# Phase II Study of Response Adapted Therapy Using Single Agent Lenalidomide in Older Adults with Newly Diagnosed, Standard Risk Multiple Myeloma

**NCT01054144**

**Version 6**

**April 15, 2016**

# Myeloma Program

SPONSOR: H. Lee Moffitt Cancer Center

STUDY NUMBER: MCC 16018

CELGENE TRACKING #: RV-MM-PI-0454

STUDY TITLE: Phase II Study of response adapted therapy using single agent lenalidomide in older adults with newly diagnosed standard risk multiple myeloma.

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PhD

SUPPORTER(S): Celgene Corporation

CLINICAL FACILITY: H. Lee Moffitt Cancer Center and Research Institute

STUDY DRUGS: Lenalidomide (Revlimid®)
Prednisone
Dexamethasone (Decadron)

PROTOCOL VERSION: Version 6 (April 15, 2016)

IRB APPROVAL DATE: 12/08/2009

***CONFIDENTIAL***

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## PRINCIPAL INVESTIGATOR SIGNATURE PAGE

**Principal Investigator:**

Signature of Investigator Date

Rachid Baz, MD

By my signature, I agree to personally supervise the conduct of this study and to ensure its conduct in compliance with the protocol, informed consent, IRB/EC procedures, instructions from Celgene representatives, the Declaration of Helsinki, ICH Good Clinical Practices guidelines, and the applicable parts of the United States Code of Federal Regulations or local regulations governing the conduct of clinical studies.

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# 1 Protocol Synopsis

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| **PROTOCOL TITLE: Phase II Study of response adapted therapy using single agent lenalidomide in older adults with newly diagnosed standard risk multiple myeloma.** | |
| **PROTOCOL NUMBER:** | MCC16018 |
| **IRB APPROVAL DATE OF PROTOCOL:** | 12/08/2009 |
| **STUDY DRUG(s):** | Lenalidomide (Revlimid®)<br>Prednisone<br>Dexamethasone (Decadron) |
| **INDICATION:** | Newly Diagnosed (standard risk) Multiple Myeloma with Active Disease |
| **STUDY PHASE:** | 2 |

**STUDY OBJECTIVES:**

**Primary:**

1- To estimate the efficacy of a response adapted approach of treatment of older adults with standard risk multiple myeloma

**Secondary:**

1. To evaluate the efficacy of single agent lenalidomide in patients with standard risk multiple myeloma

2. To evaluate the safety and efficacy of the combination of lenalidomide and prednisone in non responders to single agent lenalidomide
3. To evaluate markers of lenalidomide induced tumor immunity in patients treated with single agent lenalidomide

**STUDY DESIGN:**

This is a multi-center, single-arm, phase 2, open-label study of lenalidomide [Revlimid® (R)] based therapy in older adults with standard risk multiple myeloma. After enrollment patients will receive single agent lenalidomide. Responders (minimal response or better) after 2 cycles will continue present therapy until disease progression or intolerable toxicity. Patients with stable disease after 2 cycles will receive prednisone (100 mg orally on days 1to 5 of each cycles) in addition to lenalidomide. Patients with evidence of disease progression after 2 cycles of single agent lenalidomide will receive low dose dexamethasone (40 mg weekly) in addition to lenalidomide. Patients not receiving low dose dexamethasone and with disease progression at any time during the study will be eligible to receive low dose dexamethasone in combination with lenalidomide. Patients on lenalidomide and low dose dexamethasone who experience disease progression at any time during the study will be taken off study and treated with alternative therapies..

**STUDY ENDPOINTS**

**Primary:**

1- The 12-month progression free survival (PFS) of older adults with mildly symptomatic multiple myeloma treated on this response adapted approach (i.e. time from lenalidomide start to failure of lenalidomide and low dose dexamethasone)

**Secondary:**

1- The response rate of older adults with mildly symptomatic multiple myeloma to single agent lenalidomide, lenalidomide prednisone and lenalidomide low dose dexamethasone in patients with suboptimal responses to lenalidomide monotherapy

2- The toxicity profile of these lenalidomide based combinations

3- The progression free survival of patients treated with single agent lenalidomide

4- The 1 year overall survival (OS) of older adults with mildly symptomatic multiple myeloma treated on this response adapted approach

**Exploratory**

1-Measure a lenalidomide induced tumor specific immune response and correlate the tumor specific immune response with corticosteroid use, response to therapy and duration of response

2- To evaluate the impact of lenalidomide mono-therapy on expression of tumor suppression genes and cell cycle regulators

| | |
|---|---|
| **STUDY DURATION:** Patients will receive study therapy until evidence of disease progression on lenalidomide and low dose dexamethasone, unacceptable toxicity or withdrawal of consent | **TOTAL SAMPLE SIZE:** approximately 30 patients enrolled at Moffitt and 30 patients enrolled in a parallel identical design study in multiple sites in South Korea. |

**STUDY DRUG SUPPLIES:** Lenalidomide capsules will be supplied by Celgene Corporation at no charge through the RevAssist® program.

Commercial supplies of dexamethasone (Decadron®) and prednisone tablets will be utilized.

Commercial supplies of aspirin will be utilized.

**DOSING REGIMENS:**

- Oral Lenalidomide (R) will be administered every 28 days as follows:
  - 25 mg QD PO daily on Days 1-21 followed by 7 days rest (10 mg dose will be used for patients with a Creatinine clearance < 60 ml/min)
- Oral Prednisone (100 mg) will be administered on days 1 to 5 of every 28 days cycle in patients receiving combination lenalidomide and prednisone (LP).
- Oral dexamethasone (40 mg) will be administered once a week in patients receiving lenalidomide and low dose dexamethasone (Ld).

All subjects will also receive concomitant aspirin 81 mg PO daily. For patients who cannot tolerate aspirin, low molecular weight heparin or therapeutic doses of coumadin may be used in place of aspirin.

**Rationale for Amendment 6**

MCC16018 has enrolled 30 patients from 2/2010 to 6/2013. It has been closed to accrual since 10/2013 given it met its accrual target. Currently, six patients only continue on treatment, for now 2-4 years. We anticipate to final close the study as soon as a manuscript has been published.
Of note, lenalidomide was approved by the FDA for newly diagnosed multiple myeloma patients in 2/2015. MCC16018 involves lenalidomide based therapy for newly diagnosed multiple myeloma and is thus currently considered standard of care (although that use was considered investigational at the time of initiation and completion of accrual of the study). Accordingly, we propose to collect more limited data pertaining to the current treatment of study subject as of 2/2016 until the final closure of the trial. Specifically, we will only plan to capture only serious adverse events (SAE), response and follow up data. Patients will continue on treatment and undergo standard of care monitoring which is at the discretion of the treating physician.
The changes made with this amendment will serve several purposes:

1- Decrease the burden on patients to comply with study requirement (for example, comply with study visit timeframe).
2- Decrease the number of deviations due to non-compliance with study requirements (such as missed 24h urine protein electrophoresis, laboratory testing outside the window).
3- Decrease the burden to the study team which would otherwise continue to collect additional data which will not aid in the overall interpretation of the study results (it is unlikely that a new toxicity to lenalidomide will be encountered in this study population that have been on this treatment for now 2-4 years on average)

# 2 Schedule of Study Assessments

| Procedure | Screening/ Baseline (-28 Days) | Cycle 1 Day 1 | Cycle 2 day 28 | Every 4 Weeks (1st 6 cycles) | Maintenance Every 3 months except where Indicated [15] | Addition of Prednisone or Dexamethasone | 2 months after the addition of dexamethasone | Off Study[1] |
|---|---|---|---|---|---|---|---|---|
| Informed consent | X | - | - | - | - | - | | - |
| Inclusion/exclusion criteria | X | - | - | - | - | - | | - |
| Complete medical history | X | - | - | - | - | - | | - |
| Confirm diagnosis and stage/type MM | X | - | - | - | - | - | | - |
| Performance status (ECOG) | X | X | - | X | | X | | X |
| Concurrent therapy | X | X | - | X | | X | | X |
| **Safety Assessments:** | | | | | | | | |
| Adverse event query | - | X | - | X | X[12] | X | | X[12] |
| Concomitant Medication query | X | X | - | X | - | X | | X |
| Vital signs/ BSA | X | X | - | X | - | X | | X |
| 12-lead ECG | X | - | - | - | - | - | | - |
| Physical examination | X | X | - | X | - | X | | X |
| CBC w/diff[9] | X | X[9] | - | X[9] | - | X | | X |
| Serum Chemistry[2] | X | | - | X | - | X | | X |
| TSH, $T_3$, $T_4$[3] | X | - | - | X[3] | - | - | | - |
| Pregnancy testing and counseling[4] | X[4] | X[4] | - | X[4] | - | X | | X[4] |
| Serum Free Light Chain | X | - | - | X | - | X | | X |
| Serum B12, RBC Folate, | X[13] | - | - | - | - | - | | - |
| **Efficacy measurements:** | | | | | X | | | |
| β-2-M | X | - | - | X | - | X | | X |
| Protein electrophoresis (serum and urine) | X | - | - | X | - | X | | X |
| Quantitative immunoglobulins | X | - | - | X | - | X | | X |
| Immunofixation studies (serum and urine) | X | - | - | X | - | X | | X |
| Skeletal survey | X | - | X[14] | X[5] | - | X | | X |
| | - | - | - | X | - | X | | X |
| **Dosing:** | | | | | | | | |
| Register patient into RevAssist® program | X | | | | | - | | |
| Prescribe study drug[10] | - | X[10] | | X[10] | - | X | | - |
| Count study drug returns[10] | - | - | | X | | X | | X |
| Dispense Diary Cards | | X | | X | | X | | |
| Collect Diary Cards | | | | X | | X | | X |
| **Correlative testing** | | | | | | | | |
| Bone marrow aspiration for ancillary studies | X | | X[14] | | | X[14] | | |
| Peripheral blood collection for ancillary studies | | X[14] | X[14] | | | X[14] | X[14] | |
| **Follow-up:** | | | | | X | | | |
| Survival | | | | | | | | X[8] |

**Screening procedures must be done within 28 days of first cycle unless otherwise specified.**

**Starting with Cycle 1, Day 1, and all tests must be done +/- 7 business days of the treatment visit day. However, pregnancy testing must be done strictly as scheduled in footnote #4 below and in sections 6.5.1 and 6.7 without an allowance of +/- 7 days.**

* An unscheduled visit can occur at any time during the study. Source must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded on the appropriate CRF. Source documents for these unscheduled visits must also be maintained.

[1] All subjects are to have the designated tests performed upon discontinuation of study drug.

[2] Clinical laboratory examinations include: total protein, albumin, calcium, , glucose, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, and LDH.

[3] Serum TSH, (Thyroid Stimulating Hormone), T3 and T4 levels every 3 months

[4] Pregnancy testing for females of child bearing potential. A female of childbearing potential (a woman of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) who has not been postmenopausal for at least 24 consecutive months [i.e., who has had menses at any time in the preceding 24 consecutive months]). Pregnancy testing must be performed 10 to 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 4 weeks 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 4 weeks 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 VIII: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

[5] Skeletal survey is to be performed at baseline, upon addition of corticosteroids (prednisone and / or dexamethasone) , discontinuation, and when clinically indicated.

[6] Bone marrow biopsy is to be performed at baseline, after 2 cycles of single agent lenalidomide therapy, to confirm CR, at the time of addition of corticosteroids (prednisone and / or dexamethasone), discontinuation, and when clinically indicated.

[8] Survival follow-up to be completed every 3 months.

[9] CBC with diff. is required on Day 1Cycle 1 (unless baseline done within 7 days of Day 1), then every 2 weeks for the first 4 weeks of therapy. After the first 4 weeks of therapy, if the patient required a dose reduction of lenalidomide (Revlimid®) or the addition of cytokine support due to neutropenia encountered during the previous cycle, CBC with diff. is required at least every 2 weeks during the next cycle, otherwise CBC with diff. is required at least every 4 weeks. More frequent CBCs may be obtained at the investigator's discretion. After 4/2016, laboratory testing is at the discretion of the treating physician and in accordance with lenalidomide package insert. CBC will not be collected for the purpose of the trial but could be ordered per standard practise

[10] Lenalidomide must be prescribed through and in compliance with Celgene's RevAssist® Program. Prescriptions must be filled within 7 days. Drug returned from the previous cycle will be counted, recorded in the patient's CRF. Patients must be instructed to return all bottles (whether empty, partial or full) at each visit. Unused lenalidomide should be returned to the patient for disposition in accordance with the RevAssist® program. After April 2016, diaries and pill counts will not be performed.

[11]. During maintenance, patients will have laboratory testing per institutional standard of care approximately every 3 months.

12 After April 2016, only serious adverse events SAE will be collected.

13 At the initiation of study and yearly thereafter.

14 Ancillary bone marrow aspiration will be obtained at baseline and after 2 months of lenalidomide monotherapy. Ancillary peripheral blood samples will be obtained at baseline, after 2 months of lenalidomide monotherapy and after 2 month of addition of dexamethasone .see section 9.7.4 for details regarding ancillary studies.

15. Patients who complete the first 6 cycles of therapy, are on a stable dose of lenalidomide for more than 2 cycles and are responding to therapy are eligible for entering a maintenance schedule of visits where office visits will be every 3 months and monitoring will be pre institutional standard of care Patient will continue to be followed for disease progression per standard clinical practice.

# 3 Glossary of Abbreviations

| | |
|---|---|
| $\beta_2$-M | Beta$_2$-microblogulin |
| β-hCG | Beta - Human chorionic gonadotropin |
| AE | Adverse event |
| ALT (SGPT) | Alanine transaminase (serum glutamate pyruvic transaminase) |
| AST (SGOT) | Aspartate transaminase (serum glutamic oxaloacetic transaminase) |
| Bid | Twice per day |
| BM | Bone marrow |
| BMSC | Bone marrow stromal cells |
| BUN | Blood urea nitrogen |
| CBC | Complete blood count |
| CFR | Code of Federal Regulations |
| CR | Complete response |
| CRF | Case report form |
| CTC | Common toxicity criteria |
| DLT | Dose-limiting toxicity |
| DSMP | Data Safety Monitoring Plan |
| DVT | Deep vein thrombosis |
| EC | Ethics Committee |

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|---|---|
| ECG | Electrocardiogram |
| ECHO | Echocardiogram |
| EGR1 | Early Growth Response 1 |
| EGR2 | Early Growth Response 2 |
| EGR3 | Early Growth Response 3 |
| FDA | Food and Drug Administration |
| GCP | Good clinical practice |
| G-CSF | Granulocyte colony stimulating factor |
| GM-CSF | Granulocyte macrophage colony stimulating factor |
| IB | Investigator's Brochure |
| ICH | International Conference on Harmonization |
| IFN-α | Interferon-alpha |
| IL | Interleukin |
| IMiD | Immunomodulatory drug |
| IMWG | International Myeloma Working Group |
| IND | Investigational New Drug |
| IRB | Institutional Review Board |
| IVP | Intravenous push |
| LDH | Lactate dehydrogenase |
| mAbs | Monoclonal antibodies |

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|---|---|
| MM | Multiple myeloma |
| MTD | Maximum tolerated dose |
| NCI | National Cancer Institute |
| NK cells | Natural Killer Cells |
| PBMC | Peripheral blood mononuclear cells |
| PD | Progressive disease |
| PCR | Polymerase chain reaction |
| PDE-4 | Phosphodiesterase 4 |
| PO | Per orum – by mouth |
| PR | Partial Response |
| PS | Performance status |
| SAE | Serious adverse event |
| Q.D. | Every day |
| Q-PCR | Quantitative Polymerase Chain Reaction |
| SPARC | Secreted Protein Acidic and Rich in Cysteine |
| SD | Stable disease |
| SWOG | Southwest Oncology Group |
| TCR | T-cell receptor |
| TGFβ | Tumor growth factor beta |
| TNF | Tumor necrosis factor |

| | |
|---|---|
| TPP | Therapeutics Product Programme |
| TSH | Thyroid-stimulating hormone |
| ULN | Upper limit of normal |
| VEGF | Vascular endothelial growth factor |
| WBC | White blood cell |
| WCBP | Women of child bearing potential |
| WHO | World Health Organization |

# 4 Background and Rationale

## 4.1. Multiple Myeloma

Multiple myeloma is a plasma cell neoplasm characterized by an infiltrate of monoclonal plasma cells in the bone marrow which results in the production of a monoclonal protein. Multiple myeloma accounts for approximately 10% of hematologic malignancies and about 1% of malignancies overall[1]. Approximately 19,000 patients will be diagnosed with multiple myeloma in 2007 in the United States and the median age at the time of diagnosis is 70 years (hence most patients with multiple myeloma are older than 65 years)[1]. Bone marrow involvement may result in cytopenias, painful skeletal lytic lesions and systemic symptoms (fevers, sweats, anorexia and weight loss); while the paraprotein may cause renal dysfunction, neuronal damage, amyloid deposition, and rarely hyperviscosity. The cornerstone of therapy of multiple myeloma has traditionally included the use of corticosteroids (prednisone or dexamethasone). However, these agents have substantial toxicities especially in the multiple myeloma patient population which tends to be particularly vulnerable to those side effects (namely fluid retention, non neutropenic infections and venous thromboembolic events). The past 5 years has witnessed the introduction of novel agents (lenalidomide, thalidomide and bortezomib) with considerable efficacy especially when combined with corticosteroids[2-4]. While these novel agents have considerably changed the outlook of multiple myeloma patients, the toxicity of therapy remains significant and attempts to reduce the toxicity of therapy by minimizing corticosteroid exposure remains a significant priority.

## 4.2. Lenalidomide

### 4.2.1 Preclinical evaluation of lenalidomide

Lenalidomide is a proprietary IMiD® compound of Celgene Corporation, which markedly stimulate T-cell proliferation, as well as IL-2 and IFN-α production, but do not inhibit phosphodiesterase 4 (PDE-4)[5]. Lenalidomide (Revlimid®) is 50 to 2000 times more potent than thalidomide in stimulating T-cell proliferation triggered via the T-cell receptor (TCR), and 50 to 100 times more potent than thalidomide in augmenting IL-2 and IFN-α production. In addition, Lenalidomide triggers dose-dependent decreased secretion of TNF-α, IL-1β, and IL-6; and triggers increased secretion of IL-10. The IC50 of Lenalidomide for inhibiting LPS induced TNF-α secretion by PBMC is ~100 nM (25.9 ng/mL), whereas thalidomide has an IC50 of ~194 μM (50.2 μg/mL)[6]. Lenalidomide decreases binding of MM cells to bone marrow stromal cells (BMSCs); inhibits the production in the BM milieu of cytokines (IL-6, VEGF, TNF-α) mediating growth and survival of MM cells; blocks angiogenesis; and stimulates host anti-MM NK cell immunity[7, 8]. These preclinical studies suggest that Lenalidomide may overcome drug resistance, even to thalidomide, in MM cells.

### 4.2.2. Lenalidomide in relapsed refractory multiple myeloma

The immunomodulator lenalidomide has considerable activity in multiple myeloma. Early phase I study of single agent lenalidomide in relapsed refractory multiple myeloma have shown a response rate of approximately 30%[9, 10]. This single agent activity was confirmed in a subsequent phase II study evaluating two different doses of lenalidomide (15 mg once daily or 15 mg twice daily) for 21 of a 28 days cycle[9]. High dose dexamethasone (40 mg orally on days 1-4, 9-12, and 17-20) was added after 2 or 4 cycles in the event of disease progression or stable

disease respectively. Of 83 evaluable patients, 5 had a complete remission, 15 a partial remission, 14 had a minimal response, 39 had stable disease and the remainder had progressive disease. The rate of minimal response or better was 40%[9]. Dexamethasone was added to lenalidomide therapy in 30 non-responders, and resulted in a response in 10 patients (30% added response rate)[9]. The combination of lenalidomide and high dose dexamethasone was compared to high dose dexamethasone in two phase III trials in relapsed refractory multiple myeloma[11, 12]. This combination resulted in an overall response rate of approximately 60% and a complete response rate of 25% which was statistically superior to high dose dexamethasone[11, 12]. More importantly, the combination of lenalidomide and high dose dexamethasone resulted in an overall survival benefit compared to high dose dexamethasone[11, 12]. These results have led to the approval of lenalidomide by the Food and Drug Administration for the treatment of relapsed or refractory multiple myeloma.

### 4.2.3 INDICATIONS AND USAGE:

Revlimid® (lenalidomide) is indicated for the treatment of patients with transfusion-dependent anemia due to Low- or Intermediate-1-risk myelodysplastic syndromes associated with a deletion 5q cytogenetic abnormality with or without additional cytogenetic abnormalities. Revlimid® is also approved in combination with dexamethasone for the treatment of patients with multiple myeloma that have received at least one prior therapy.

### 4.2.4 Adverse Events

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

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

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

### 4.2.5 Lenalidomide in newly diagnosed multiple myeloma

The phase II experience of lenalidomide and high dose dexamethasone in newly diagnosed multiple myeloma resulted in a response rate of 91% and generated interest in larger randomized studies evaluating this combination in this patient population[3]. The Eastern Cooperative Oncology Group randomized patients with newly diagnosed multiple myeloma to lenalidomide and low dose dexamethasone or lenalidomide and high dose dexamethasone[13]. The patients who received high dose dexamethasone in combination with lenalidomide had a superior response rate after 4 cycles of therapy (82% compared to 70% with low dose dexamethasone and lenalidomide, $p<0.01$), but had an inferior 1 year overall survival rate (87% versus 96%, $p<0.001$) and had a higher induction mortality (5% versus 0.5%, $p=0.006$)[13]. In addition, the patients who received high dose dexamethasone and lenalidomide had a higher rate of toxicity in the form of venous thromboembolic events, infectious complications, and neutropenia[13]. From these clinical observations, one can conclude that a better tolerated less intensive therapy will result in better survival (long term) outcomes in older adults with multiple myeloma.

### 4.2.6 Rationale for the evaluation of single agent lenalidomide in newly diagnosed mildly symptomatic multiple myeloma

While corticosteroids have been shown to result in apoptosis and decreased proliferation of multiple myeloma cells, they have also been noted to inhibit the stimulatory effects of lenalidomide on T cell and NK cell[14]. Hence, a lenalidomide based therapeutic approach excluding corticosteroids would take better advantage of the immunomodulatory effects of lenalidomide. In addition, clinical results corroborate such an approach: E4A03 study suggest that a lower dose of dexamethasone is associated with a superior survival outcome compared to higher dose of dexamethasone. These findings were more striking in older adults who are more vulnerable to the toxicities of dexamethasone (greater than 65 years of age)[13]. Accordingly, we propose to evaluate single agent lenalidomide in patients with newly diagnosed multiple myeloma who are only mildly symptomatic from their disease but who fulfill the requirement for active treatment initiation. This would be expected to result in better tolerance to therapy, less toxicity but more potential for eliciting the immunomodulatory effects of lenalidomide.

### 4.2.7 Measuring lenalidomide induced humoral immune response

Immunomodulation is one of the proposed mechanisms of action of lenalidomide and thalidomide in multiple myeloma. Because most of the clinical evaluations of lenalidomide in multiple myeloma have included concomitant corticosteroid use, firm evidence of immunomodulation and a lenalidomide induced tumor specific immune response has not been demonstrated *in vivo*. Noonan et al. have recently demonstrated enhanced humoral response to pneumococcal vaccination in multiple myeloma patients who received lenalidomide prior to vaccination as compared to patients receiving vaccination prior to lenalidomide therapy[15]. This data suggests an enhanced humoral immune response during lenalidomide therapy. Accordingly,

we propose to evaluate the impact of lenalidomide monotherapy on the development of a humoral immune response directed to common tumor antigens.

#### 4.2.7.1 Serametrix® serum profiling assay

The Serametrix serum profiling assay enables the multiplex detection of serum antibodies to key tumor antigens. The assay utilizes a proprietary protein microarray that contains protein antigens that are known to be immunogenic in cancer. The use of automated liquid handling equipment ensures high reproducibility, high throughput and low sample volumes. The assay has sufficient sensitivity and dynamic range to measure physiological levels of serum antibody and is therefore an effective tool in the measurement of humoral immune responses in cancer.

The Serametrix protein microarray contains approximately 100 tumor antigens. Each antigen is derived from sequence-verified full-length human clones. These are expressed in insect cells and the consequent eukaryotic glycosylation helps to ensure authentic epitopes are maintained. The proteins were selected from published scientific literature in consultation with leading academic tumor immunologists. The criteria for selection included demonstrable immunogenicity, association with cancer and suitability for use as biomarker.

### 4.2.8 Lenalidomide induced expression of tumor suppressor genes

A number of mechanisms of actions have been postulated to account for lenalidomide activity in multiple myeloma including direct tumor growth inhibition, upregulation of tumor suppressor genes and immunomodulation. Lenalidomide has been shown to induce the expression of various tumor suppressor genes (EGR1, EGR2, EGR3, p15, p21, p27 and SPARC) in multiple myeloma cells lines[14, 16, 17]. These studies have not been replicated in samples from patients and induction of these tumor suppressors could be an early predictor of response to lenalidomide. As

such, we propose to evaluate the expression of the above tumor suppressor genes after treatment of patients with single agent lenalidomide and correlate the induction of the tumor suppressor genes to clinical responses.

### 4.3. Corticosteroids in induction therapy for multiple myeloma.

The optimal dosage of corticosteroids in combination with lenalidomide in patients with newly diagnosed myeloma has not clearly been established. In older adults with multiple myeloma, several groups have attempted to investigate the optimal corticosteroid in induction therapy stemming from the lower tolerance to dexamethasone of older adults with multiple myeloma. One such investigation conducted by the national cancer institute of Canada compared induction therapy in older newly diagnosed multiple myeloma patients with melphalan and prednisone to therapy with melphalan and dexamethasone[18]. They noted a higher rate of grade 3 and 4 infections in the dexamethasone arm without a response or survival benefit to that agent[18]. Similar findings were reported by investigators of the Intergroupe Francais du Myelome (IFM) who compared induction therapy with melphalan and prednisone compared to dexamethasone based therapy in older adults with multiple myeloma[19]. These results prompted us to evaluate prednisone as the corticosteroid partner of lenalidomide in patients who do not achieve a response after 2 cycles of single agent lenalidomide and yet have not evidence of disease progression. This combination was safely delivered as reported in two investigations where lenalidomide and alternate day prednisone were used as maintenance therapy in relapsed and newly diagnosed patients[20].

# 5. Study Endpoints

**Primary:**

1- The 12-month progression free survival (PFS) of older adults with mildly symptomatic multiple myeloma treated on this response adapted approach (i.e. time from start of lenalidomide to failure of lenalidomide and low dose dexamethasone)

**Secondary:**

1- The response rate of older adults with mildly symptomatic multiple myeloma to single agent lenalidomide, lenalidomide prednisone and lenalidomide low dose dexamethasone in patients with suboptimal responses to lenalidomide monotherapy

2- The toxicity profile of these lenalidomide based combinations

3- The progression free survival of patients treated with single agent lenalidomide

4- The 1 year overall survival (OS) of older adults with mildly symptomatic multiple myeloma treated on this response adapted approach

**Exploratory**

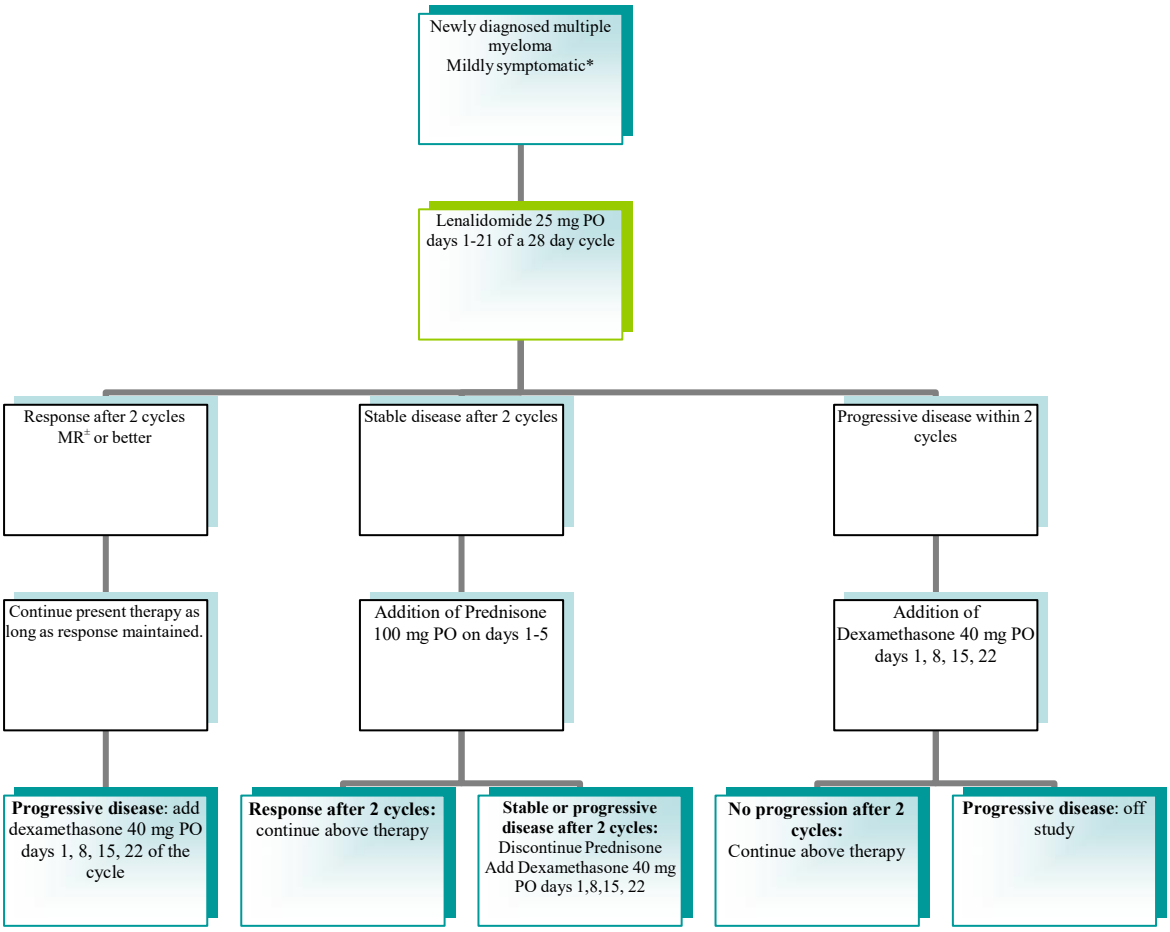
1- Measure a lenalidomide induced tumor specific immune response and correlate the tumor specific immune response with corticosteroid use, response to therapy and duration of response

2- To evaluate the impact of lenalidomide mono-therapy on expression of tumor suppression genes and cell cycle regulators

# 6. Investigational Plan

## 6.1. Overall design

This is a phase 2 trial evaluating a lenalidomide based response adapted strategy in older adults with newly diagnosed multiple myeloma. Subjects will be started on single agent lenalidomide. In the event of disease progression, low dose dexamethasone will be added (see diagram below). In the event of stable disease after 2 cycles of therapy, the use of an alternate corticosteroid (prednisone) will be added to lenalidomide therapy (see diagram below). In the event of a minimal response after 2 cycles of single agent lenalidomide therapy, such therapy will be continued until disease progression (see diagram below).




*Subject replacement and evaluable patients*

Subjects who discontinue study drug, other then for progression, prior to completing one cycle of therapy will be replaced.

## 6.2. Discussion of design

Older adults or subjects not willing or eligible for post induction high dose therapy and stem cell transplantation will be offered participation into this study. This is in line with findings from the ECOG E4A03 study which noted a decreased survival among patients receiving higher dose dexamethasone compared to low dose dexamethasone specifically in the subgroup of patients older than 65 years of age[13]. In addition, patients enrolled on this response adapted clinical

trial would be either not willing or ineligible to undergo *immediate* (post 4 cycles of induction) high dose therapy and stem cell transplantation. The rationale underlying this exclusion criterion related to the fact that patients wishing to undergo *immediate (post induction)* high dose therapy usually are treated with more aggressive front line regimens.

Mildly symptomatic patients will be selected for participation in this study. The rationale for the selection of this population lies in the fact that patients with aggressive disease at presentation (patients with significant symptoms) are probably best treated with combination therapy in order to achieve a higher likelihood of response (as evidenced by E4A03 where patients receiving higher dose dexamethasone in combination with lenalidomide had a higher response rate than patients receiving a lower dose of dexamethasone in combination with lenalidomide)[13]. Empirically, defining this patient population objectively can be difficult but we propose the following definition of mildly symptomatic disease: good performance status (ECOG 0-1), absence of severe cytopenias or renal failure, as well as low risk as defined by β2-microglobulin level and lack of adverse cytogenetic features[21].

In addition, this study will evaluate the role of an alternative corticosteroid in combination with lenalidomide. Prednisone is known to be a better tolerated corticosteroid than dexamethasone without a compromise in the efficacy. This was seen in a recent report of a clinical trial by the national cancer institute of Canada study comparing melphalan prednisone to melphalan dexamethasone (grade 3 and 4 infections; 9 versus 15%, p=0.03)[18]. In addition, the intergroupe francais du myelome (IFM) had noted similar finding in older adults with newly diagnosed myeloma randomized to melphalan prednisone or dexamethasone based induction[19]. Both trials did not note a superiority of dexamethasone based induction to the prednisone based induction.

The primary endpoint of this study will be the progression free survival of patients treated with this response adapted approach. This is defined as the time from enrollment to failure of lenalidomide and low dose dexamethasone. Outcomes of this cohort of patients treated with this response adapted approach would be compared to patients treated with lenalidomide and low dose dexamethasone. If this response adapted approach results in similar or improved outcomes compared to therapy with lenalidomide and low dose dexamethasone, this approach would be favored since it likely result in less toxicity by using an overall lower dosage of corticosteroid.

# 7. Study population

Male and female subjects with documented newly diagnosed multiple myeloma who meet all of the eligibility criteria in Section 7.1.1 below will be enrolled into the study.

## 7.1. Inclusion and exclusion criteria

Subjects are to be assessed for suitability for entry into the study based on the following inclusion and exclusion criteria.

### 7.1.1. Inclusion criteria

Subjects must meet all of the following inclusion criteria to be eligible for enrollment into the study:

1. Understand and voluntarily sign an informed consent form.
2. Age ≥65 years or not eligible for high dose therapy and autologous stem cell transplant.
3. Able to adhere to the study visit schedule and other protocol requirements.

4. Diagnosed with multiple myeloma and be considered to have active disease. Patients must not have received an active chemotherapy regimen or Dexamethasone. Patients may have received palliative radiotherapy at least 2 weeks prior to the study start.
5. Measurable myeloma paraprotein levels in serum (≥ 0.5 g/dL), urine (≥ 0.2 g excreted in a 24-hour urine collection sample) or by serum free light chains (involved free light chain greater than 100mg/L)
6. Eastern Cooperative Group (ECOG) Performance Status of 0 or 1.
7. Serum bilirubin levels ≤1.5 times the upper limit of the normal range for the laboratory (ULN).
8. Serum AST or serum ALT] levels ≤2 x ULN
9. Must have adequate bone marrow function:
    a. Absolute neutrophil count ≥ 1,000 cells/$mm^3$ (1.0 x $10^9$/L).
    b. Platelets ≥ 100,000 /$mm^3$.
10. Hemoglobin > 8 g/dL
11. Must have adequate renal function: Renal function assessed by calculated creatinine clearance as follows (see Appendix VI: Cockcroft-Gault estimation of CrCl):
    a. Calculated creatinine clearance ≥ 30ml/min by Cockcroft-Gault formula. See section below, "Prescribing Information", regarding lenalidomide dose adjustment for calculated creatinine clearance ≥ 30ml/min and < 60ml/min.
12. Low risk myeloma is defined as the absence of the following adverse features[21]
    i. t(4;14) by FISH or metaphase cytogenetics
    ii. t(14,16) or t(14;20) by FISH or metaphase cytogenetics
    iii. Deletion 17q13 by FISH
    iv. Deletion 13 by metaphase analysis
    v. Aneuploidy by metaphase analysis

vi. B2 microglobulin > 5.5

13. Able to tolerate one of the following thromboprophylactic strategies: aspirin, low molecular weight heparin or warfarin (coumadin).
14. All study participants must be registered into the mandatory RevAssist® program, and be willing and able to comply with the requirements of RevAssist®.
15. Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide for Cycle 1 (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 4 weeks before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a female of child bearing potential even if they have had a successful vasectomy. See Appendix VIII: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

### 7.1.2. Exclusion criteria

The presence of any of the following will exclude a subject from study enrollment:

1. Ongoing severe infection requiring intravenous antibiotic treatment.
2. Life expectancy of less than 3 months.

[†] 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).

3. Performance status of 2, 3 or 4
4. Prior malignancy, except for adequately treated basal cell or squamous cell skin cancer, in-situ cervical cancer, or other cancer from which the subject has been disease-free for at least 2 years.
5. Solitary bone or solitary extramedullary plasmacytoma as the only evidence of plasma cell dyscrasia.
6. Uncontrolled medical problems such as diabetes mellitus, congestive heart failure, coronary artery disease, hypertension, unstable angina, arrhythmias), pulmonary, hepatic and renal diseases unless renal insufficiency is felt to be secondary to multiple myeloma.
7. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.
8. Pregnant or lactating females.
9. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
10. Known hypersensitivity to thalidomide.
11. Use of any other experimental drug or therapy within 28 days of baseline.
12. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.
13. Any prior use of lenalidomide.
14. Concurrent use of other anti-cancer agents or treatments.
15. Known seropositive for or active viral infection with human immunodeficiency virus (HIV), hepatitis B virus (HBV) or hepatitis C virus (HCV). Patients who are seropositive because of hepatitis B virus vaccine are eligible.

# 8. Treatments

### 8.1.1. Investigational drug and reference therapy

#### 8.1.1.1. Supplier(s)

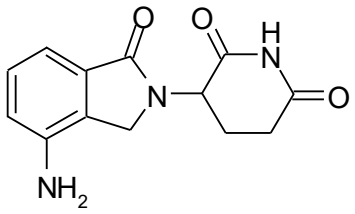
Celgene Corporation will supply Revlimid® (lenalidomide) to study participants at no charge through the RevAssist® program. All physicians who prescribe lenalidomide for research subjects enrolled into this trial and all research subjects enrolled into this trial must be registered in and must comply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

Commercial supplies of dexamethasone, prednisone, low molecular weight heparin, coumadin and aspirin will be used for this study.

#### 8.1.1.2. Lenalidomide Description

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

**Chemical Structure of Lenalidomide**




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

The empirical formula for lenalidomide is $C_{13}H_{13}N_3O_3$, and the gram molecular weight is 259.3.

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

**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.

**Dosage form**

Lenalidomide will be supplied as capsules for oral administration. Lenalidomide will be supplied as 5 mg and 25 mg capsules for oral administration.

**Prescribing Information**

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

The planned dose of lenalidomide for investigation is 25 mg/day, orally on days 1 - 21 followed by 7 days rest (28 day cycle). Dosing will be based on CrCl:

Lenalidomide will be given at a dose of 25 mg once daily on days 1 to 21, every 28 days for those patients with a subjects with a creatinine clearance of ≥ 60 mL/min by Cockroft-Gault formula.

Subjects with a creatinine clearance of ≥ 30 mL/min but < 60 mL/min by Cockroft-Gault formula will begin lenalidomide at 10 mg once daily on days 1 to 21, every 28 days.

The lenalidomide dose may be increased to dose 15 mg at the start of Cycle 3 if hematologic toxicities have not occurred.

Dosing will be in the morning at approximately the same time each day. Lenalidomide capsules should be swallowed whole, and should not be broken, chewed or opened.

If a dose of lenalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up.

Patients who take more than the prescribed dose of lenalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

**Special Handling Instructions**

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

### 8.1.1.3. Study Drug Storage

*Lenalidomide*

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

*Dexamethasone and prednisone*

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

### 8.1.1.4. Record of administration

Subjects will receive diary cards to record when medications are taken. Diary cards will be collected at the end of each cycle or every 3 cycles in maintenance.

Accurate records will be kept in the source documents of all drug administration (including prescribing and dosing). After April 2016, diary card will no longer be used

*Dexamethasone*

Commercial dexamethasone is available as 4 mg tablets for oral administration.

*Prednisone*

Commercial prednisone is available as 50 mg tables for oral administration

*Low Molecular Weight Heparin, Coumadin or Aspirin:*

Commercial low molecular weight heparin, coumadin or aspirin for oral administration will be utilized.

### 8.1.2. Treatment assignments

Subjects will be entered in to the study sequentially in the order they are registered.

### 8.1.3. Prior/Concomitant therapy

All medications (prescription and non-prescription), treatments and therapies taken from 28 days prior to the start of study drug, Lenalidomide, through to the last dose of study drug, must be recorded on the appropriate page of the data collection system. Subjects will be supplied a diary to record their concomitant medications. After April 2016, diary card will no longer be used.

#### 8.1.3.1. Allowed concomitant therapy

The use hematopoietic growth factors for subjects in this study are permitted when used to treat neutropenia and anemia. In addition, low dose prednisone (up to 10 mg/day) may be used for the treatment and prevention of lenalidomide induced neutropenia. Therapies considered necessary

for the subject's well being may be administered at the discretion of the Investigator. These therapies may include bisphosphonates, palliative radiation therapy, antibiotics, analgesics, antihistamines, or other medications as well as transfusions of red blood cells, platelets, or fresh frozen plasma given to assist in the management of complications associated with multiple myeloma. Low dose corticosteroid therapy, (the equivalent up to 10 mg a day of prednisone) for the treatment of the patient existing autoimmune, rheumatologic or inflammatory conditions is allowed.

#### 8.1.3.2. Prohibited concomitant therapy

Concomitant use of other anti-myeloma therapy while the subject is on study drug is prohibited. No new investigational therapies shall be initiated while the subject is on study drug.

### 8.1.4. Treatment compliance

To monitor treatment compliance, reconciliation of Lenalidomide capsules will be done at each study visit. Subject diaries will be provided to assist in the collection of dosing information between study visits. After April 2016, diary card will no longer be used and reconciliation of lenalidomide capsule will not be performed.

### 8.1.5. Dose modification or interruption

Subjects will be evaluated for adverse events at each visit using the National Cancer Institute Common Toxicity Criteria (NCI CTCAE) version 4.0 to grade severity. All subjects who are discontinued due to an adverse event should be followed for as long as necessary to document the resolution or stabilization of the event.

#### 8.1.5.1. Dose Reduction Steps for Lenalidomide

**Table 1: Lenalidomide dose levels**

| Starting Dose | Dose level –1 | Dose Level -2 | Dose Level –3 | Dose Level -4 |
|---|---|---|---|---|
| 25 mg PO days 1-21 of a 28 days cycle | 15 mg PO days 1-21 of a 28 days cycle | 10 mg PO days 1-21 of a 28 days cycles | 5 mg PO days 1-21 of a 28 days cycles | Discontinue |

Lenalidomide dose reductions will be done as per the instruction below and as illustrated in the following example.

Example 1: A patient is being treated with lenalidomide 25mg daily on Days 1-21 every 28 days and requires a lenalidomide dose reduction per Table 1. The patient will start their next cycle of therapy with lenalidomide 15 mg daily on Days 1-21 every 28 days.

Lenalidomide will always be dosed daily on Days 1-21 every 28 days. The minimum lenalidomide dose is 5 mg/day on days 1 – 21 every 28 days. If this dose is not tolerated, lenalidomide must be discontinued.

**Table 2: Dose Modification Guidelines for Lenalidomide**

| CTCAE CATEGORY ADVERSE EVENT | CTCAE GRADE | TREATMENT ADJUSTMENT Maintenance Phase |
|---|---|---|
| Neutropenia | Grade 3 with fever grade 4 | Hold lenalidomide for remainder of cycle if the toxicity occurs in the latter 2 weeks of the cycle and resume the next cycle at the dose detailed below. Alternatively if the toxicity occurred during the first 2 |

| | | |
|---|---|---|
| | | weeks of the cycle, then hold lenalidomide until the toxicity improves to ≤ grade 2 and resume lenalidomide as detailed below.<br>First occurrence: when resolved to ≤ grade 2 begin next cycle with one dose level reduction of lenalidomide or continue same dose with cytokine or low dose prednisone support.<br>Second occurrence: when resolved to ≤ grade 2 begin next cycle with one level dose reduction of lenalidomide or continue same dose with cytokine support if not already implemented.<br>Subsequent dose reductions of lenalidomide are permitted at the investigators discretion. |
| Thrombocytopenia | Grade 4 | Hold lenalidomide for remainder of cycle if the toxicity occurs in the latter 2 weeks of the cycle and resume the next cycle with one dose level reduction in lenalidomide. Alternatively if the toxicity occurred during the first 2 weeks of the |

| | | |
|---|---|---|
| | | cycle, then hold lenalidomide until the toxicity improves to ≤ grade 2 and resume lenalidomide with one dose level reduction . . |
| Cardiac toxicity | Arrhythmia ≥ grade 2 | Hold lenalidomide until resolved to ≤ grade 1. Resume at one dose level reduction of lenalidomide. |
| | Arrhythmia ≥ grade 3 | Discontinue protocol therapy. |
| | Congestive heart failure ≥ grade 2 | Discontinue lenalidomide at the investigators discretion. |
| Hyperthyroidism/ Hypothyroidism | Any grade | Hold lenalidomide and evaluate patient. May resume therapy at the same dose once patient is stable at investigators discretion. |

| | | |
|---|---|---|
| Non desquamating rash | Grade 2 | Hold lenalidomide for remainder of cycle if the toxicity occurs in the latter 2 weeks of the cycle and resume the next cycle with one dose level reduction in lenalidomide if the toxicity resolves to less than grade 2. Alternatively if the toxicity occurred during the first 2 weeks of the cycle, then hold lenalidomide until the toxicity improves to < grade 2 and resume lenalidomide with one dose level reduction .. |
| | Grade 3 or 4 | Discontinue protocol therapy. |
| Desquamating rash or Erythema Multiforme | Any grade | Discontinue protocol therapy. |

| | | |
|---|---|---|
| Allergic reaction or hypersensitivity | Grade 2 or 3 | Hold lenalidomide for remainder of cycle if the toxicity occurs in the latter 2 weeks of the cycle and resume the next cycle with one dose level reduction in lenalidomide if the toxicity improves to less than grade 2. Alternatively if the toxicity occurred during the first 2 weeks of the cycle, then hold lenalidomide until the toxicity improves to less than grade 2 and resume lenalidomide with one dose level reduction. |
| | Grade 4 | Discontinue lenalidomide |
| Venous thrombosis/embolism | ≥ Grade 3 | Hold (interrupt) dose, consider therapeutic anticoagulation; restart at investigator's discretion (maintain dose level) |

| | | |
|---|---|---|
| Other non-hematologic toxicity except those events specifically attributed to dexamethasone as outlined in table 4. | Grade 3 / 4 | Hold lenalidomide for remainder of cycle if the toxicity occurs in the latter 2 weeks of the cycle and resume the next cycle with one dose level reduction in lenalidomide. Alternatively if the toxicity occurred during the first 2 weeks of the cycle, then hold lenalidomide until the toxicity improves to ≤ grade 2 and resume lenalidomide with one dose level reduction. |

#### 8.1.5.2. Dose reduction steps for corticosteroids

For patients assigned to receive corticosteroids as part of the trial therapy, dose reduction steps for prednisone and dexamethasone should follow the guidelines in the following tables. Table 2 refers to dose levels for the corticosteroids used on this clinical trial: prednisone and dexamethasone. Table 3 suggests dose reduction schema dictated by specific adverse events.

**Table 3: Dose Reduction Steps for Dexamethasone and / or Prednisone**

| **Starting Dose** | **Dose level –1** | **Dose Level -2** | **Dose Level –3** |
|---|---|---|---|
| 40 mg daily on days 1 – 4 every 28 days | 20 mg daily on days 1 – 4 every 28 days<br><br>**<u>Dose level -1a</u>** | 10 mg daily on days 1 – 4 every 28 days | Discontinue |

| | | | |
|---|---|---|---|
| | 40 mg daily on days 1, 2, and 3 followed by 20 mg on day 4 followed by 12 mg on day 5 followed by 8 mg on day 6 | | |
| Prednisone 100 mg PO days 1-5 every 28 days | 50 mg PO days 1-5 of a 28 day cycle | 25 mg PO days 1-5 of a 28 day cycle | Discontinue |

**Table 3: Dose Modification Guidelines for corticosteroids (Dexamethasone and / or Prednisone)**

| CTCAE CATEGORY ADVERSE EVENT | ADVERSE EVENT | TREATMENT ADJUSTMENT |
|---|---|---|
| Gastrointestinal | Dyspepsia, gastric or duodenal ulcer, gastritis<br>Grade 1-2 | Treat with H2 blockers, sucralfate, or Omeprazole. If symptoms persist despite above measures, decrease corticosteroid dose by 2 dose levels permanently |
| | > Grade 3 | Hold corticosteroids until symptoms are adequately controlled. Reduce by 2 dose levels along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue corticosteroids and do not resume. |
| | Acute pancreatitis | Discontinue corticosteroids and do not resume |
| Cardiovascular | Edema<br>> Grade 3 | Diuretics as needed, and decrease corticosteroids dose by 1 dose level; if edema persists despite above measures |

| | | |
|---|---|---|
| | | decrease dose by 2 dose levels from the initial dose; discontinue corticosteroids and do not resume if symptoms persist despite reduction. |
| Neurology | Confusion or Mood alteration<br>> Grade 2 (interfering with function<br>+/- interfering with activities of daily<br>living) | Hold corticosteroids until symptoms resolve to ≤ grade1. Reduce dose by 2 dose levels from current dose.<br>If symptoms persist despite above measures, discontinue corticosteroids and do not resume. |
| Musculoskeletal | Muscle weakness<br>> Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily<br>living) | Decrease corticosteroids dose by 1 dose level; If weakness persists despite above measures decrease dose by 2 dose levels from the initial dose. Discontinue corticosteroids and do not resume if symptoms persist despite reduction. |
| Metabolic | Hyperglycemia<br>> Grade 3 or higher | Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures,<br>decrease dose by 1 dose level decrements until levels are satisfactory |

### 8.1.6. Initiation of a new cycle of therapy

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

- Absolute neutrophil count > 500 cells/$mm^3$
- Thrombocytopenia ≤ grade 2 and there is no bleeding;
- Any therapy-related rash, allergic reaction/hypersensitivity, sinus bradycardia or other cardiac arrhythmia, or confusion/mood-alteration adverse event that may have occurred has resolved to ≤ Grade 1 severity
- Any other therapy-related adverse event that may have occurred has resolved to ≤ Grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, evaluate the subject weekly through an exam and relevant evaluations by the Investigator. A new cycle of lenalidomide treatment will not be initiated until the toxicity has resolved as described above. If a new cycle is delayed for > 4 weeks, the Principal Investigator will be notified. The above criteria will not be used after April 2016, a new cycle of therapy may be initiated per the treating physician discretion consistent with standard of care use of lenalidomide.

### 8.1.7. Discontinuation from treatment

The following events are considered sufficient reasons for discontinuing a subject from study drug:

- Subject declines further study participation.
- Adverse event(s) (AEs) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of study drug.

- Major violation of the study protocol.

- Progression of disease/unsatisfactory therapeutic effect

- Death
- Pregnancy or a positive pregnancy test
- Discontinuation of lenalidomide for any reason
- Subject lost to follow-up
- If for any other reason, must be specified in the data collection system.

Study Closure

Reasons for discontinuation should be recorded in the data collection system and in the subject's medical records.

## 8.2. Visit schedule and assessments

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form and are screened for entry into the study. For those subjects who fail screening the reason(s) for exclusion must be recorded in the subject's source documents.

A schedule of the assessments can be found in Section 2, **Schedule of Study Assessments**. All scheduled visits will have a ±7-day window unless otherwise stated.

An unscheduled visit can occur at any time during the study. The date for the visit and any data generated must be recorded on the data collection system. Source documents for these unscheduled visits must also be maintained.

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

After April 2016 patients will be followed per standard of care at the discretion of the treating physician.

# 9. Safety assessments

The following safety assessments will be done at baseline and at scheduled intervals throughout the duration of the study (see Section 2, Schedule of Study Assessments). Unless otherwise noted, all laboratory testing will be conducted in the local laboratory. After April 2016, safety assessments will not be mandated by the trial but rather will be at the discretion of the treating physician in accordance with standard of care management of multiple myeloma patients on lenalidomide.

## 9.1. Physical examination

Routine physical examination including vital signs (blood pressure, pulse, temperature), height, and weight. Height is only collected at the baseline physical examination.

## 9.2. Clinical laboratory evaluations

*General Laboratory Testing*

*Serum chemistries*

Total protein, albumin, calcium, phosphate, glucose, uric acid, total bilirubin, alkaline phosphatase, AST (SGOT), ALT (SGPT), sodium, potassium, chloride, carbon dioxide, blood urea nitrogen, creatinine, and LDH.

*Hematology*

Red blood cell (RBC) count, hemoglobin, hematocrit, MCV, MCH, MCHC, white blood cell (WBC) count and differential, absolute neutrophil count (ANC), and platelet count.

*Specific Laboratory Testing*

*Myeloma Specific*

SPEP, 24 hour UPEP, β2 microglobulin, serum and urine immunofixation, serum free light chain

*Supportive*

Serum B12, RBC Folate, Ferritin, ESR

Thyroid-stimulating hormone, total triiodothyronine ($T_3$) and total thyroxine ($T_4$).

## 9.3. Pregnancy testing for FCBP - β-hCG

Serum or urine pregnancy testing β-hCG with a sensitivity of at least 50 mIU/mL is to be done on FCBP only per Appendix VIII.

## 9.4. Electrocardiogram (ECG)

12-lead electrocardiogram.

## 9.5. Prior/Concomitant therapy

All concomitant therapies (prescription and non-prescription) taken 28 days prior to the start of study drug, Lenalidomide, and during the course of the study (from start of study drug until the last dose of study drug) will be collected. All therapies taken while the subject is on study drug will be recorded in the subject's data collection system. After April 2016, concomitant therapy will not be collected

## 9.6. Adverse events

All serious adverse events must be reported to Celgene Clinical Affairs within 24 hours of the investigational staff's knowledge; this includes any event that occurs during the participation of the trial regardless of associated therapy, severity or relationship

### 9.6.1. Serious Adverse Event (SAE) Definition

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

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

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

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

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

### 9.6.2. Adverse Event Reporting

Lenalidomide was approved by the FDA for newly diagnosed multiple myeloma patients in 2/2015. MCC16018 involves lenalidomide based therapy for newly diagnosed multiple myeloma and is thus currently considered standard of care (although that use was considered investigational

at the time of initiation and completion of accrual of the study). Moreover, the adverse event profile of lenalidomide is now well established. Finally, as of April 2016, all the current study patients have been on present therapy for a minimum of 2 years and a continued collection of all adverse events will not leads to a meaningful change in the adverse event profile of lenalidomide. Accordingly, as of April 2016, we will only collect serious adverse events (SAE) and will no longer collect other adverse events encountered after that time.

### 9.6.3. Pregnancies

Pregnancy of a female subject or the female partner of a male subject occurring while the subject is on study drug or within 4 weeks after the subject's last dose of study drug are considered expedited reportable events. If the subject is on study drug the study drug is to be discontinued immediately and the subject is to be instructed to return any unused portion of the study drug to the Investigator. Within 24 hours of the investigator's knowledge, all pregnancies must be reported to Celgene Corporation World Wide Safety Surveillance (WWDSS) by phone and facsimile.

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

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

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

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

In the case of a live "normal" birth, Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) should be advised as soon as the information is available.

### 9.6.4. Celgene Drug Safety Contact Information:

Celgene Corporation
Worldwide Drug Safety Surveillance (WWDSS)
86 Morris Avenue
Summit, NJ 07901
**Toll Free: (800) 640-7854**
**Phone: (908) 763-9667**
**Fax: (908) 673-9115**
E-mail: drugsafety@celgene.com

## 9.7. Investigator Reporting Responsibilities

The conduct of the study will comply with all FDA safety reporting requirements. Given that the FDA has granted an IND exemption for this study, an annual report is not required.

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

### 9.7.1. Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator should inform Celgene of any **SAE** within 24 hours of being aware of the event. This must be documented on Celgene SAE form, an acceptable institution SAE from or a FDA 3500 or MEDWATCH form. This form must be completed and supplied to Celgene within 24 hours of the investigator's knowledge of the event.. The date of awareness should be noted on the report. 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), if available. Information not available at the

time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MEDWATCH. A final report to document resolution of the SAE is required. The Celgene protocol number (RV-MM-PI-0454) should be included on SAE reports 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.

**Moffitt Cancer Center will only be responsible to report to Celgene those events that occur at Moffitt.**

### 9.7.2. Report of Adverse Events to the Institutional Review Board

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

### 9.7.3. Investigator Reporting to the FDA

Adverse drug reactions that are **Serious, Unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) in writing by each investigator/physician engaged

in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

*Adverse event updates/IND safety reports*

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

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

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

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file (see Section 13.4 **Study records requirements**).

### 9.7.4. Efficacy assessments

#### 9.7.4.1. Myeloma paraprotein

Serum and urine protein electrophoresis, quantitative immunoglobulins, serum and urine immunofixation studies (see Section 2, Schedule of Study Assessments). Response will be assessed using the Uniform response criteria set forth by the International myeloma working group (IMWG) (See Appendix II). Response will be assessed at least every 3 months in the maintenance setting.

As of April 2016, given all patients are in maintenance, patients will be followed for follow up and survival. Response assessment is not mandated per the trial and per institutional standard of care and to occur at a minimum of every 3 months.

#### 9.7.4.2. Bone marrow aspiration/ biopsy

At baseline, after 2 cycles of lenalidomide monotherapy, at the end of study, to confirm complete response, and as clinically indicated (see Section 2, Schedule of Study Assessments).

#### 9.7.4.3. Skeletal survey

Radiographic assessment of the bones to be done at baseline, end of study, to confirm complete response, and as clinically indicated (see Section 2, Schedule of Study Assessments).

### 9.7.5. Correlative and translational studies

All patients will be encouraged to participate in the correlative / translational studies outlined below. However, patients will have the option to decline such participation and still be eligible for inclusion in the study if they meet all other requirements and assessments. Correlatives / translational studies will involve additional bone marrow aspiration specimen (optimally up to 20 cc additional aspiration needed) and peripheral blood specimens. Bone marrow plasma cells from patients with multiple myeloma will be isolated with CD138 positive beads. RNA will be extracted and expression of tumor suppression genes will be assayed by real time reverse transcriptase polymerase chain reaction (RT-PCR) at baseline and after 2 cycles of mono-therapy with lenalidomide.

#### 9.7.5.1. Effects of Lenalidomide Monotherapy on Tumor Suppressor Genes

CD138 positive plasma cell will be isolated from the bone marrow aspirate of patients at diagnosis and after 2 cycles of lenalidomide using CD138 positive selection. RNA will be extracted. Quantitative PCR (Q-PCR) will be performed to

assay the expression of the following target genes: EGR1, EGR2, EGR3, p15, p21, p27 and SPARC. These studies will be performed by the Moffitt Core Lab under the direction of Christopher Cubitt. We estimate 15 paired samples will be obtained to compare the expression of the above mentioned genes pre and post 2 cycles of lenalidomide monotherapy.

9.7.5.2. Demonstration of Lenalidomide Induced Humoral Immune Response

Peripheral blood will be collected at the time of study start (C1D1), after 2 cycles of lenalidomide monthotherapy, at the time of addition of dexamethasone, and 2 cycles after the addition of dexamethasone. Serum will be used for the detection of lenalidomide induced humoral immune response using the serametrix assay. Samples will be stored at -20ºC prior to assay in the lab of Dr. Javier Pinilla.

9.7.5.3. Effects of lenalidomide monotherapy and in combination with corticosteroids on T cells subsets

Peripheral blood collected at the time of study start (C1D1), after 2 cycles of lenalidomide monthotherapy, at the time of addition of dexamethasone, and 2 cycles after the addition of dexamethasone will be used for the determination of changes in T cell subsets with lenalidomide monotherapy and after the addition of dexamethasone. The determination of T cell subset will be performed by flow cytometry. Samples will be collected, processed (ficoll separation and slow freeze at -120ºC ) and stored under the care of Dr. Javier Pinilla. A total of 5 green top tube per sample will be obtained.

9.7.5.4. Effects of single agent lenalidomide on global gene expression profile of malignant plasma cells.

RNA extracted from CD138 positive cells isolated from the bone marrow aspirate of patients with myeloma at baseline and after 2 cycles of lenalidomide monotherapy will be subjected to affymatrix array for global gene expression profiling and changes in gene expression before and after treatment will be correlated.

9.7.5.5. Significance of Notch signaling in myeloma

RNA will be isolated form CD138 positive cells and the expression of notch receptors, ligants and targets by Q-pCR will be compared among responder and non responders to lenalidomide. These experiments will be performed by Dr. Yulia Nefedova.

9.7.5.6. Post Translational modification of protein drug targets in myeloma using mass spectrometry

Cell pellets of comprised of CD138 positive cells will be used for proteomic studies. Using quantitative mass spectrometry, protein expression and selected post-translational modifications will be monitored for apoptotic proteins, nuclear factor kappa B survival signaling, and existing drug targets. The impact of exposure to lenalidomide on the malignant cell proteome will thus be examined. These studies will be performed by Dr. John Koomen.

9.7.5.7. Prioritization of samples for correlative/translational studies

Recognizing that not all patients will consent to the ancillary studies noted above and for some of the patients who do consent, the quantity of quality sample might not be sufficient for all experiments above, the following priority for sample usage for correlative studies is proposed (mainly applicable to bone marrow aspiration samples):

1- induction of tumor suppressor genes by lenalidomide

2- Post translational modification of protein drug targets in myeloma using mass spectrometry

3- Significance of Notch signaling in myeloma

4- Differential gene expression profile of malignant plasma cell treated in vivo with lenalidomide as monotherapy

# 10. Protocol Amendments/Deviations

## 10.1. Protocol amendments

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

## 10.2. Protocol deviations

When an emergency occurs that requires a deviation from the protocol for a subject, a deviation will be made only for that subject. The physician in attendance in such an emergency will, if circumstances and time permit, contact Principal Investigator (Rachid

Baz, MD) prior to the deviation immediately by telephone. If time does not allow for this, the Investigator will notify Dr. Baz of the deviation as soon as possible in writing and by phone.

Such contacts will be made as soon as possible to determine whether or not the subject (for whom the deviation from protocol was effected) is to continue in the study. The subject's medical records will completely describe the deviation from the protocol and state the reasons for such deviation and document the contact or attempted contact with Dr. Baz. In addition, the Investigator will notify the IRB/EC in writing of such deviation from protocol.

Non-emergency minor deviations from the protocol will be permitted only with prior agreement from the Principal Investigator.

# 11. Data Management

## 11.1. Study monitoring and auditing

## 11.2. Scientific Review Committee (SRC)

The Cancer Center maintains two full board Scientific Review Committees (SRC), meeting every other week (the first Wednesday and third Thursday of every month) as well as one Behavioral Ad-Hoc SRC.

Each SRC conducts a formal internal peer review of all clinical protocols and general scientific oversight of interventional clinical research. Protocols are reviewed for scientific merit, adequate study design, safety, availability of targeted study population, and feasibility of timely completion of all proposed research projects to be conducted by

its assigned programs at the Cancer Center. Each SRC is responsible for evaluating the risk/benefit assessment and corresponding data and safety monitoring plan as part of the scientific review and approval process. The SRC will refer any potential conflicts of interest identified in the proposed research to the Conflict Committee.

### 11.3. PI Responsibility

The PI of each study is ultimately responsible for every aspect of the design, conduct and actions of all members of the research team. This includes the final analysis of the protocol. The PI is responsible for ensuring that:

- All protocols include a DSMP and procedures for its implementation commensurate with the risk and complexity of the study. The DSMP must include a structured adverse event determination, monitoring and reporting system, including standardized forms and procedures for referring and/or treating subjects experiencing adverse events. The plan must include data and safety-monitoring procedures for subjects enrolled who may be receiving a part of their protocol-required treatment at community sites.
- In all cases, the PI of the study will have primary responsibility for ensuring that the protocol is conducted as approved by the SRC and IRB. The PI will ensure that the monitoring plan is followed, that all data required for oversight of monitoring are accurately reported to a DSMB and/or to the PMC and IRB as required, that all adverse events are reported according to protocol guidelines, and that any adverse actions reflecting patient safety concerns are appropriately reported.

### 11.4. The Protocol Monitoring Committee (PMC)

The PMC monitors its assigned ongoing research protocols for: adverse event reporting, data and safety monitoring, and internal audit findings. The PMC, upon review of any agenda item, may approve the study for continuation, require revisions, suspend or close a protocol.

Investigators of studies, which are designated to be reviewed by the PMC for data and safety monitoring, shall provide a statistical report of the study's progress and summary of adverse events and deviations based on the phase of the study and the associated risk of the study or more often if applicable. The external DSMB (if applicable) shall forward its report for high-risk studies designated for external review at least annually or more often if applicable.

### 11.5. Research Compliance Division (RCD)

RCD of the Corporate Compliance Office is the coordinating center for internal audits of clinical trials conducted at the Cancer Center. The audit procedure is a formal, comprehensive, source document review of all clinical trials. External audit reports that meet the criteria of the internal audit may be accepted in lieu of an internal audit.

The (RCD) shall provide a report to the PMC of internal audit findings for PMC action. A representative of the RCD will be present to discuss the audits with the PMC. For cause audits will be discussed during an executive session of the PMC. Only members (voting and ex-officio) may attend this session.

### 11.6. Investigator responsibilities

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

Investigators, or designee, must enter study data onto a 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, and TPP), providing direct access to the facilities where the study took place, to source documents, to the data collection system, 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 any visits and be made available to the Celgene representatives so that the accuracy and completeness may be checked.

This study may be subject to an independent audit at the investigational site, which will be conducted by Celgene's Quality Assurance personnel or designee. Full consultation with appropriate personnel will be made prior to and during such an audit. The Investigator must be available during the audit.

If the Investigator is contacted by any regulatory authority regarding an audit for this study or any other study, the Investigator is to contact Celgene immediately.

## 12. Bio-statistical Consideration

This is a phase 2 trial evaluating a lenalidomide based response adapted strategy in older adults with newly diagnosed multiple myeloma. Descriptive statistics will be

used to summarize patients' demographic and clinical characteristics collected at each visit. Mean, standard deviation and range will be calculated for continuous variables, and frequency and percentage will be generated for categorical variables. The distribution (frequency and percentage) of patients treated with single agent lenalidomide, lenalidomide + prednisone, and lenalidomide+low dose dexamethasone will be presented.

## 12.1. Sample size:

The primary endpoint is 12-month PFS for the overall response adaptive approach. Based on the E4A03 and SWOG 2032 studies, the 12-month PFS is approximately 70% for patients treated with lenalidomide low dose dexamethasone. The sample size determination is primarily based on the consideration of providing an estimate of the 12-month PFS with reasonable precision. We estimate the 12-month PFS in the response adapted approach is 85%. With a sample size of 60 evaluable patients (30 from Moffitt and 30 from sites in South Korea), its 95% confidence interval is 73.4-92.9%.

## 12.2. Efficacy evaluation

### 12.2.1 Primary efficacy analysis

Progression free survival (PFS) is defined as the time from start of lenalidomide monotherapy to the first occurrence of disease progression or death on study from any cause, whichever occurs earlier. All treated patients will be included in efficacy endpoint analysis. Those patients who are treated on this trial but have not had a relevant event at the time of last follow-up will be included in the analyses of these endpoints as censored observations.

The primary endpoint is the point estimate of the 12-month PFS rate for the overall response adaptive approach. Number and percentage of patients who survived greater or equal to 365 days without disease progression will be summarized. The 95% confidence interval will be calculated using the exact binominal method. The PFS curves will be estimated by the Kaplan-Meier method. Median and its 95% confidence intervals will be estimated.

### 12.2.2 Secondary efficacy analysis

Response will be assessed using the Uniform response criteria set forth by the International myeloma working group (IMWG) (See Appendix II). Frequencies and percentages will be used to summarize for all response categories. The response in this trial is defined as complete remission (CR), stringent complete remission (SRC), very good partial remission (VGPR) and partial remission (PR). The response rate for patients treated with single agent lenalidomide, lenalidomide and prednisone and lenalidomide and low dose dexamethasone will be calculated as the percentage of responders, and the 95% confidence interval will be calculated using the exact binominal method. Logistic regression will be used to investigate relationships of the response rates with baseline and other relevant covariates, if appropriate.

Overall survival (OS) is defined as the time from study entry to death of any cause. The OS curves will be estimated by the Kaplan-Meier method. Median and its 95% confidence intervals will be estimated. The effect of baseline and other relevant covariates will be investigated with Cox regression models, when appropriate. Confidence intervals for the survival probabilities at different points will be constructed as needed. The PFS curve for the patients treated with single agent lenalidomide will also

be calculated using the Kaplan-Meier method.

### 12.2.3 Safety analysis

The following safety analyses will be performed using data from all subjects who receive any study drug. Adverse events will be classified using the MedDRA classification system. The severity of the toxicities will be graded according to the NCI CTCAE v 4.0 whenever possible.

In the by-subject analysis, a subject having the same event more than once will be counted only once. Adverse events (AE) will be summarized by worst NCI CTCAE grade. The patient incidence of AEs will be summarized by system organ class, preferred term, severity and relationship to study drug. Adverse events leading to death or to discontinuation from treatment, events classified as NCI CTCAE v 4.0 grade 3 or higher, study-drug-related events, and serious adverse events will be listed separately. Laboratory data will be graded according to NCI CTCAE v 4.0 severity grade. Cross tabulations will be provided to summarize frequencies of abnormalities. The physical examine results (such as blood pressure, pulse, temperature) at each visit will be summarized using descriptive statistics.

### 12.2.4 Evaluation of the group difference between participants from Moffitt and South Korea

The study participants will be enrolled half from Moffitt and half from multiple sites in South Korea. The important demographic and clinical characters associated with the endpoints were addressed in the inclusion and exclusion criteria so these two groups should be comparable at baseline. Although there are currently no reports suggesting a difference tolerance or response in Korean patients to lenalidomide as compared to

European / North American patients, we will evaluate the ethnic effect for our study endpoints for conservative purpose. For survival endpoints (PFS and OS), the log-rank test will be applied to evaluate the ethnic effect. For response rate and adverse event proportion, the Fisher's exact test will be applied for testing the ethnic effect. If there are no significant differences between these two groups, we will provide the overall results using the combined data sources. If ethnic effects are observed for some endpoints, statistical models will be applied for adjusting the ethnic effect. Cox regression models and logistic models will be applied for adjusting the ethnic effect for the survival and binary endpoints, respectively.

**12.2.5 Analysis on exploratory aims**

The first exploratory aim is to measure a lenalidomide induced tumor specific immune response and correlate the tumor specific immune response with corticosteroid use (addition of dexamethasone or prednisone), response to therapy and duration of response. Antibody titer, measurement of tumor specific immune response, will be obtained at 4 different time points: at baseline, after 2 cycles of lenalidomide monthotherapy, at the time of addition of dexamethasone, and 2 cycles after the addition of dexamethasone.

Descriptive statistics (mean, standard deviation, median, and inter-quartile range) will be used to describe antibody titer distributions for the overall response adaptive approach and by treatment in different time points. For evaluating lenalidomide effect on immune response, the antibody titer change from baseline to after 2 cycles of lenalidomide monthotherapy will be summarized using descriptive statistics. For evaluating corticosteroid effect on immune response, the antibody titer change from baseline to either time of addition of dexamethasone or 2 cycles after the addition of dexamethasone will be summarized. These lenalidomide and corticosteroid effect will be analyzed using

either the pair t-test if the original or transformed data are normally distributed, or the Wilcoxon sign rank test whenever the normality assumption cannot be justified. The antibody titer change will also be compared between response to therapy (yes/no) using either the student's t-test or Wilcoxon rank sum test. Duration of response is defined as the time from study start to the time of disease progression on lenalidomide and dexamethasone. Cox regression model will be applied to evaluate the association between antibody titer change and duration of response.

The second exploratory aim is to evaluate the impact of lenalidomide mono-therapy on expression of tumor suppression genes and cell cycle regulators. The expressions of interest are in the following target genes: EGR1, EGR2, EGR3, p15, p21, p27 and SPARC. The 15 paired samples will be obtained pre and post 2 cycles of lenalidomide monotherapy. The gene expression data will be pre-processed using appropriate background correction, normalization, and transformation. The processed expression data will be used for further analyses. For each gene expression, the expression differences between pre and post 2 cycles of lenalidomide monotherapy will be described using descriptive statistics and the impact of lenalidomide mono-therapy will be evaluated using either the paired t-test or Wilcoxon sign rank test.

# 13. Regulatory Considerations

## 13.1. Institutional review board/ethics committee approval

The protocol for this study has been designed in accordance with the general ethical principles outlined in the Declaration of Helsinki. The review of this protocol by the IRB/EC and the performance of all aspects of the study, including the methods used for

obtaining informed consent, must also be in accordance with principles enunciated in the declaration, as well as ICH Guidelines, Title 21 of the Code of Federal Regulations (CFR), Part 50 Protection of Human Subjects and Part 56 Institutional Review Boards.

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

A copy of the IRB/EC approval for the protocol and the Informed Consent is to be provided to Celgene. The approval for both the protocol and informed consent must specify the date of approval, protocol number and version, or amendment number.

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

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

### 13.2. Informed consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any study related procedures as per Good Clinical Practices (GCP) as set forth in the CFR and ICH guidelines.

Documentation that informed consent occurred prior to the subject's entry into the study and the informed consent process should be recorded in the subject's source documents. The original consent form signed and dated by the subject and by the person consenting

the subject prior to the subject's entry into the study, must be maintained in the Investigator's study files.

A sample of the informed consent to be used in the study is to be forwarded to Celgene prior to submitting it to the IRB/EC for approval.

### 13.3. Subject confidentiality

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit Celgene representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

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

### 13.4. Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of data collection and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in

the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

**Premature discontinuation of study**

**13.4.1. Single center**

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

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

**13.4.2. Study as a whole**

Any possible premature discontinuation would have to be documented adequately with reasons being stated, and information would be issued according to local requirements after discussions and agreement between the PI's sponsor (s) and regulatory authorities at the institutions (e.g., IRB/EC, regulatory authorities, etc.).

# 14. Appendices

## Appendix I: Classification of the plasma cell dyscrasias[22] & International Staging System (ISS)[23]

| MGUS | Asymptomatic multiple myeloma | Symptomatic multiple myeloma |
|---|---|---|
| Serum M protein < 30g/L &<br><br>Clonal bone marrow plasmacytosis <10%<br><br>No other B cell lymphoproliferative disorder<br><br>No related organ and tissue impairment | Serum M protein ≥ 30g/L or<br><br>Clonal bone marrow plasmacytosis ≥ 10%<br><br>No related organ and tissue impairment | M protein in the serum or urine &<br><br>Clonal bone marrow plasmacytosis or plasmacytoma<br><br>Related organ and tissue impairment* |

*Related Organ Tissue Impairment

- Hypercalcemia
- Renal dysfunction
- Anemia: hemoglobin 2 g/dL below the lower limit of normal
- Lytic bone lesions (solitary plasmacytoma requires >30% PC)
- Symptomatic hyperviscosity

- Amyloidosis (requires >30% PC)

- 

- Recurrent bacterial infections (>2/year)

**International Staging System[23]:**

| | |
|---|---|
| I | β2m < 3.5 mg/dL<br><br>Albumin≥3.5g/dL |
| II | 5.5> β2m ≥ 3.5 mg/dL<br><br>Or<br><br>Albumin <3.5g/dL and β2m < 3.5 mg/dL |
| III | β2m ≥ 5.5 mg/dL |

**Appendix II: Uniform Response Criteria as defined by the International**

**Myeloma Working Group[22]**

All relapse categories require two consecutive assessments made at anytime

before classification as relapse or disease progression and/or the institution of

any new therapy.

Measurable disease is defined as:

| | |
|---|---|
| Complete remission | • Negative immunofixation on the serum and urine, *and*<br>• Disapppearance of any soft tissue plasmacytomas , *and*<br>• ≤5% plasma cells in the bone marrow (confirmation with repeat bone marrow is not needed) |
| Stringent Complete remission | • CR as defined above, and<br>• Normal free light chain (FLC) ratio, and<br>• Absence of clonal cells in the bone marrow by immunohistochemistry or immunofluorescence, based on a κ/λ ratio of > 4:1 or < 1:2 performed on a minimum of 100 plasma cells (confirmation with repeat bone marrow is not needed) |
| Very Good Partial Remission | • Serum and urine M-protein detectable by immunofixation but not on electrophoresis, or<br>• 90% or greater reduction in serum M-protein plus urine M-protein level of < 100 mg per 24 hours |
| Partial Remission | • ≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90%, or to <200mg per 24 h<br>• If the serum and urine M-protein are unmeasurable*, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria<br>• In addition to the above listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required |
| Minimal remission | • 25-49% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥50% but less than 90%<br>• In addition to the above listed criteria, if present at baseline, a ≥25% reduction in the size of soft tissue plasmacytomas is also required |
| Stable Disease | • Not meeting criteria for CR, VGPR, PR or progressive disease |

| | |
|---|---|
| Progressive Disease<br><br>V. 3 12/06/2010 | Increase of ≥25% from baseline in serum M-component, and the absolute increase must be ≥0.5 g/dl. If the starting M-component is ≥5 g/dl, increases ≥1 g/dl are sufficient to define relapse.<br>• Increase of ≥25% from baseline in urine M-component, and the absolute increase must be ≥200 mg/24 hours<br>• Only in patients without measurable serum and urine M-protein levels: Increase of ≥25% from baseline in the difference between involved and uninvolved FLC levels, and the absolute difference must be >10 mg/dl<br>• Increase of ≥25% from baseline in bone marrow plasma cell percentage, and the absolute % must be ≥10% (relapse from CR has the 5% cutoff versus 10% for other categories of relapse)<br>• Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas<br>• Development of hypercalcemia (corrected serum calcium >11.5 mg/dl or >2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder. |

- Serum M-protein ≥ 1 g/dl (≥ 10 gm/l) [10 g/l]

- Urine M-protein ≥ 200 mg/24h

Serum FLC assay: Involved FLC level ≥ 100 mg/dl (≥ 100 mg/l) provided serum FLC

ratio is abnormal

## Appendix III: ECOG Performance Status Scale

| SCORE | DESCRIPTION |
|---|---|
| **0** | Fully active, able to carry on all pre-disease performance without restriction. |
| **1** | 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** | Dead. |

## Appendix IV: 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.The risks to a fetus are not known. However, because lenalidomide is related to thalidomide, and thalidomide is known to cause severe birth defects, the following requirements must be observed.

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

Criteria for females of childbearing potential (FCBP)

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

The investigator must ensure that:

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

Contraception

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

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

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

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

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

Pregnancy testing

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

**Before starting lenalidomide**

*Female Patients:*

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

*Male Patients*:

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

**During study participation and for 28 days following lenalidomide discontinuation**

*Female Patients:*

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

- Pregnancy testing and counseling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Lenalidomide treatment must be temporarily discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after lenalidomide discontinuation.

*Male Patients:*

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

Additional precautions

- Patients should be instructed never to give lenalidomide to another person.
- Female patients should not donate blood during therapy and for at least 28 days following discontinuation of lenalidomide.
- Male patients should not donate blood, semen or sperm during therapy or for at least 28 days following discontinuation of lenalidomide.
- Only enough lenalidomide for one cycle of therapy may be prescribed with each cycle of therapy.

## Appendix V NCI CTC Version 4.0

Toxicity will be scored using NCI CTC Version 4.0 for toxicity and adverse event reporting. A copy of the NCI CTC Version 4.0 can be downloaded from the CTEP homepage: (**http://ctep.info.nih.gov**). All appropriate treatment areas have access to a copy of the CTC Version

## Appendix VI: Cockcroft-Gault estimation of CrCl:

Cockcroft-Gault estimation of creatinine clearance (CrCl):
(Cockcroft, 1976; Luke 1990)

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

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

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