stem cell transplantation for non-progressive myeloma within the previous six months[31]. Patients were randomly assigned to placebo (307 patients) or 10 mg to 15 mg of lenalidomide daily (307 patients) until relapse.

After a median follow-up of 24 months, only 25% of the lenalidomide group experienced progression or death compared with 47% of the placebo group. Maintenance with lenalidomide improved three- year PFS from randomization by 34% in the placebo group compared with 68% in lenalidomide group (HR=0.46). Benefits were seen regardless of response to induction therapy[10].

These 2 studies have consolidated the role of maintenance therapy, in particular lenalidomide, after autologous stem cell transplantation. It is unknown whether use of post-transplant maintenance lenalidomide until disease progression will provide similar EFS and OS to either tandem transplantation or a single transplant followed by consolidation and maintenance. This is currently being actively investigated. However, maintenance therapy with low dose lenalidomide has been widely embraced and most patients will be receiving this treatment following HDM/ASCT.

3.2 Rationale for the study

As mentioned above, all patients with multiple myeloma treated with the currently available treatment modalities and strategies will eventually relapse. Patients on maintenance lenalidomide are no exception to this rule. However, it is currently unknown whether these patients whose disease progress, while on low dose lenalidomide as maintenance therapy, will respond to treatment with higher doses (considered standard doses, but for the purpose of this trial referred to as intensification) of lenalidomide. Currently it is widely perceived among physicians that these patients have a disease that is lenalidomide resistant and there is an actual risk of these patients being denied access to a potentially very effective agent, if given at higher (standard) dose.

3.2.1 Rationale for Lenalidomide Intensification Dose

The maximum tolerated dose (MTD) of lenalidomide as a daily dose is 25 mg with dose-limiting toxicity (DLT) being grade 3/4 myelosuppression. The Phase I trial of single agent lenalidomide demonstrated higher response rates with increasing dosage with 20%, 66%, and 69% of patients having at least a minimal response when receiving 10 mg, 25 mg, and 50 mg respectively[32]. Based on the pharmacokinetic data of the phase I trial, and the favorable toxicity profile observed, a randomized Phase II study has been reported that examined a higher dose with an interrupted schedule: 15 mg twice daily versus 30 mg daily on a 3 weeks on / 1 week off schedule [33]. This study examined 70 patients randomized to the two schedules. Fifty-seven patients were analyzed for toxicity and 46 for response. In this heavily pre-treated group of patients, 24% had a CR or PR or minimal response and only 16% had progressive disease. One patient developed grade 3 neuropathy. The most common grade 1 and 2 toxicities were fatigue, self-limited rash, muscle cramps and diarrhea. Grade 3 or 4 myelosuppression was seen in 26% (n=15) of patients. Eleven of these 15 patients had undergone a prior autologous transplant; most (n=11) were on the 15 mg twice a day dose. The daily dosing schedule was felt to be more favorable based on its toxicity profile and simplicity of administration with best opportunity for compliance. There was no evidence that an interrupted schedule enhanced long-term tolerability or response. Thus, there is data supporting the dose related response to lenalidomide and its optimal efficacy/tolerability ratio with 25 mg given daily for 21 days every 28 days.

3.2.2 Rationale for patient population under study

3.2.2.1 Relapse Patterns Post-Autologous Stem Cell Transplantation

The two largest reports of the natural history of relapse post autograft in myeloma were both reported prior to the advent of lenalidomide and bortezomib. Alegre et al. reported on the outcomes of 280 patients who had relapsed after transplantation and had data available in the Spanish registry[34]. The clinical patterns of relapse fell into one of four categories:

a) Insidious relapse characterized by asymptomatic elevations of the blood or urine protein occurred in 18% of patients.
b) Classic relapse characterized by an increase in monoclonal component along with clinical symptoms occurred in 66% of patients
c) Plasmacytomas occurred in 14% of patients and was characterized by presentation with multiple extramedullary plasmacytomas.
d) Plasmacytic leukemia as the initial clinical manifestation of relapse occurred in 2% of patients.

Median overall survival after relapse was 14 months for the whole group with a significant difference in the OS of patients with the insidious form of relapse when compared to those with symptomatic or plasma cell leukemia patterns of relapse (18 months vs 12 months v/s 5 months respectively; $p < 0.001$).

Lenhoff et al. reviewed the outcomes of 397 patients who had relapsed after autologous transplantation between 1994 and 1997[35]. The patterns of relapse after transplantation were classified based on a modification of a model presented by Alegre *et al*. The insidious pattern accounted for 31% , the classical pattern for 51%, and the plasmacytoma pattern for 14% of all relapses and characterized by bone marrow or extramedullary plasmacytoma with minor or no other signs of relapse and finally transformed disease which accounts for 4% of relapses and presents as plasma cell leukemia or immunoblastic lymphoma. No association was found between the pattern of relapse and any of the clinical features at diagnosis. The insidious form of relapse was significantly less common in patients who had attained complete response after transplantation than in patients who had not (17% versus 40% of the relapses, respectively). Patients who relapsed with transformed disease had a significantly shorter duration of first response after transplantation (median 3 months) compared to patients relapsing with an insidious (median 20 months), classical (median 20 months) or plasmacytoma (median 24 months) pattern. Survival was related to the type of relapse and longest in patients with the insidious pattern (median 39 months) and shortest in patients with transformed disease (median 2 months). Patients with the classical pattern of relapse were subdivided into two groups; those with skeletal clinical symptoms only at relapse (n=46) and those with additional symptoms such as cytopenias, hypercalcemia, renal insufficiency, etc. (n=37). Patients with only skeletal symptoms had a median survival after relapse of 30 months, while those with additional symptoms had a significantly shorter median survival of 18 months.

Patients relapsing with an insidious or classical form of disease with skeletal events only, or after a long lasting first response were likely to respond well to conventional salvage therapy. In contrast, relapse with multiple symptoms, transformed disease or a short duration of first response implied bad prognosis. Of the 162 patients who relapsed 49% received a melphalan based salvage regimen with 59% having at least a 25% reduction in tumor burden, 34% received a VAD like re-induction with a 46% response rate, 8% received thalidomide with a 67% response rate and 8% received a second autograft as salvage therapy with an 83% response rate. Response to relapse therapy was important for survival after relapse. Patients with a partial response or better to relapse therapy had a median survival of 36 months vs 37 months for minor responders and 8 months for nonresponders. The median survival after start of relapse therapy was 33 months for complete and partial responders and 26 months for minor responders and 7 months for non responding patients. Sixty-one patients have been treated for subsequent.

More recently Kumar et al reported on the outcomes of patients relapsing after autologous transplant in the era of lenalidomide and bortezomib therapy[36]. Among 494 patients, undergoing auto-SCT within 12 months of diagnosis they identified 124 patients who had relapsed within 12 months of high dose therapy, this group had a significantly shorter median overall survival (OS) from diagnosis (26.6 vs 90.7 months) and from SCT than those relapsing later in the course of their disease. Median survival from relapse was only 10.8 months in the early relapse group compared to 41.8 months for the rest. Among the 97 patients who relapsed early after transplant, patients who received thalidomide, bortezomib and/or lenalidomide) had a better survival than those that did not receive those drugs 15.9 months vs 4.5 months. Benefits of exposure to lenalidomide, bortezomib or thalidomide were confirmed in a larger series of 387 patients reported by the same authors. Those relapsing after the year 2000 had a median overall survival of 23.9 versus 11.8 months ($P < .001$) for those who relapsed prior to this date. Patients treated with thalidomide, lenalidomide, or bortezomib had longer survival from relapse (30.9 vs 14.8 months; $P < .001$)[37].

With the results of CALGB100104 and IFM05 it is likely that many patients will now be relapsing on lenalidomide maintenance which consists of lower doses of lenalidomide without dexamethasone. Based on the results of the phase I study of lenalidomide we hypothesize that intensifying the dose of lenalidomide could potentially re-establish control of the disease in up to 30% of myeloma patients with asymptomatic relapses, therefore saving the use of other agents for future use.

3.2.2.2 MSKCC Experience with Relapse after HDM/ASCT

We have recently reviewed the pattern of relapse in 40 patients who have participated in CALGB 100104 clinical trial and enrolled at MSKCC between 2005 and 2009. Among these 40 patients, relapse from CR or progression has occurred in 16 patients. The first evidence for relapse/progression was detected by Immunofixation in four patients who were in CR; SPEP with increase in M spike in five patients (3 who were in PR and 2 in VGPR); and free light chain assay in five patients (four who were in CR and one in PR). Only two among the 16 patients were found to have relapse/progression of disease after development of symptoms due to organ damage, triggering an evaluation by MRI that lead to the diagnosis of relapse/progression. This data would

indicate, contrary to the previous two reports detailed above by Lenhoff et al. and Alegre et al., that asymptomatic relapse (referred to as insidious relapse by these authors) is currently the most common pattern of relapse nowadays. This is most likely related to the availability of the free light chain assay which allows earlier detection of disease relapse and progression. In addition, the prospective aspect of the CALGB 100104 clinical trial that called for a rigorous monitoring of the patients every three months, certainly contributed to the earlier detection of relapse and progression prior to the development of organ damage. Despite the small sample of this observation, we are confident that the most common form of relapse and/or progression in patients receiving maintenance therapy after HDM/ASCT is asymptomatic. Hence, we anticipate that patient recruitment within this population will be facilitated.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

In this multi-center Phase II single arm trial, 53 patients fulfilling the eligibility criteria, will be treated with lenalidomide 25 mg PO daily for 21 out of 28 day cycles. The patients' responses to the treatment will be assessed after every cycle. Patients who have asymptomatic POD after 2 cycles will have dexamethasone added at a dose of 40 mg PO weekly. Patients who have at least SD after 2 cycles will continue lenalidomide single agent until asymptomatic POD, at which time they will have dexamethasone added at a dose of 40 mg PO weekly. Patients will be taken off study if they have symptomatic POD after any cycle, if they have any type of POD after dexamethasone is added, or if they do not tolerate the treatment. The patients taken off study due to any type of POD, will be considered failures for the primary response endpoint if progression occurred within 6 months. Patients who are removed from study prior to completing 2 cycles of therapy for reasons other than POD will be considered inevaluable for response and will be replaced. Accrual will continue until 53 evaluable patients have been accrued. Patients who have received any study drug will be evaluated for safety.

4.2 Intervention

Patients with *asymptomatic POD* while on maintenance lenalidomide after HDM/ASCT or on continuous/maintenance therapy after initial treatment will be enrolled on this clinical trial and will undergo the following interventions:

- Patients will have their disease fully reassessed in order to establish a new pre-therapy baseline within 2 weeks of initiation of treatment.
- Patients will receive lenalidomide at a dose of 25 mg PO daily for 21 days out of 28-days-cycles.
- Patient will be evaluated for response and toxicity after every cycle.
- Patients with at least SD after 2 cycles of lenalidomide will continue on lenalidomide until asymptomatic POD, at which time dexamethasone will be added at a dose of 40 mg PO weekly at the next cycle.

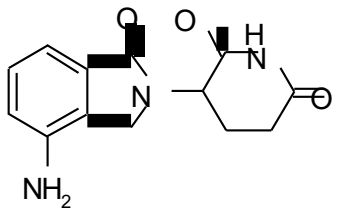
- Patients with asymptomatic POD after 2 or more cycles of lenalidomide will have dexamethasone added to lenalidomide at a dose of 40 mg PO weekly at the next cycle.
- Patients with further asymptomatic POD after at any cycle of lenalidomide and dexamethasone will be taken off study and treated at the discretion of the treating physician. Note that further POD after the addition of dexamethasone will be determined compared to the new M spike baseline just prior to the addition of dexamethasone.
- Note that patients with ***symptomatic*** POD at any point in time during treatment will be taken off study.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1 Lenalidomide

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 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.

5.1.1 Clinical Pharmacology

Mechanism of Action:

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

Pharmacokinetics and Drug Metabolism:

Absorption:

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

Pharmacokinetic 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). No plasma accumulation was observed with multiple daily dosing. 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. Peak and overall plasma concentrations were dose proportional over the dosing range of 5mg to 50mg. 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.

5.1.2 Supplier(s)

Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through Celgene's Revlimid Risk Evaluation and Mitigation Strategy™ (REMS) (formerly known as RevAssist® Program).

5.1.3 Dosage form

Lenalidomide will be supplied as capsules for oral administration.

5.1.4 Packaging

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

5.1.5 Storage

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

5.1.6 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 Celgene Corporation's Revlimid REMS® program. Per standard Revlimid REMS® program requirements, all physicians who prescribe lenalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in, and must comply with, all requirements of the Revlimid REMS® program.

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

5.1.7 Pregnancy Testing

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

Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of

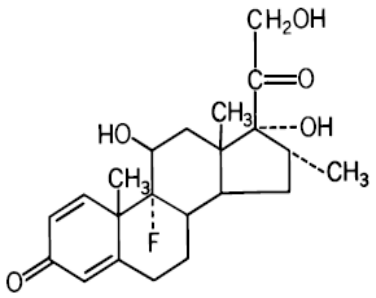
lenalidomide (see Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

5.2 Dexamethasone

5.2.1 Description

Dexamethasone is a synthetic adrenocortical steroid. Corticosteroids are naturally-occurring chemicals produced by the adrenal glands located above the kidneys. Corticosteroids affect the function of many cells within the body and suppress the immune system. Corticosteroids also block inflammation and are used in a wide variety of inflammatory diseases affecting many organs.

The molecular weight for dexamethasone is 392.47. It is designated chemically as 9-fluoro-11β,17,21-trihydroxy-16α-methylpregna-1,4-diene-3,20-dione. The empirical formula is $C_{22}H_{29}FO_5$ and the structural formula is:



Dexamethasone is stable in air and almost insoluble in water.

5.2.2 Form

Dexamethasone is a white to practically white, odorless, crystalline powder. It is available in 2 or 4 mg tablets (commercially) for oral administration. Each tablet contains dexamethasone as the active ingredient, and the following inactive ingredients: calcium phosphate, lactose, magnesium stearate, and starch. The tablet shell may contain the following: D&C Yellow 10, FD&C Yellow 6, and/or FD&C Blue 1.

5.2.3 Storage and Stability

All investigational study drugs will be stored in a locked, safe area to prevent unauthorized access. Dexamethasone should be stored at controlled room temperature, 68-77◦F (20-25◦C) and not frozen, and according to label requirements.

5.2.4 Handling

Dexamethasone should be handled by trained pharmacy staff. The use of gloves and other appropriate protective clothing is recommended as necessary.

5.2.5 Availability and ordering

Dexamethasone supply will be obtained through commercial supply. The investigator will order drug supply from commercial supply and will not be provided for the current trial.

5.2.6 Preparation

Dexamethasone is an oral drug, and does not require specific preparation details.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

Patients fulfilling the following criteria will be eligible for entry into this study:

- Patients must be 18 years of age or above at the time of enrollment.
- Patients must show evidence of *asymptomatic* relapse and/or progression of disease (increasing M spike in serum or urine by consensus criteria) while on lenalidomide maintenance after HDM/ASCT as part of initial line of therapy. Patients who have not had an HDM/ASCT as part of initial line of therapy but who are on continuous/maintenance lenalidomide after initial therapy will be permitted on study.
- Patient must have myeloma that is measurable by either serum or urine evaluation of the monoclonal component or by assay of serum free light chains. Measurable disease is defined as one or more of the following: serum M-protein $\geq$ 0.5 g/dl, urine M-protein $\geq$ 200 mg/24 h, and/or serum FLC assay: involved FLC level > 10 mg/dL with abnormal serum FLC ratio.
- Patients must have adequate organ function including: Hepatic function with Bilirubin < 2x the upper limit of normal and ALT and AST < 3 x the upper limit of normal; renal function with creatinine clearance $\geq$ 60 ml/min using the Cockcroft-Gault formula; hematologic function as defined by an absolute neutrophil count > 1000 neutrophils per microliter, platelet > 50,000 platelets per microliter and hemoglobin of $\geq$ 9 gm/dL without transfusion support.
- All study participants must be registered into the mandatory Revlimid REMS® program, and be willing and able to comply with the requirements of the REMS® program.
- Females of child bearing potential (FCBP)[1] must adhere to the scheduled pregnancy testing as required in the Revlimid REMS® program. FCBP must have a negative serum

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

or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days) andmust either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. See Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

6.2 Subject Exclusion Criteria

The following patients will be ineligible for registration onto this study:

- Patients with *symptomatic* relapse and/or progression of multiple myeloma. (Appendix A).
- Patients with plasma cell leukemia.
- Karnofsky performance score less than 70% or ECOG performance status greater than 2.
- Patients with uncontrolled bacterial, viral or fungal infections (currently taking medication and progression of clinical symptoms).
- Patients with prior malignancies except resected basal cell carcinoma or treated cervical carcinoma in situ or other cancer treated with curative intent > 5 years previously. Cancer treated with curative intent < 5 years previously will not be allowed unless approved by the Protocol Chairs.
- Female patients who are pregnant (positive -HCG) or breastfeeding. (Lactating females must agree not to breast feed while taking lenalidomide).
- Patients seropositive for the human immunodeficiency virus (HIV).
- Prior organ transplant requiring immunosuppressive therapy.
- Patients who were previously exposed to higher doses of lenalidomide and who developed severe adverse events at higher doses that preclude incremental dosing.

7.0 RECRUITMENT PLAN

This study will be conducted at MSKCC and other collaborating medical centers that are members of the newly established Tri-State Transplant Consortium. It is anticipated that 15 patients will be enrolled from MSKCC and 38 patients will be enrolled from the collaborating centers. At MSKCC, patients will be recruited from the large population of patients who currently undergo (or have undergone) HDM/ASCT either on the currently accruing transplant clinical trial (IRB # 09-171), or past clinical trial (IRB # 05-080), which both include maintenance therapy with lenalidomide after HDM/ASCT as part of management; patients will also be recruited among patients who have been transplanted off protocol and receive maintenance lenalidomide after transplantation, a practice that has been gaining momentum in the past year. Patients who have not had an ASCT as part of initial line of therapy but are on continuous/maintenance lenalidomide will also be permitted on study.This trial will also be open at collaborating centers which have agreed to participate and we anticipate that a substantial proportion of patients will

be accrued through this collaboration. All patients will be registered through MSKCC. All patients will be enrolled and followed by physicians at MSKCC and collaborating centers. All co-investigators agree to follow the treatment in the protocol and to conduct the proposed investigation according to recognized principles of good clinical practice. Participation is voluntary. Efforts will be made to ensure that women and minority groups are adequately represented in this trial. Each patient must be informed about the neoplastic nature of his/her disease and willingly consent to participating in this study. Every patient will be informed of the procedures to be followed, the potential benefits, side effects, risks, and discomforts of the trial and of potential therapeutic alternatives. All participants will be required to sign statements of informed consent and research authorization that conform to FDA, IRB and HIPAA guidelines. Informed consent will be documented by the use of a written consent form that has been approved by the MSKCC IRB.

Potential research subjects will be identified by a member of the patient's treatment team, the protocol investigator, or research team at Memorial Sloan-Kettering Cancer Center (MSKCC). If the investigator is a member of the treatment team, s/he will screen their patient's medical records for suitable research study participants and discuss the study and their potential for enrolling in the research study. Potential subjects contacted by their treating physician will be referred to the investigator/research staff of the study.

The principal investigator may also screen the medical records of patients with whom they do not have a treatment relationship for the limited purpose of identifying patients who would be eligible to enroll in the study and to record appropriate contact information in order to approach these patients regarding the possibility of enrolling in the study. This will allow the study team to keep track of all patients on lenalidomide maintenance therapy for multiple myeloma that may subsequently be eligible to enroll onto this study. The study staff and PI will review lists from Darwin queries. The patients on these queries will be tracked via a log.

During the initial conversation between the investigator/research staff and the patient, the patient may be asked to provide certain health information that is necessary to the recruitment and enrollment process. The investigator/research staff may also review portions of their medical records at MSKCC in order to further access eligibility. They will use the information provided by the patient and/or medical record to confirm that the patient is eligibile and to contact the patient regarding study enrollment. If the patient turns out to ineligible for the research study, the research staff will destroy all information collected on the patient during the initial conversation and medical records review, except for any information that must be maintained for screening log purposes.

In most cases, the initial contact with the prospective subject will be conducted either by the treatment team, investigator or the research staff working in consultation with the treatment team. The recruitment process outlined presents no more than minimal risk to the privacy of the patients who are screened and minimal PHI will be maintained as part of a screening log. For these reasons, we seek a (partial) limited waiver of authorization for the purposes of (1) reviewing medical records to identify potential research subjects and obtain information relevant to the enrollment process; (2) conversing with patients regarding possible enrollment; (3)

handling of PHI contained within those records and provided by the potential subjects; and (4) maintaining information in a screening log of patients approached (if applicable).

This limited waiver will apply only to MSKCC. Any participating sites that require a limited waiver must obtain it from their own local IRB/Privacy Board (PB) via a separate protocol addendum or request. It is the responsibility of the MSKCC staff to confirm the participating data collection site(s) have a limited waiver approved by their local IRB(s)/PBs.

8.0 PRETREATMENT EVALUATION

The following tests will be done within 7 days prior to enrollment:

- Mandatory pregnancy test, serum or urine HCG (sensitivity of at least 50 mIU/mL) for FCBP.

  Women are required to have 2 pregnancy tests prior initiation of lenalidomide as follows (Appendix B):
  - The first is required within 10 to 14 days prior to prescribing lenalidomide
  - The second within 24 hours of prescribing lenalidomide and prescription must be filled within 7 days.

The following tests will be done within 14 days prior to enrollment:

- History and physical exam including vital signs, height, weight, performance status, and toxicity assessment using CTCAE 4.0.

- Serum M-spike studies: Serum protein electrophoresis (SPEP), serum immunofixation (IF) and quantitative immunoglobulins, and serum free light chain assay

- Urine M-spike studies: Twenty-four hour urine for total volume and total protein (TV, TP), immunofixation (IF), protein electrophoresis (UPEP), N-telopeptides and creatinine clearance using the Cockcroft-Gault formula

- Comprehensive Metabolic Panel (includes Albumin, Alkaline Phosphatase, ALT, AST, BUN, Calcium, Carbon dioxide, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein), beta2-microglobulin, C-reactive protein, LDH

- CBC with differential

- INR/PTT, BNP, and troponin.

- Electrocardiogram (EKG)

- Mandatory pregnancy test, serum or urine HCG (sensitivity of at least 50 mIU/mL) for FCBP.

  Women are required to have 2 pregnancy tests prior initiation of lenalidomide as follows

(Appendix B):

- The first is required within 10 to 14 days prior to prescribing lenalidomide
- The second within 24 hours of prescribing lenalidomide and prescription must be filled within 7 days.

The following tests will be performed within 56 days prior to patient enrollment:

- Hepatitis A, B, C serologies and HIV I/2 test
- A skeletal survey that should be reviewed at MSKCC or the participating site if not performed at MSKCC or the participating site. (Please note: the skeletal survey is not required if a PET scan has been completed)
- PET scan or total body MRI if available (optional)
- A routine bone marrow examination, including biopsy sample for H & E stain and immunohistochemical staining for CD 138, CD20, kappa and lambda light chains; bone marrow aspirate samples for Giemsa staining, flow-cytometry, cytogenetic analysis, and FISH analysis for chromosomes 1, 4, 11, 13, 14, 17 abnormalities

9.0 TREATMENT/INTERVENTION PLAN

9.1 Treatment Plan

- Lenalidomide dose will begin at 25 mg PO daily for 21 days of a 28-day-cycle adjusted for toxicity, if necessary. Once the dose of lenalidomide is reduced for toxicity, no dose-re- escalation is permitted.
- If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.
- Patients taking more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.
- Only one cycle of therapy may be dispensed to the patient each month. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.
- Special Handling Instructions: Females of childbearing potential should not handle or administer lenalidomide unless they are wearing gloves.
- Record of administration: Accurate records will be kept in the source documents of all drug administration (including prescribing and dosing). Patients will be instructed to bring their complete medication diary (refer to Appendix D) to each study visit for assessment of compliance.

- Patient will be evaluated for response and toxicity after every cycle and the response to lenalidomide intensification will be assessed after every cycle of therapy.

    - Patients with at least SD after 2 cycles of lenalidomide will continue on lenalidomide until asymptomatic POD at which time dexamethasone will be added at a dose of 40 mg PO weekly for the next cycle.

    - Patients with asymptomatic POD after 2 cycles of lenalidomide will have dexamethasone added to lenalidomide at a dose of 40 mg PO weekly with the next cycle.

    - Patients with further asymptomatic POD after any cycle of lenalidomide and dexamethasone will be taken off study and treated at the discretion of the treating physician. Note that further POD after the addition of dexamethasone will be determined compared to the new M spike baseline just prior to the addition of dexamethasone.

- Once patients are started on dexamethasone, they will also receive prophylaxis medication including Bactrim DS, one tablet PO TIW, fluconazole, 100 mg PO Daily, ASA 81 mg PO daily, and a PPI.

- Note that patients with ***symptomatic*** POD at any point in time during treatment will be taken off study.

9.2 Cycle Delay and Dose Modification Guidelines

Within a week prior to the first day of each new treatment cycle, the patient will be evaluated for possible toxicities that may have occurred due to previous doses. Toxicities will be assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), version 4.0. Cycle delays and dose modifications will be made based on the toxicity experienced during the previous cycle of therapy or the ones encountered on any of the treatment days. Doses of study drug that need to be held WITHIN a cycle are skipped and will not be made up later in the cycle.

9.2.1. Instruction for Initiation of a New Cycle

A new course of treatment may begin on the scheduled Day 1 of a new cycle if:

- The ANC is ≥ 1,000/μL
- The platelet count is ≥ 50,000/μL
- Hemoglobin is ≥ 8g/dL
- Any drug-related side effect rash, allergic reaction/hypersensitivity, sinus bradycardia/

other cardiac arrhythmia adverse event, dyspepsia, gastritis, gastric or duodenal ulcer or confusion or mood alterations that may have occurred has resolved to ≤ grade 1 severity

- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of lenalidomide will not be initiated until the toxicity has resolved as described above. If the toxicity does not resolve after four weeks of delay, the patient will be taken off study.

If dosing of lenalidomide was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle.

If dosing of lenalidomide was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with dose modifications as described in Section 9.2.3.

9.2.2. Lenalidomide Dose Reduction Guidelines

Table 3: Dose Modification for Lenalidomide

NCI CTC v3.0 Toxicity Grade	Day 2 – 14 of Cycle	≥ Day 15 of Cycle
Grade 3 neutropenia associated with fever (temperature ≥ 38.5°C or Grade 4 neutropenia)	· Hold (interrupt dose) · Follow CBC weekly · If neutropenia has resolved 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 the cycle · If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the dose maintained for the next cycle at the treating physician's discretion
Thrombocytopenia ≥ Grade 3 (platelet count < 50,000/mm^3)	· Hold (interrupt dose) · Follow CBC weekly · If thrombocytopenia resolves to ≤ grade 2 prior to Day 21, restart at next lower dose level and continue the cycle until Day 21 · Hold anticoagulation for platelet count < 50,000/mm^3	· Omit lenalidomide for remainder of cycle · Hold anticoagulation for platelet count < 50,000/mm^3

Anemia ≥ Grade 3 (Hgb < 8g/dL	· Hold (interrupt dose) · Follow CBC weekly · If anemia resolves to ≤ grade 2 prior to Day 21, restart at next lower dose level and continue the cycle until Day 21	· Omit lenalidomide for remainder of cycle
Non-blistering rash 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	· Omit lenalidomide for remainder of cycle
Non-blistering rash Grade 4	· Discontinue lenalidomide study drug	· 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	· Hold (interrupt) dose · Follow at least weekly · If toxicity resolves to ≤ grade 1 prior to Day 21, restart at next lower dose level and continue the cycle until Day 21	· Omit lenalidomide for remainder of cycle
Sinus bradycardia/other cardiac arrhythmia ≥ Grade 3	· Discontinue lenalidomide study drug	· Discontinue lenalidomide study drug
Allergic reaction or hypersensitivity Grade 2-3	· Hold (interrupt) dose · Follow at least weekly · If toxicity resolves to ≤ grade 1 prior to Day 21, restart at next lower dose level and continue the cycle until Day 21	· Omit lenalidomide for remainder of cycle
Allergic reaction or hypersensitivity Grade 4	· Discontinue lenalidomide study drug	· 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
Other non-hematologic toxicity assessed as Lenalidomide-related ≥ Grade 3	· Hold (interrupt dose) · Follow at least weekly · If toxicity resolves to ≤ grade 1 prior to Day 21, restart at next lower dose level and continue the cycle until Day 21	· Omit lenalidomide for remainder of cycle
Hyperthyroidism or hypothyroidism	· Omit lenalidomide for remainder of cycle, evaluation etiology, and initiate appropriate therapy · See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level	· Omit lenalidomide for remainder of cycle, evaluation etiology, and initiate appropriate therapy · See Instructions for Initiation of a New Cycle and reduce the dose of lenalidomide by 1 dose level

9.2.3. Lenalidomide Dose Reduction Levels

Lenalidomide Dose Reduction Steps	
Starting Dose	25 mg daily for 21 days every 28 days
Dose Level -1	20 mg daily for 21 days every 28 days
Dose Level -2	15 mg daily for 21 days every 28 days
Dose Level -3	10 mg daily for 21 days every 28 days
Dose level -4	5 mg daily for 21 days every 28 days
Dose level -5	Discontinue lenalidomide

9.2.4 Dexamethasone Dose Reduction Guidelines

Table 4: Dose Modification for Dexamethasone		
Dyspepsia	≥ Grade 3	· Hold (interrupt) dexamethasone until ≤ grade 1 · Reduce dexamethasone by 1 dose level and restart

Gastritis, gastric or duodenal ulcer	≥ Grade 3	· Hold (interrupt) dexamethasone until ≤ grade 1 · Reduce dexamethasone by 1 dose level and restart
Edema	≥ Grade 3	· Reduce dexamethasone by 1 dose level · Use diuretics, as needed
Confusion or mood alternations	≥ Grade 2	· Hold (interrupt) dexamethasone until ≤ grade 1 · Reduce dexamethasone by 1
Muscle weakness	≥ Grade 3	· Reduce dexamethasone by 1 dose · If symptoms persist, continue to reduce dexamethasone by 1 dose level, as needed
Hyperglycemia	≥ Grade 3	· Reduce dexamethasone by 1 dose level · Treat with insulin or oral hypoglycemics, as needed
Acute pancreatitis	≥ Grade 3	· Discontinue dexamethasone and take patient off study
Other non-hematologic toxicity assessed as dexamethasone related	≥ Grade 3	· Hold dexamethasone for remainder of cycle · Reduce dexamethasone by 1 dose level

9.2.5 Dexamethasone dose reduction levels

Dexamethasone Dose Reduction Steps	
Starting Dose	40mg weekly on days 1, 8, 15 and 22 of each 28-day cycle
Dose Level -1	20mg weekly on days 1, 8, 15 and 22 of each 28-day cycle

Dose Level –2	12mg weekly on days 1, 8, 15 and 22 of each 28-day cycle
Dose Level -3	4mg weekly on days 1, 8, 15 and 22 of each 28-day cycle

9.3 Supportive Care

- Monthly IV bisphosphonates (either Zometa or Pamidronate according to institutional preference) may be initiated or continued according to local institutional practice.
- Patients can receive filgrastim or pegylated filgrastim for an ANC < 109/L.
- Radiation therapy is not permitted concurrently in this trial.
- Transfusion thresholds for blood product support should be per institutional guidelines. All blood products will be irradiated.
- Treating physicians should be aware of the increased risk of DVT and PE with lenalidomide when combined with dexamethasone and have heightened vigilance regarding this possible toxicity. There is no clear evidence that the risk of DVT is increased on lenalidomide alone. Aspirin 325 mg/day orally should be administered during lenalidomide therapy when associated with dexamethasone unless the patient is treated with alternate prophylaxis of either low molecular weight heparin or Coumadin. This will be left to the discretion of the treating physician.
- Concurrent use of erythropoietin requires full anticoagulation of patients with therapeutic doses of LMWH or Coumadin. Anticoagulation should be held for platelet counts <50,000/mm3.
- Prophylaxis therapy should be added when patient start dexamethasone including fluconazole 100mg PO daily, Bactrim DS, three days a week, and a PPI daily.

10.1 EVALUATION DURING TREATMENT/INTERVENTION

During the intervention period, the patients will be assessed in the clinic before initiation of every cycle and will have the following evaluation done before every cycle, within one week of day 1 of the cycle:

- History and physical exam including vital signs, weight, and performance status.
- Review medication diary. Patients will be given a medication diary at the beginning of each cycle to document lenalidomide administration.
- CBC with differential and platelet count
- Comprehensive metabolic panel with LDH and phosphorus. The comprehensive metabolic panel includes albumin, alkaline phosphatase, ALT, AST, BUN, calcium, carbon dioxide, chloride, creatinine, glucose, potassium, sodium, total bilirubin, and total protein.

- Myeloma response assessment: Including serum studies (Protein electrophoresis, Quantitative Immunoglobulins, Immunofixation and free light chain assay) and 24h urine studies (protein electrophoresis, Total protein, Immunofixation, and creatinine clearance)
- Toxicity assessment using CTCAE 4.0: maximum grade and status of ≥ grade 2 adverse events.
- Bone marrow aspiration and biopsy to be performed only when indicated to document CR or progression.
- Radiological evaluation when needed to document response or progression.
- Required evaluation for Lenalidomide: Pregnancy test, serum or urine HCG (sensitivity of at least 50 mIU/mL) for female of childbearing potential (FCBP):
- FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (Appendix B).
- All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. The counseling must be done on Day 1 of each cycle (or at a minimum of every 28 days) and at drug discontinuation. See Appendix: Education and Counseling Guidance Document. A Lenalidomide Information Sheet (Appendix D) will be supplied with each medication dispense.

The same evaluation will repeated at the end of study, within 4 weeks of the last dose. On day 15 of each cycle the patient will have a CBC. Pre-screening assessments may be used for Cycle 1/Day 1 if they were complete within 7 days of initiation of cycle 1.

Correlative Studies

Patients who give their consent to optional sample collection for research studies will have blood samples (6 CPT tubes and 1 SST tube) collected for research on immune function prior to lenalidomide dose escalation, Cycle 1, Day 15 (+/- 3 days) following dose escalation, prior to addition of dexamethasone, and Day 15 (+/- 3 days) following the addition of dexamethasone. Research blood samples will be collected during the time of standard toxicity evaluation during lenalidomide therapy. The standard treatment schedule includes a 7 day rest period prior to the administration of the next cycle. Thus, the day 15 time point has been selected to allow for an analysis of immune endpoints during the period when study drug is being administered. In addition, 5-7 cc of bone marrow aspirate (in EDTA) will be collected at the time of registration. Samples will be sent to MSKCC for central processing, cataloguing, and storage.

Time Point	Window for Collection	Tubes
Baseline/pre-lenalidomide escalation	Day -7(consent must be signed) through Cycle 1/Day 1	5-7cc bone marrow aspirate (6) CPT tubes (1) SST tube
Cycle 1/Day 15	Cycle 1/ Day 15 (+/- 3 days)	(6) CPT tubes (1) SST tube
Pre-dexamethasone addition	Between asymptomatic progression and addition of dexamethasone	(6) CPT tubes (1) SST tube
Day 15 post-dexamethasone addition	Day 15 (+/- 3 days) post-dexamethasone addition	(6) CPT tubes (1) SST tube

Schedule of Study Assessments

Required Studies / Testing	Pretreatment within 8 weeks	Pretreatment within 28 days	Pretreatment within 14 days	Before Every Cycle (within 1 week of day 1)[8]	On day 15 of each cycle	End o Stud (Within weeks of dose)
Informed Consent		X				
History and Physical Examination (Height[7] and Weight)			X	X		X
Vital Signs			X	X		X
Review medication diary				X		X
Toxicity assessment			X	X		X
Pregnancy Test[2]			X[3]	X[3]		X[3]
Register patient into the Revlimid REMS™ program			X			
Performance Status (Karnofsky Performance Score or ECOG)			X	X		X
CBC with Differential and platelet count			X	X	X	X
Comprehensive Metabolic Panel[6]			X	X		X
LDH, Phosphorus			X	X		X
B2 Microglobulin, Albumin			X	X		X
INR/PTT, BNP, troponin			X			
Hepatitis A, B, and C and HIV 1/2 test	X					
Serum Multiple Myeloma Disease Assessment · Protein electrophoresis · Quantitative			X	X		X

Immunoglobulins · Immunofixation · Serum Free Light Chain Assay						
24 hour Urine Multiple Myeloma Disease assessment · Protein electrophoresis · Immunofixation · Total volume, total protein · Creatinine clearance ·			X	X[5]		X
EKG			X			
Skeletal Survey	X[1,10]					X
PET scan or total body MRI if available (optional)	X[1]					
Bone Marrow Aspirate and Biopsy for · Morphology · Cytogenetics and FISH analysis · Tissue Banking	X[1]					X[4]
Optional Research Blood[9]		X				
Optional Research Bone Marrow Aspirate	X					

[1] To be performed within 8 weeks of registration.

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

[3] Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy); at discontinuation of lenalidomide and at Day 28 post the last dose of lenalidomide. Females with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide and at Day 14 and Day 28 post the last dose of lenalidomide (see Appendix: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods)

[4] Unilateral bone marrow aspirate and biopsy will be done only to confirm complete remission in patients with negative biochemical evidence of disease.

[5] If the baseline urine paraprotein level is less than 200mg/24hrs, the UPEP is not required.

[6] Albumin, Alkaline Phosphatase, ALT, AST, BUN, Calcium, Carbon dioxide, Chloride, Creatinine, Glucose, Potassium, Sodium, Total Bilirubin, Total Protein

[7] Height only required during pretreatment evaluation.

[8] Pre-screening assessments may be used for Cycle 1/Day 1 if they were complete within 7 days of initiation of cycle 1.

[9] Optional blood will be collected prior to dose escalation (baseline), 15 days (+/- 3 days) post dose escalation, prior to addition of dexamethasone, and 15 days (+/- 3 days)post addition of dexamethasone.

[10] A skeletal survey is only required for screening if PET scan was not completed.

11.0 TOXICITIES/SIDE EFFECTS

The patients will be evaluated every 28 days before initiation of a new cycle of treatment. All toxicities with a maximum grade and status of ≥ grade 2 will be graded using the Common Terminology Criteria for

Adverse Events (CTCAE) Version 4.0.

11.1 Expected Side Effects of Lenalidomide

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 the following:

Likely:

Feeling tired (fatigue)
Loss of strength (asthenia)
Loose, frequent bowel movements (diarrhea)
Difficulty moving bowels (constipation)
Altered sense of taste (dysgeusia)
Nose bleed (epistaxis)
Decrease in red blood cells that can cause tiredness (anemia)
Decrease in white blood cells that can make you more prone to infections (neutropenia)
Decrease in platelets which can cause you to bruise or bleed easily(thrombocytopenia)
Blurred vision
Abnormal sense of touch
Pain and decreased sensastion in nerves

Less Likely:

Fever
Problem with moving food through digestive system (gastrointestinal motility disorder)
Weight loss, loss of appetite
Dry mouth
Nausea
Vomiting
Chills
Indigestion (dyspepsia)
Muscular weakness
Stroke
Tingling sensation (paresthesia)
Swelling or edema (including peripheral)
Itching and dry skin (pruritis)
Rash
Sores on the skin (pyoderma gangrenosum)
Cough
Shortness of breath (dyspnea)
Fainting (syncope)
Dizziness
Drowsiness
Headache
Difficulty sleeping (insomnia)
Bleeding
Difficulty breathing (respiratory distress)

Excessive sweating (hyperhidrosis)
Fever with a decrease in white blood cells that help fight infections (febrile neutropenia)
Shortage of all types of blood cells including red blood cells, white blood cells, and platelets (pancytopenia)
Infection, especially when white blood cell count is low
Blood clots (thromboembolic event)
Excessive loss of body water (dehydration)
High blood sugar (hyperglycemia)
Uncontrolled blood sugar (diabetes mellitus)
Higher than normal blood uric acid (hyperuricemia)
Higher than normal level of iron in body (iron overload)
Lower than normal level of thyroid hormone (hypothyroidism)
Lens of eye becomes cloudy (cataracts)
High blood pressure (hypertension)
Low blood pressure (hypotension)
Joint pain (arthralgia)
Back pain
Muscle pain (myalgia)
Muscle cramp / spasm
Altered mood
Depression
Irregular heartbeat (atrial fibrillation)
Failure of the heart (cardiac failure)
Heart attack (acute myocardial infarction)
Fast heartbeat (tachycardia)
Not enough blood flow to heart muscle (myocardial ischemia)
Kidney damage (renal failure)
Abnormal liver function tests

Rare but Serious

Fever with a decrease in white blood cells that help fight infections (Febrile neutropenia)
Blood clot in or around the lungs (Pulmonary embolism)
Deep vein thrombosis or blood clots in larger blood vessels
Atrial fibrillation or irregular heartbeat
Pneumonia or an infection of the lungs
Sepsis or an infection of the blood
Inflammation of the pancreas, which causes increase in pancreatic enzymes (lipase), which could result in abdominal pain and discomfort
Allergic reaction which may cause rash, low blood pressure, wheezing, shortness of breath, swelling of the face or throat (anaphylaxis)
Kidney failure or inability of the kidneys to remove waste from the body
Muscle breakdown (rhabdomyoiysis)
Swelling of the lungs
Severe skin rash with blisters that can involve the inside of the mouth and other parts of the body (erythema multiforme)
Serious allergic skin reactions that begin as a rash in one area and later cover more of the body, leading to separation of the top layer of skin (Stevens- Johnson syndrome /

toxic epidermal necrolysis)
Damage to organs in the body when donor cells attack host organs, which may cause yellowing of the eyes and skin, itchy dry skin, or muscle weakness (Graft versus host disease)
Complications caused by the break-down products of dying cancer cells, which can include high potassium, high phosphorous, high uric acid in the blood and urine, low calcium, and can result in kidney damage (Tumor lysis syndrome)
Cancer of bone marrow caused by chemotherapy
A new cancer resulting from treatment of earlier cancer
Low blood cell counts that may cause infection, anemia, spontaneous bleeding, or easy bruising (Myelodysplastic syndrome)
Increase in size of the cancerous lymph nodes, rash, and slight fever (Tumor flare reaction)
Brain damage which may cause headache, seizure, or blindness (leukoencephalopathy)

11.2 Expected Side Effects of Dexamethasone

Likely

- Increased appetite
- Weight gain
- Sleep disturbance
- Hypertension
- Fluid retention, ankle swelling
- Bruising
- Susceptibility to Infection
- Mood changes
- Slow wound healing
- Depression
- Hyperglycemia, which may lead to fatigue, weight loss, excessive thirst and frequent urination.

Less Likely

- Loss of appetite
- Muscle twitching
- Increased thirst, frequent urination
- Increased perspiration
- Diarrhea
- Nausea
- Headache
- Bone thinning
- Spinal fracture or fracture of bones
- Tachycardia
- Fungal infections

- Anxiety

Unlikely

- Blurred vision
- Personality changes
- Hypokalemia
- Swelling and/or redness of skin
- Allergic skin reactions
- Itching
- Hirsutism
- Muscle weakness or loss of muscle mass
- Rupture of tendons
- Menstrual cycle disturbances
- Facial puffiness, leading to the appearance of a “moon face” hormonal disturbances
- Hiccups.
- Development of diabetes

Rare but serious

- Stomach ulcers with bleeding that may cause hematemesis, blood in the stool and abdominal pain.
- Bowel perforation, irritation and bleeding of the esophagus
- Heart failure
- Allergic reaction that may lead to shortness of breath, abdominal cramps and hypotension
- Convulsions, brain swelling,
- Cataracts
- Glaucoma and increased blood pressure in the eye
- Pancreatic inflammation, abdominal swelling
- DVT or PE
- Aseptic necrosis of the hip

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Patients enrolled in this trial must have *asymptomatic* progression of disease only. The new baseline that will be used for comparison to assess the response to lenalidomide intensification with or without the addition of dexamethasone at 6 months will have to be established within two weeks prior to day 1 of cycle 1. Prior values will not be acceptable.

Patients’ disease status at each data collection period will be evaluated based on the International Uniform Response Criteria. All disease responses, including after addition of dexamethasone, will be relative to the established baseline disease status within 2 weeks prior to day1 of cycle 1, i.e. prior to lenalidomide intensification.

International Uniform Response Criteria (modified)

Stringent Complete Response (sCR):

- sCR requires, in addition to CR (defined below), all of the following:
- Normal free light chain ratio (FLC).
- Absence of clonal cells in bone marrow by immunohistochemistry or immunofluorescence.

Complete Response (CR) requires *all* of the following:

- Absence of the original monoclonal paraprotein in serum and urine by routine electrophoresis and by immunofixation.
- Less than 5% plasma cells in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed;
- No increase in size or number of lytic bone lesions on radiological investigations (development of a compression fracture does not exclude CR)*; and,
- Disappearance of soft tissue plasmacytomas.

**If not clinically indicated, radiographs are not required to document CR.*

Very Good Partial Response (VGPR) requires, in addition to PR (defined below), all of the following:

- Serum or urine paraprotein detectable by immunofixation but not on electrophoresis,
  OR
- Greater than or equal to 90% reduction in serum paraprotein plus urine paraprotein <100 mg/24hrs.

Partial Response (PR) requires one of the following:

- Greater than or equal to 50% reduction in the level of the serum monoclonal paraprotein and/or reduction in 24 hour urinary monoclonal paraprotein either by greater than or equal to 90% or to <200 mg/24 hours in light chain disease.
- If the only measurable non-bone marrow parameter is FLC, greater than or equal to 50% reduction in the difference between involved and uninvolved FLC levels or a 50% decrease in level of involved FLC with 50% decrease in ratio,
- If the bone marrow is the only measurable parameter, greater than or equal to 50% reduction in bone marrow plasma cells given that the baseline count was greater or equal to 30%,
- Greater than or equal to 50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination).

Minor Response (MR)

- ≥ 25% to ≤ 49% reduction in the level of serum monoclonal protein (SPEP)
- If present, a 50% to 89% reduction in 24-hour light chain excretion, which still exceeds 200 mg/24 hr.
- If the serum and urine M-protein are unmeasurable a ≥25% to ≤49% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria.
- 25% to 49 % reduction in the size of soft tissue plasmacytomas (by clinical or radiographic examination)

Stable Disease (SD)

- Patients who do not meet criteria for sCR, CR, VGPR, PR or progressive disease are considered to have stable disease (SD).

Progressive Disease (POD) requires one or more of the following:

- >25% increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 0.5 g/dL.
- >25% increase in 24-hour urine protein electrophoresis, which must also be an absolute increase of at least 200 mg/24 hours.
- >25% increase in the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dl),
- >25% increase in plasma cells in a bone marrow aspirate or on trephine biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of existing bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas.
- Development of hypercalcemia (corrected serum Ca >11.5 mg/dL or >2.8 mmol/L) not attributable to any other cause.

Note that the development of a compression fracture does not exclude continued response and may not indicate progression.

13.0 CRITERIA FOR REMOVAL FROM STUDY

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

- Symptomatic POD, i.e. *with organ damage* at any point in time during the treatment
- Asymptomatic POD, i.e. *without organ damage* after at least one cycle of lenalidomide and dexamethasone
- Adverse event(s) that, in the judgment of an Investigator, may cause severe or permanent harm or which rule out continuation of study drug

- Major violation of the study protocol
- Withdrawal of consent
- Patient is lost to follow-up
- Suspected or confirmed pregnancy. If pregnancy or a positive pregnancy test does occur in a study subject or the partner of a male study subject during study participation, study drug must be immediately discontinued.

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

14.0 BIOSTATISTICS

The primary objective of this study is to estimate overall response rate (≥ PR) to lenalidomide intensification with or without dexamethasone at 6 months. A single stage design that differentiates between response rates of 15% and 30% will be used to assess efficacy of lenalidomide intensification with or without dexamethasone.
The probabilities of a type I error (falsely accepting a non-promising therapy) and type II error (falsely rejecting a promising therapy) are set to 0.10 and 0.10, respectively. The null hypothesis response rate is based on the response rates ranging from 12.5% to 16.4% to the standard of care therapy in patients previously exposed to thalidomide who have relapsed or refractory disease (reference Webber and Dimopoulos papers[38,39]). A total of 53 patients will be accrued. At the conclusion of the study, if a least 12 of the 53 patients respond by 6 months the treatment will be declared a success. At the end of the study, the response rate will be estimated and a confidence interval will be constructed.

We expect to accrue 53 patients in two years with approximately 10-15 patients accrued from MSKCC and the remaining patients accrued from the other centers.

The incidence of toxicities of grade 2 or higher toxicities (CTCAE version 4.0), the incidence of probable viral fungal and bacterial infections, and the incidence of treatment-related mortality, i.e., from causes other than relapse or progression, will be recorded for each patient after each cycle and at the end of study visit. Safety data will be described in a variety of ways, both graphically and in tabular form.

Progression free survival is defined as the time from treatment initiation to relapse/progression, death, initiation of non-protocol anti myeloma therapy, or last follow-up. Overall survival is defined as time from treatment initiation until death or last follow-up. Progression free and overall survival will be estimated using the Kaplan-Meier method.

We will estimate the response rate (CR, VGPR, and PR) by 6 months from initiation of lenalidomide intensification of lenalidomide given as single agent. For this calculation, patients who have asymptomatic progression after 2 cycles of lenalidomide and receive dexamethasone will be considered failures.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

Confirm eligibility as defined in the section entitled Criteria for Patient/Subject Eligibility.

Obtain informed consent, by following procedures defined in section entitled Informed Consent Procedures.

During the registration process registering individuals will be required to complete a protocol specific Eligibility Checklist.

All participants must be registered through the Protocol Participant Registration (PPR) Office at Memorial Sloan-Kettering Cancer Center. PPR is available Monday through Friday from 8:30am – 5:30pm at 646-735-8000. Registrations must be submitted via the PPR Electronic Registration System (http://ppr/). The completed signature page of the written consent/RA or verbal script/RA, a completed Eligibility Checklist and other relevant documents must be uploaded via the PPR Electronic Registration System.

15.1.1 Research Participant Registration for Collaborating Sites

Central registration for this study will take place at Memorial Sloan Kettering Cancer Center (MSKCC).

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to fax registration/eligibility documents to **Clinical Trials Office, MCT Core Research Staff at (646-227-2482).**

The following documents must be sent for each enrollment **within 24 hours** of the informed consent form being signed:

- The completed or partially completed MSKCC eligibility checklist
- The signed informed consent and signed HIPAA Authorization form (Research Authorization)
- Supporting source documentation for eligibility questions (laboratory results, pathology report, radiology reports, MD notes, physical exam sheets, medical history, prior treatment records, and EKG report).

Upon receipt, the research staff at Memorial Sloan-Kettering Cancer Center will conduct an interim review of all documents. If the eligibility checklist is not complete, the patient will be registered PENDING and the site is responsible for sending a completed form within 30 days of the consent.

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good

standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

Once eligibility has been established and the participant is registered, the participant will be assigned an MSKCC Clinical Research Database (CRDB) number (protocol participant number). This number is unique to the participant and must be written on all data and correspondence for the participant. This protocol participant number will be relayed back to study staff at the registering site via e-mail and will serve as the enrollment confirmation.

15.2 Randomization

There is no randomization in this study

16.1 DATA MANAGEMENT ISSUES

All patients will be enrolled on protocol at MSKCC and other collaborating centers. We expect to enroll the necessary 53 patients onto the study in 2 years.

A Research Study Assistant (RSA) will be assigned to the study at MSKCC. The responsibilities of the RSA include project compliance, data collection, abstraction and entry, data reporting, regulatory monitoring, problem resolution and prioritization, and coordination of the activities of the protocol study team.

The data collected for this study will be entered into electronic Case Report Forms (eCRFs) by the assigned MSKCC RSA. Source documentation will be available to support the computerized patient record.

16.1.1 Data and Source Documentation for Collaborating Sites

Data

Electronic Case Report Forms (eCRFs), directions for use and sign off requirements have been generated for this study. The MSKCC Principal Investigator or designee will provide eCRFs to participating sites. The participating Site PI is responsible for ensuring these forms are completed accurately and in a timely manner.

Source Documentation

Source documentation refers to original records of observations, clinical findings and evaluations that are subsequently recorded as data. Source documentation should be consistent with data entered into eCRFs. Relevant source documentation to be submitted throughout the study includes:

- Baseline measures to assess pre–protocol disease status (ex. Skeletal survey, bone marrow)

- Treatment records
- Grade 2-5 toxicities/adverse events not previously submitted with SAE Reports
- Response designation

Source documentation should include a minimum of two identifiers to allow for data verification. MSK will maintain the confidentiality of any subject-identifable information it may encounter.

16.1.2 Data and Source Documentation Submission for Participating Sites

The site is responsible for data entry using the Electronic Data Capture (EDC) system. Instructions for EDC access and guidelines are provided in the study procedure manual.

16.1.3 Data and Source Documentation Submission Timelines for Participating Sites

Data and source documentation to support data should be transmitted via the EDC system to MSKCC according to the following chart:

	Baseline	During Treatment Cycles	SAE	End of Therapy
SUBMISSION SCHEDULE				
Source Documentation	Within 24 hours (see section 15.1.1)		Within 24 hours (see section 17.2.1 and 17.3); updates to be submitted as available	
CRFs	Within 7 days of visit	within 14 days of the end of cycle		Within 14 days of visit
REQUIRED FOLDERS/FORMS				
Screening Folder	**X**			
Baseline Folder	**X**			
Adverse Event Form	**X**	**X**	**X**	**X**
Concomitant Medications Form	**X**	**X**		**X**
Correlative Form (if applicable)	**X**	**X**		**X**
Cycle (#) Folder		**X**		
Off Study Folder				**X**
Serious Adverse Event Form			**X**	

16.1.4 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the

participating sites, which the sites will resolve electronically in the EDC system. MSKCC will perform oversight of the data management of this trial.

Participating sites should respond to data queries within 14 days of receipt.

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action

Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

16.1.1 Investigator responsibilities:

Monthly telephone conference calls will be conducted among the collaborating center staff. Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations.

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

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

16.1.2 Retention of Records:

All documentation 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.]), and all IRB correspondence will be retained for at least 3 years

after the investigation is completed.

16.1.3 Quality Assurance for Participating Sites

Each site participating in the accrual of patients to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation. Audits may be accomplished in one of two ways: (1) selected patients records can be audited on-site at participating sites or (2) source documents for selected patients will be sent to MSKCC for audit. Audits will usually be determined by patient accrual numbers and rate of accrual, but can also be prompted by reported SAEs or request of Lead PI.

Audits will be conducted at least once shortly after initiation of patient recruitment at a site, and if possible, at the end or closeout of the trial at a site and during the trial if the trial lasts 3 or more years. At a minimum, audits will be conducted once a year but more frequently, if indicated.

The audit will include a review of source documentation to evaluate compliance for:

- Informed consent documents and procedures
- Adherence to eligibility criteria
- Protocol defined treatment
- Required baseline, on study and follow-up protocol testing
- IRB documents (submitted amendments, annual continuing review reports, SAEs)
- Required specimen submission
- Pharmacy review, if applicable
- Case Report Form submissions to MSKCC: timing and accuracy

A wrap-up session will be conducted at the outside site and preliminary findings will be discussed with the outside site PI and research team. The preliminary results will be sent to the MSKCC PI.

Each audit will be summarized and a final report will be sent to the PI at the audited participating institution within 30 days of the audit. The report will include a summary of findings, patient by patient case review, specific recommendations on any performance and/or shortcomings and request for corrective action, when necessary. When corrective action is required, the participating institution must reply within 45 days of receipt of audit report with their corrective action plan.

A copy of the audit report and corrective action plan (if applicable) submitted by the outside site must be sent to the MSKCC IRB, CRQA and maintained in the department's protocol regulatory binder.

16.1.4 Response Review

Since therapeutic efficacy is a stated primary objective, patients' responses at all sites are subject to review by MSKCC's Therapeutic Response Review Committee (TRRC). Radiology, additional lab reports and possibly bone marrow biopsies and/or aspirates will need to be obtained from the outside sites for MSKCC TRRC review and confirmation of response assessment. These materials must be sent to MSKCC within sixty days of request to the site.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled "Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials" which can be found at: http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://smsk_psps9/dept/ocr/OCR%20Website%20Documents/Clinical%20Research%20Quality%20Assurance%20(CRQA)/MSKCC%20Data%20and%20Safety%20Monitoring%20Plan.pdf

There are several different mechanisms at MSKCC by which clinical trials are monitored for data, safety and quality. There are institutional processes in place for quality assurance (e.g., protocol monitoring, compliance and data verification audits, therapeutic response, and staff education on clinical research QA) and departmental procedures for quality control, plus there are two institutional committees that are responsible for monitoring the activities of our clinical trials programs. The committees: Data and Safety Monitoring Committee (DSMC) for Phase I and II clinical trials, and the Data and Safety Monitoring Board (DSMB) for Phase III clinical trials, report to the Center's Research Council and Institutional Review Board.

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored, in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

Prior to implementing this protocol at MSKCC, the protocol, informed consent form, HIPAA authorization and any other information pertaining to participants must be approved by the MSKCC Institutional Review Board/Privacy Board (IRB/PB). Prior to implementing this protocol at the participating sites, approval for the MSKCC IRB/PB approved protocol must be obtained from the participating site's IRB.

The following documents must be provided to MSKCC before the participating site can be initiated and begin enrolling participants:

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form and HIPPA Authorization
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site

- Documentation of Good Clinical Practice (GCP) training for the PI and co-PI at each participating site
- Participating site laboratory certifications and normals

Upon receipt of the required documents, MSKCC will formally contact the site and grant permission to proceed with enrollment.

16.3.1 Amendments

Protocol amendments

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

Each change to the protocol document must be organized and documented by MSKCC and first approved by the MSKCC IRB/PB. Upon receipt of MSKCC IRB/PB approval, MSKCC will immediately distribute all non expedited amendments to the participating sites, for submission to their local IRBs.

Participating sites must obtain approval for all non expedited amendments from their IRB within 90 calendar days of MSKCC IRB/PB approval. If the amendment is the result of a safety issue, or makes eligibility criteria more restrictive, sites will not be permitted to continuing enrolling new participants until the participating site IRB approval has been granted.

The following documents must be provided to MSKCC for each amendment within the stated timelines:

- Participating Site IRB approval
- Participating Site IRB approved informed consent form and HIPAA authorization

16.3.2 Additional IRB Correspondence

Continuing Review Approval

The Continuing Review Approval letter from the participating site's IRB and the most current approved version of the informed consent form should be submitted to MSKCC within 7 days of expiration. Failure to submit the re-approval in the stated timeline will result in suspension of study activities.

Deviations and Violations

A protocol deviation on this study is defined as a request to treat a research participant who does not meet all the eligibility criteria, pretreatment evaluation, or who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC

or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC as soon as possible. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

Participating sites should report deviations and violations to their institution's IRBs as soon as possible per that site's institutional guidelines. Approvals/acknowledgments from the participating site IRB for protocol deviations and violations should be submitted to MSKCC as received.

Other correspondence

Participating sites should submit other correspondence to their institution's IRB according to local guidelines, and submit copies of that correspondence to MSKCC.

16.3.3 Document maintenance

The MSKCC PI and the Participating Site PI will maintain adequate and accurate records to enable the implementation of the protocol to be fully documented and the data to be subsequently verified.

The participating sites will ensure that all participating site IRB correspondence (IRB approval letters referencing protocol version date and amendment number, IRB approved protocol, appendices, informed consent forms, deviations, violations, and approval of continuing reviews) is maintained in the regulatory binder on site and sent to MSKCC.

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic. After study closure, the participating site will maintain all source documents, study related documents and CRFs for 3 years.

16.4 Noncompliance

If a participating site is noncompliant with the protocol document, accrual privileges may be suspended and/or contract payments may be withheld (if applicable), until the outstanding issues have been resolved.

17.0 PROTECTION OF HUMAN SUBJECTS

Participation in this trial is voluntary. All patients will be required to sign a statement of informed consent, which must conform to MSKCC and collaborating centers IRB guidelines.

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

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 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.

Potential risks and benefits

The potential risks of this therapy may outweigh the potential benefit in an individual patient. The potential risks to patients are related to drug induced adverse effects and are outlined in Section 11.0. Appropriate exclusion criteria for patients are listed in Section 6.0: Patient Eligibility. Appropriate exclusion of patients with significant organ dysfunction or infection will help avoid treatment-related toxicity. Careful monitoring of laboratory parameters and patient symptoms, along with serial assessment for disease recurrence, will be carried out routinely in order to minimize the risk of adverse effects during this study.

Alternatives/Options for treatment

Patients with newly diagnosed standard-risk multiple myeloma have many treatment options. Alternative therapy for patients who choose not to enroll on this study include standard chemotherapy, autologous or allogeneic stem cell transplant, thalidomide, steroids, bortezomib, lenalidomide, some combination of the above, other clinical trials, observation, or supportive care.

Costs

Patients will be responsible for all costs related to treatment and complications of treatment, including all hospitalizations. Patients will not be responsible for the cost of lenalidomide, research blood tests and research bone marrow samples.

17.1 Privacy

MSKCC's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

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 their 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

17.2 Serious Adverse Event (SAE) Reporting

An adverse event is a new or unexpected event or a worsening of an existing condition in a subject that occurs during treatment and within the study period, whether or not considered to

be treatment-related.

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

- Results in death
- Is life-threatening: 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.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity: Persistent or significant disability or incapacity" means that there is a substantial disruption of a person's ability to carry out normal life functions.
- Is a congenital anomaly or birth defect
- Is an important medical event: Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in situations where none of the outcomes listed above occurred. Important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above should also usually be considered serious. Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse. A new diagnosis of cancer during the course of a treatment should be considered as medically important.

The following event must also be reported in an expedited manner:

- Pregnancy (see section 17.4)

Reporting SAE to IRB At MSKCC:

Any SAE must be reported to the IRB/PB as soon as possible but no later than 5 calendar days. The IRB/PB requires a Clinical Research Database (CRDB) SAE report be submitted electronically to the SAE Office at sae@mskcc.org. The report should contain the following information:

Fields populated from the CRDB:

- Subject's name (generate the report with only initials if it will be sent outside of MSKCC)
- Medical record number
- Disease/histology (if applicable)
- Protocol number and title

Data needing to be entered:

- The date the adverse event occurred
- The adverse event
- Relationship of the adverse event to the treatment (drug, device, or intervention)
- If the AE was expected
- The severity of the AE
- The intervention
- Detailed text that includes the following information:
  - An explanation of how the AE was handled
  - A description of the subject's condition
  - Indication if the subject remains on the study
  - If an amendment will need to be made to the protocol and/or consent form

The PI's signature and the date it was signed are required on the completed report.

17.2.1 Reporting SAE to Study Supporter (Celgene Corporation)

The investigator should first inform the MSKCC PI or designee of any SAE (regardless of causality) within 24 hours of being aware of the event. The MSKCC RSA will then inform Celgene and collaborating center of these SAEs. The date of awareness should be noted on the report. This must be documented on a CRDB AE report or Celgene SAE Report Template. Either of these forms must be completed and supplied to Celgene within 24 hours of learning of the event by the MSKCC RSA. If applicable, follow-up and resolution reports as described below must be reported to Celgene. The Celgene tracking number (RV-MM-PI-641) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

In addition to completing appropriate patient demographic and suspect medication information, the report should include the following information:

- Treatment regimen (dosing frequency, combination therapy)
- Protocol description (and number, if assigned)
- Description of event, severity, treatment, and outcome if known
- Supportive laboratory results and diagnostics
- Investigator's assessment of the relationship of the adverse event to each investigational product and suspect medication

The investigator will determine which events are associated with the use of the study drugs.

For reporting purposes, an AE should be regarded as possibly related to the use of the investigational product if the investigator believes:

- There is a clinically plausible time sequence between onset of the AE and study drug administration; and/or

- There is a biologically plausible mechanism for the study drug causing or contributing to the AE; and
- The AE cannot be attributed solely to concurrent/underlying illness, other drugs, or procedures.

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.

Follow-up information may be added to a previously submitted report by any of the following methods:

- Adding to the original report and submitting it as follow-up
- Adding supplemental summary information and submitting it as follow-up with the original form
- Summarizing new information and faxing it with a cover letter including subject identifiers (i.e. D.O.B. initial, subject number), protocol description and number, if assigned, suspect drug, brief adverse event description, and notation that additional or follow-up information is being submitted (The patient identifiers are important so that the new information is added to the correct initial report)

17.3 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approvals/acknowledgements must be sent to MSK upon receipt.
- Participating sites are responsible for reporting all SAEs to the MSKCC PI via fax or e-mail within 24 hours of learning of the event.
- Participating sites should notify the MSKCC PI of any grade 5 event immediately.
- Participating sites should use the SAE Report Template to report SAEs to MSK.

SAE contact information for the Coordinating Center is listed below:

FAX: (646) 227-2482 to the attention of the MSKCC MCT Core/Clinical Trials Office Research Staff

EMAIL: Hani Hassoun, MD (hassounh@mskcc.org)

Responsibility of MSKCC

- The MSKCC Research Staff is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.2 and to the Celgene Corporation as described in 17.2.1.

- The MSKCC PI is responsible for informing all participating sites about all unexpected SAEs that are either possibly, probably or definitely related to the study intervention within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.
- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.4 Safety Reports

- MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
- MSKCC must submit safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per the local IRB institutional guidelines.

Adverse Drug Reaction Reporting

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patient, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

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

Pregnancy Reporting

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

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported

as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form.

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

Male Subjects

If a female partner of a male subject taking investigational product becomes pregnant, the male subject taking lenalidomide should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Celgene Drug Safety Contact Information:

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

Adverse event updates/IND safety reports

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

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

The Investigator shall notify his/her IRB promptly of these new serious and unexpected AE(s) or significant risks to subjects.

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB, on file.

Annual Reports to Celgene

This study meets requirements for IND exemption. Annual report must be submitted to Celgene for review/approval:

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.

18.1 INFORMED CONSENT PROCEDURES

Before protocol-specified procedures are carried out, consenting professionals will explain full details of the protocol and study procedures as well as the risks involved to participants prior to their inclusion in the study. Participants will also be informed that they are free to withdraw from the study at any time. All participants must sign an IRB/PB-approved consent form indicating their consent to participate. This consent form meets the requirements of the Code of Federal Regulations and the Institutional Review Board/Privacy Board of this Center. The consent form will include the following:

1. The nature and objectives, potential risks and benefits of the intended study.
2. The length of study and the likely follow-up required.
3. Alternatives to the proposed study. (This will include available standard and investigational therapies. In addition, patients will be offered an option of supportive care for therapeutic studies.)
4. The name of the investigator(s) responsible for the protocol.
5. The right of the participant to accept or refuse study interventions/interactions and to withdraw from participation at any time.

Before any protocol-specific procedures can be carried out, the consenting professional will fully explain the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must agree to the Research Authorization component of the informed consent form.

Each participant and consenting professional will sign the consent form. The participant must receive a copy of the signed informed consent form.

18.1 FOR PARTICIPATING SITES

The investigators listed on the protocol cover page and their qualified designees at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

Signed copies of the informed consent should be distributed as follows: One copy will be given to the participant to be retained for their personal records. One copy will be maintained on file at the MSKCC. The third copy will be confidentially maintained by the participating institution.

A note will be placed in the medical record documenting that informed consent was obtained for this study, and that the participant acknowledges the risk of participation.

19.1 REFERENCES

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20.0 APPENDICES

Appendix A: Criteria For Symptomatic Relapse And Progression Of Multiple Myeloma

Appendix B: Lenalidomide Risks Of Fetal Exposure, Pregnancy Testing Guidelines And Acceptable Birth Control Methods

Appendix C: Cockcroft-Gault Estimation Of Crcl

Appendix D: Medication Diary/Log For Lenalidomide And Dexamethasone

Appendix E: ECOG Performance Status

APPENDIX A: CRITERIA FOR SYMPTOMATIC AND ASYMPTMATIC RELAPSE AND PROGRESSION OF MULTIPLE MYELOMA

Patients will be considered as having *symptomatic* relapse/progression of disease if they show evidence of disease relapse or progression by serum or urine studies according to consensus criteria, AND present any of the following organ dysfunctions that are deemed to be related to disease progression:

[C] Calcium elevation in the blood (serum calcium > 10.5 mg/l or upper limit of normal)
[R] Progressive renal insufficiency (serum creatinine > 2mg/dl)
[A] Progressive anemia with hemoglobin < 9 g/dl

[B] New lytic lesion by skeletal survey

Patients will be considered as having asymptomatic relapse/progression if they show evidence of disease relapse or progression by serum or urine studies according to consensus criteria without evidence of organ damage as defined above.

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

Risks Associated with Pregnancy

The use of lenalidomide in pregnant females and nursing mothers has not been studied nor has the effect of the lenalidomide on human eggs and sperm. Lenalidomide is structurally related to thalidomide. Thalidomide is a known human teratogenic active substance that causes severe life-threatening birth defects. An embryofetal development study in animals indicates that lenalidomide produced malformations in the offspring of female monkeys who received the drug during pregnancy. The teratogenic effect of lenalidomide in humans cannot be ruled out. Therefore, a risk minimization plan to prevent pregnancy must be observed.

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

Criteria for females of childbearing potential (FCBP)

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

The investigator must ensure that:

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

Contraception

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

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

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

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking lenalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to one of the effective method listed above. The risk of venous thromboembolism continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.
Implants and levonorgestrel-releasing intrauterine systems are associated with an increased risk of infection at the time of insertion and irregular vaginal bleeding. Prophylactic antibiotics should be considered particularly in patients with neutropenia.

Pregnancy testing
Medically supervised pregnancy tests with a minimum sensitivity of 50 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting lenalidomide

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

***Male Patients*:**
Must agree to practice complete abstinence or agree to use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following lenalidomide discontinuation

Female Patients:

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

Male Patients:

- Must practice complete abstinence or use a condom during sexual contact with pregnant females or females of childbearing potential throughout the entire duration of lenalidomide treatment, during dose interruptions and for at least 28 days following lenalidomide discontinuation, even if he has undergone a successful vasectomy.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study patient during study participation, the investigator must be notified immediately.
- Male patients should not donate semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.
-

Additional precautions

- Patients should be instructed never to give lenalidomide to another person.
- Patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.
- Any unused lenalidomide must be returned as instructed through Revlimid REMS™.

APPENDIX C: Cockcroft-Gault estimation of CrCl:

Cockcroft-Gault estimation of creatinine clearance (CrCl):

(Cockcroft, 1976; Luke 1990)

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \quad \textbf{(Males)}$$

$$\text{CrCl (mL/min)} = \frac{(140 - \text{age}) \times (\text{weight, kg})}{72 \times (\text{serum creatinine, mg/dL})} \times 0.85 \quad \textbf{(Females)}$$

APPENDIX D: Pill Diary for IRB #11-107

Number of Pills Given:_____
Total Daily Dose:_____
(To be Completed by RN)

Pill Bottle(s) returned: Circle **Yes** or **No**
Number of Pills **returned**:_____

PLEASE FILL OUT AND BRING THIS SHEET AT YOUR NEXT VISIT. This log should be completed each time you take the study medication at home, and returned at the end of each cycle. If you miss a dose, please indicate in the table below.

CYCLE #: _____ # of WEEKS_____

Day	Date	Number of Lenalidomide capsules taken (please indicate time)	Dexamethasone tablets taken (please indicate time)
EXAMPLE	1/1/2011	2, 4:00 PM	1, 3:00 PM
1			
2			
3			
4			
5			
6			
7			
8			
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27			
28			

PatientSignature: _____ Date: _____
Consenting Professional/Research RN Signature: _____ Date: ___
Consenting Professional/Research RN
Comments:_____
_____

APPENDIX E: ECOG Performance Status

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