Weill Cornell Medical College

TITLE: Lenalidomide and Dexamethasone (Rd) versus Clarithromycin [Biaxin®] / Lenalidomide [Revlimid®] / Dexamethasone (BiRd) as Initial Therapy in Multiple Myeloma.

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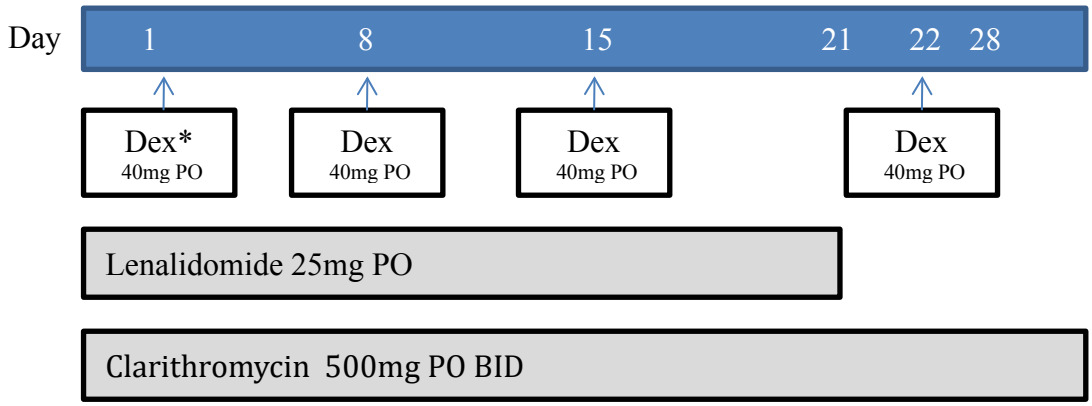
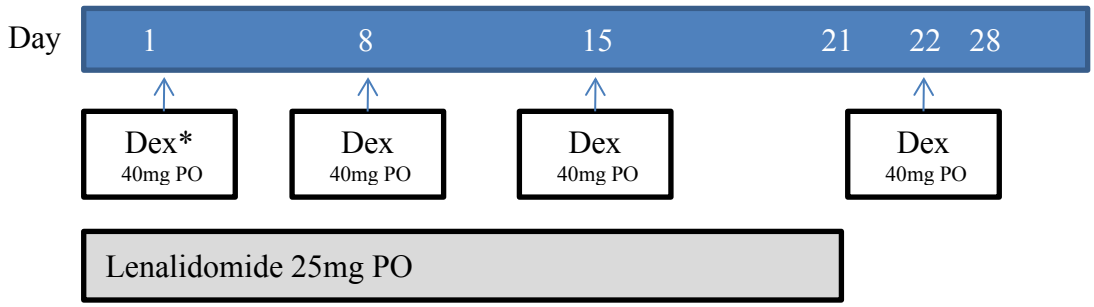
1.0 STUDY SCHEMA

1.1 BiRd medication schedule (one cycle)



Lenalidomide will be given for days 1-21 followed by a 7 day rest period for each 28-day cycle.
*Dexamethasone at a dose of 20mg on Days 1, 8, 15, 22 will be used for subjects ≤75 years old.

1.1 Rd medication schedule (one cycle)



Lenalidomide will be given for days 1-21 followed by a 7 day rest period for each 28-day cycle.
*Dexamethasone at a dose of 20mg on Days 1, 8, 15, 22 will be used for subjects ≤75 years old.

1.3 Schedule of Assessments

Procedure	Screening <28 days prior to start date (unless otherwise indicated)	Cycle 1 Day 1	Cycle 1 Days 8, 15, 22	All Other Cycles Day 1	End of Study[9]	Follow-Up Phase (Every 6 months)
Complete medical history with quality of life assessment.	X	X		X		
Physical exam, KPS, vital signs, height and weight	X	X		X		
CBC with differential	X	X	X	X	X	
Complete metabolic profile[1,2]	X	X	X	X[2]	X	
Generate / review new drug diary		X		X		
Collect / review prior drug diary				X	X	
SPEP, IF, quantatative immunoglobulins[3]	X	X		X	X	
Serum free light chains[3]	X	X		X	X	
24-hour urine for UTP, UPEP, UIF[3]	X	X		X	X	
β_2M[3]	X					
CRP	X					
Urinalysis	X					
Pregnancy test[4]	X	X		X	X	
Register patient into RevAssist® program[5]	X					
Skeletal survey, MRI, or whole body PET/CT scan	X[6]			X[8]	X[8]	
Bone marrow biopsy and aspirate[7]	X[6]			X[8]	X[8]	
Concurrent medication use survey	X	X		X		
Electrocardiogram	X					
Drug dispensation[6]		Continuous				
Adverse event		Continuous				

monitoring						
Obtain Follow-Up anti-cancer treatments						X
Obtain disease status, physical status, survival information, and if any occurrence of secondary primary malignancies						X

1. Includes sodium, potassium, chloride, CO_2, calcium, blood urea nitrogen (BUN), serum creatinine and calculated creatinine clearance, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT/AST, SGPT/ALT, LDH, Uric Acid. Phosphorus and magnesium are performed at screening and Cycle 1 Day 1.
2. To include Thyroid Stimulating Hormone (TSH) at screening, and every 3 months beginning with cycle 4 (more often if clinically indicated).
3. UTP = urine total protein; UPEP = urine protein electrophoresis; UIF = urine immunofixation; SPEP = serum protein electrophoresis; IF = serum immunofixation; β_2M = beta-2 microglobulin.
4. Pregnancy test for females of child-bearing potential (FCBP). A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur within 10 – 14 days and again within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). FCBP with regular or no menstruation must have a pregnancy test weekly for the first 28 days and then every 28 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide (whichever comes later) and at Day 28 post the last dose of lenalidomide (whichever comes later). FCBP with irregular menstruation must have a pregnancy test weekly for the first 28 days and then every 14 days while on therapy (including breaks in therapy), at discontinuation of lenalidomide (whichever comes later) and at Day 14 and Day 28 post the last dose of lenalidomide (whichever comes later) (see Appendix III: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
5. Lenalidomide must be prescribed through and in compliance with Celgene's RevAssist® program. Prescriptions of lenalidomide must be filled within 7 days.
6. To occur within 6 weeks of treatment
7. Iliac crest bone marrow aspirate for cytological review, including cytogenetics, FISH studies, flow cytometry (when available), and core biopsy for immunohistochemistry.
8. To confirm complete remission, progression, or when clinically indicated
9. An additional safety assessment will be done 30 days (+/- 7 days) following the last dose of study drug.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Study Objectives

2.1.1 To evaluate the efficacy of clarithromycin (Biaxin), lenalidomide (Revlimid), and dexamethasone (Decadron) combination therapy (BiRd), compared to lenalidomide and dexamethasone (Rd) alone as an induction therapy for patients with newly diagnosed, transplant ineligible, previously untreated multiple myeloma (MM).

2.1.2 To determine the progression free survival (PFS) of the BiRd regimen compared to Rd.

2.1.3 To compare objective response rate (ORR) of BiRd versus Rd.

2.1.4 To determine and compare duration of response (DOR), event free survival (EFS), time to progression (TTP), and overall survival (OS) of BiRd versus Rd.

2.1.5 To assess safety and drug toxicity in each arm.

2.1.6 To determine relative dose intensity for each component of protocol medication prescribed.

2.1.7 To evaluate and compare minimal residual disease following therapy of BiRd versus Rd.

2.18 To determine and compare the PFS2 (time from study entry until 2nd instance of disease progression) of BiRd versus Rd.

2.19 To assess determine and compare quality of life assessments for BiRd vs Rd.

2.2 Study Endpoints

- Progression free survival
- Response rate by IMWG criteria (see Appendix I)
- Event free survival (an event is defined by coming off protocol for any reason, including progression of disease, lack of disease response, regimen intolerability, or death).
- Overall survival
- Duration of response
- Time to progression
- Progression free survival 2: time from study entry until 2nd instance of disease progression

- Quality of life: as measured by Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-Fatigue) Scale (Appendix IX) as part of a quality of life assessment.
- Regimen toxicities, as defined by CTCAE V4.0

3.0 BACKGROUND AND RATIONALE

3.1 Disease Information

Multiple Myeloma (MM) is a neoplastic disorder of unknown etiology characterized by an abnormal proliferation of plasma cells producing excess quantities of a single immunoglobulin protein isotype (M-protein). Malignant plasma cells expand and accumulate in the bone marrow, leading to cytopenias, imbalance of bone formation and resorption, and the production of monoclonal protein.[1] It is estimated that over 21,000 new cases of myeloma are diagnosed in the US each year accounting for approximately 1% of all cancers and 10-15% of all hematological malignancies.[2] The disease is twice as common in persons of African descent as compared to Caucasians. MM usually occurs in older individuals with a median age of 69 years old.[3] There is currently no cure, and available therapies are only able to slow disease progression, prolong survival, and minimize symptoms.

3.2 Prognosis

The overall median survival for patients with MM is 36 months, with International Staging System stage I, II, and III patients surviving a median of >60, 41, and 23 months respectively.[4] Several prognostic factors have been identified. An elevated serum level of beta-2 micro-globulin (ß2M), a component of the class I HLA molecule, is a powerful prognostic indicator of shortened survival.[5] Since ß2M is excreted by the kidney, renal insufficiency will increase serum levels of ß2M. The plasma cell labeling index (PCLI) identifies the percentage of proliferating plasma cells in S phase of the cell cycle and is powerful independent predictor of progression and survival.[6] Chromosomal abnormalities, such as translocations t(4;14), del 17p, and t(14;16) confer poor prognosis.[7,8] Investigators have found that achieving a complete remission early on in the disease may be important in predicting long-term survival.[9,10] Indeed, Kyle *et. al* suggested that an objective response to standard therapy is by far the most important feature of long-term survivors.[11] Major controlled trials have confirmed this seminal observation even in the context of high-dose chemotherapy.[12] Based on those observations, the goal of achieving an early complete remission should allow patients to sustain long-term survival and perhaps lead to a cure.

Myeloma is still an incurable disease and obtaining an initial long disease-free interval prior to relapse is important to prolong patient survival and improve quality of life. At the present time, there is still a need for new and effective induction therapies for the newly diagnosed multiple myeloma patients to achieve this goal.

3.3 Treatment

Oral dexamethasone and intermittent oral melphalan and prednisone (MP) were widely used standard conventional therapies for MM for many years. Responses, defined as a 50% or greater decrease in paraprotein (aka M-protein or M-spike), were seen in approximately 30-60% of patients. Duration of response to these agents is generally 1.5 to 2 years, with median survival from time of initiation of therapy of approximately 24 to

30 months. Cures are not achieved. Relapses are often marked by the development of drug resistance and by a more aggressive clinical course. Thus, subsequent remissions are more difficult to achieve and are progressively shorter.[13]

Various combination chemotherapy regimens have been developed in an attempt to improve remission rates and duration. These include vincristine, melphalan, cyclophosphamide, carmustine, and prednisone (M2), , vincristine, doxorubicin, and dexamethasone (VAD), vincristine, melphalan, cyclophosphamide, and prednisone alternating with vincristine, carmustine, doxorubicin, and prednisone (VMCP/VBAP), doxorubicin, carmustine, cyclophosphamide, and melphalan (ABCM), amongst other regimens. [14] [15] [16] [17]Although these regimens may produce higher response rates and in some cases more rapid tumor mass reduction, a survival advantage has not been demonstrated. Those eligible are often recommended to undergo autologous stem cell transplant, though age and other factors render the majority of patients unable to undergo a successful transplant.

With the advent of novel agents such as thalidomide, lenalidomide and bortezomib there has been a marked improvement in outcomes particularly in younger and fit patients.[18] These agents are discussed more fully below.

3.4 Dexamethasone

Dexamethasone is a synthetic steroid with anti-inflammatory, anti-proliferative, immunomodulatory abilities found to cause apoptosis of myeloma cells.[19] The benefit of VAD (vincristine, doxorubicin, and dexamethasone) over high-dose dexamethasone is marginal (overall response rate 50-55%). A study by the Dutch Hematology-Oncology Group HOVON reports equal overall response rates of 68% when VAD was administered as an IV push and when dexamethasone was given at 40 mg PO QD x 4 only.[20] These results suggest that the concurrent administration of VA (vincristine and doxorubicin) does not add major cytoreduction. The results of the 91-155 study at Memorial Sloan-Kettering Cancer Center in which dexamethasone was comparatively intensified show a much higher response rate despite the poor prognostic characteristics of the cohort.[9] These results indicate that the intensification of dexamethasone is an important factor in determining responses, providing compelling evidence that dexamethasone is by far the most important component in this combination.

3.5 Clarithromycin (Biaxin®)

Biaxin®, or clarithromycin, is a semi-synthetic macrolide antibiotic indicated for the treatment of mild to moderate infections caused by susceptible strains of microorganisms. Pre-clinical studies have shown that Biaxin® has an immunomodulatory effect and may have antineoplastic properties mediated in part by suppression of Interleukin-6 and other cytokines.[21] Biaxin® has also been shown to modulate the serum half-life of a number of corticosteroids and concurrent biaxin / corticosteroid administration may increase total time of corticosteroid exposure.[22] Based upon these properties, the group at Cedars Sinai Comprehensive Cancer Center began a trial using Biaxin® 500mg PO BID for the treatment of newly diagnosed and relapsed/refractory MM patients.[23] Of the 30 patients

treated, 6 patients achieved a complete response, 7 achieved a partial response, 6 patients had stable disease, 4 had a mixed response and 7 patients were too early to evaluate. Follow up studies by other groups in Canada and France have failed to duplicate these promising results.[24]

3.6 Biaxin®, Low-dose Thalidomide and Dexamethasone

Prior experience at the New York Presbyterian Hospital using the combination of Biaxin®, low-dose thalidomide and dexamethasone (BLTD) for the treatment of patients with newly diagnosed and relapsed/refractory MM and Waldenstrom's macroglobulinemia have revealed impressive results.[25] Of 40 evaluable patients, 37 (93%) achieved a response. Five patients (13%) achieved a complete remission defined by complete disappearance of M-spike and no serologic evidence of disease. Complete (normalization of Ig spike), major (>75% reduction of Ig spike), and partial (>50% reduction of Ig spike) response rates were 40%, 13%, and 27% respectively. A subset of responding patients had been previously resistant to Thalidomide, Dexamethasone, or a combination of the two. These results suggest a synergistic effect amongst the three agents. The response criteria defined above are substantially more stringent than the widely used SWOG criteria. Using the latter, we have obtained a near CR rate (> 75% reduction in Ig spike) of 66%. In order to further our understanding of these findings we have completed a trial randomizing newly diagnosed multiple myeloma patients to receive either low-dose thalidomide or dexamethasone. Patients without a satisfactory response (<50% drop in tumor mass) after 8 weeks of treatment had Biaxin® added to their regimen. Results showed that the addition of Biaxin® to either regimen seem to dramatically improve both response rate and time to response, even in patients who were previously unresponsive to low-dose thalidomide or dexamethasone. [*unpublished results*]. Using BLTD as a foundation, we sought new approaches to achieve an increase the CR rate, specifically in the form of BiRd therapy (discussed below).

3.7 Lenalidomide (Revlimid®)

Lenalidomide (Revlimid®) is an oral analog of thalidomide with greater potency to activate immunomodulatory effects and inhibit angiogenesis when compared to thalidomide. Both lenalidomide and thalidomide are members of Celgene's proprietary class of compounds called IMiDs® which are characterized by their immunomodulatory and anti-angiogenic activity. In vitro studies comparing the effects of IMiDs® on the production of cytokines and multiple myeloma cell proliferation activity found that lenalidomide was 50 to 2000 fold more potent than thalidomide.[26] In addition, lenalidomide's toxicity profile is unique, with fewer non-hematologic side-effects when compared to thalidomide with more predictable and manageable toxicities.

Two phase I studies of heavily pretreated subjects with relapsed or refractory multiple myeloma were conducted to identify the MTD and to evaluate the safety of oral lenalidomide.[27] Myelosupression was found to be the DLT and the MTD was determined to be 25 mg/day. No significant somnolence, constipation, or neuropathy was observed. The first phase I study, 17 (71%) of 24 evaluable patients achieved >25% reduction of the myeloma paraprotein and in the second study, 20% of patients achieved a > 50%

paraprotein reduction (responders received 25-50 mg/day). The results from phase II trials of lenalidomide given at 30 mg per day for 21 days every 28 days suggest that oral lenalidomide is active in advanced multiple myeloma and is well tolerated. Of 46 evaluable subjects with relapsed or refractory MM, 39 (85%) achieved at least stable disease, including 2 subjects with complete resolution of paraprotein.[28]

Thus, early studies suggest that lenalidomide is active against advanced multiple myeloma and is well tolerated. Currently it is approved in combination with dexamethasone for treatment of relapsed multiple myeloma after a phase III study investigating the effectiveness of lenalidomide with high dose dexamethasone compared to high dose dexamethasone alone in newly diagnosed patients found response for the combination therapy was superior (61% vs. 20%).[29] In addition, in vitro analysis determining the effect of low dexamethasone on the anti-myeloma properties of lenalidomide found that dexamethasone works synergistically in antagonizing lenalidomide's immunostimulatory effects and enhancing its antiproliferative properties while independently inhibiting myeloma cell proliferation.

3.8 Rationale for BiRD Combination in Multiple Myeloma

While new anti-myeloma therapies such as bortezomib and immunomodulatory drugs have been developed, multiple myeloma remains an incurable malignancy. Given that obtaining a complete remission with therapy will allow patients with newly diagnosed multiple myeloma to enjoy a higher quality of life and longer duration of freedom from disease symptoms, finding an optimally effective and well-tolerated regimen is imperative.

Based on the immunodulatory effect of biaxin, the unique anti-myeloma activity of lenalidomide, and the synergistic properties of dexamethasone, the combination of BiRd has demonstrated to be highly effective in the treatment of multiple myeloma, and is anticipated to provide superior outcomes when compared to lenalidomide and dexamethasone therapy alone. A phase II study of clarithromycin (500mg twice daily), lenalidomide (25mg daily for 21 days out of a 28 day cycle), and low dose dexamethasone (40mg weekly) called the BiRd regimen was conducted. [30] By replacing thalidomide with lenalidomide into our former BLTD treatment platform, we achieved an overall response rate of 90.3%, and a higher CR rate compared with the earlier BLTD data, 30% vs. 13%. Retrospective case matched analysis comparing patients induced with BiRd vs Rd found that the addition of clarithromycin to Rd significantly increased patient's rate of response, with 90.3% vs 79.1% of patients achieving PR or greater, and 45.8% vs 13.9% of patients achieving CR.[31] While promising, randomized phase III studies are needed to confirm the superiority of BiRd compared with RD in terms of response rates and survival.

This study is intended to investigate the efficacy of combination therapy with an induction phase utilizing a combination clarithromycin (Biaxin®), lenalidomide (Revlimid®), dexamethasone (Decadron®), in multiple myeloma patients who are newly diagnosed and require treatment when compared to patients who receive lenalidomide

and dexamethasone alone. Randomized phase III studies are needed to confirm the superiority of BiRd compared with Rd in terms of response rates and survival. We anticipate the addition of lenalidomide and biaxin will lead to a greater CR rate, shorter times to response, and less toxicity. The primary endpoints of this trial include best response rate, toxicities, progression free survival, event free survival, and overall survival.

4.0 INVESTIGATIONAL PLAN

4.1 Study Design

This phase III study, open-label, randomized study investigating lenalidomide and dexamethasone with and without biaxin in subjects with newly diagnosed, previously untreated multiple myeloma. Eligible subjects will be randomized in a 1:1 ratio to receive a regimen consisting of either biaxin, lenalidomide, and low dose dexamethasone (BiRd arm), or lenalidomide and low dose dexamethasone (Rd arm). Up to 306 patients will be enrolled.

BiRd Arm

Subjects on the BiRD arm will receive biaxin, revlimid, and dexamethasone in 28-day cycles. Dosing is as follows:

- Clarithromycin 500mg PO twice daily on days 1-28 for a 28-day cycle. If a dose of clarithromycin 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. Vomited doses will not be made up.

- Lenalidomide 25mg PO daily on days 1-21 of a 28-day cycle for patients with a calculated creatinine clearance of ≥60 cc/min. Patients with a calculated creatinine clearance of <60 cc/min will receive 15 mgs PO daily on days 1-21 of a 28 cycle. 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. Vomited doses will not be made up.

- Dexamethasone 40mg PO will be given on days 1, 8, 15, 22 of a 28-day cycle. Missed or vomited doses will not be made up. If subject cannot tolerate oral dexamethasone, it will be given intravenously.

Rd Arm

Subjects on the Rd arm will receive revlimid, and dexamethasone in 28-day cycles. Dosing is as follows:

- Lenalidomide 25mg PO daily on days 1-21 of a 28-day cycle for patients with a calculated creatinine clearance of ≥60 cc/min. Patients with a calculated clearance of <60 cc/min will receive 15 mgs PO daily on days 1-21 of a28 cycle. 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. Vomited doses will not be made up.

- Dexamethasone 40mg PO will be given on days 1, 8, 15, 22 of a 28-day cycle. Missed or vomited doses will not be made up. If subject cannot tolerate oral dexamethasone, it will be given intravenously.

Correlative studies: Relative dose intensity: Projected total dose per cycle of each component of assigned drug will be divided by the actual dose received and a ratio will be assessed for each cycle delivered.

MRD: Minimal residual disease testing will be performed in subjects who achieve complete response. MRD testing may be performed either by flow cytometry or PCR, whichever is more readily available at the study institution.

Subjects will continue their randomized treatment assignment until disease progression or unacceptable toxicity (whichever occurs first). In case toxicity precludes dosing of one agent (i.e dexamethasone, clarithromycin, lenalidomide), treatment regimen will continue with the remaining agents. Subjects unable to receive ALL the components of the assigned treatment arms will be removed from study after reasonable attempts to dose reduce and manage side effects. Subjects with elevations of AST/ALT greater than three times the upper limit of normal, with concomitant elevation of bilirubin 2 times the upper limit of normal, not attributable to disease, should be discontinued from treatment. Subjects can also be removed from study at investigator's discretion, or if they withdraw consent. At completion or early discontinuation of treatment, subjects will be followed for 30 additional days or up to the initiation of subsequent treatment (whichever occurs first), after which they will be off the active treatment phase of the study. Long term follow up for disease status and survival will proceed until the subject has withdrawn consent, is lost to follow up, or has died.

4.1.4 Disease Assessment

At the end of every cycle (which may coincide with day 1 of the new cycle), response and toxicity will be evaluated. During cycle 1, patients will have lab work done weekly (CBC with differential and blood electrolytes) and female of childbearing potential will have their pregnancy testing done on Day 1, (see Appendix III). All patients will remain on study until disease progression or side effects become excessive.

4.2 Recruitment Plan

A reasonable estimate for accrual of patients for this study is 10-15 patients per month. The anticipated time for completion of this trial is about 2-3 years. Detailed informed consent in plain language will be given to patients for review in either the inpatient or outpatient setting and sufficient time will be given to answer all the questions related to the study. After consent has been signed, pretreatment evaluations will be completed and as outlined in Table 1, Schedule of Assessments, patients will start treatment.

5.0 CRITERIA FOR PATIENT ELIGIBILITY

5.1 Inclusion Criteria

Each subject must meet all of the following inclusion criteria to be eligible to participate in this study:

- Subject must voluntarily sign and understand written informed consent.
- Subject is ≥65 years at the time of signing the consent form.
- Subject has histologically confirmed multiple myeloma that has never before been treated (see Appendix II).
- Subject has no prior anti-myeloma treatment therapy within 14 days prior to initiation of study treatment except for corticosteroids with a maximum allowed dosage equivalent to three pulses of dexamethasone (40mg daily for 4 days equals one pulse). Patients may have received prior adjuvant antiresorptive therapy (i.e., pamidronate or zoledronic acid) as routine care, or radiation therapy as palliation for pain and/or spinal cord compression.
- Subject has measurable disease as defined by > 0.5 g/dL serum monoclonal protein, >10 mg/dL involved serum free light chain (either kappa or lambda) provided that the serum free light chain ratio is abnormal, >0.2 g/24 hrs urinary M-protein excretion, and/or measurable plasmacytoma(s) of at least 1cm in greatest dimension as measured by either CT scanning or MRI.
- Subject has a Karnofsky performance status ≥60% (>50% if due to bony involvement of myeloma (see Appendix IV).
- Subject is able to take prophylactic anticoagulation as detailed in section 9.1 (patients intolerant to aspirin may use warfarin or low molecular weight heparin).
- Subject is registered into the mandatory RevAssist® program, and is willing and able to comply with the requirements of RevAssist® program.
- If subject is a female of childbearing potential (FCBP),† she must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of prescribing lenalidomide (prescriptions must be filled within 7 days) and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking lenalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with females of child bearing potential even if they have had a successful vasectomy. See

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

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

- Subject has a life expectancy ≥ 3 months
- Subjects must meet the following laboratory parameters:
  - Absolute neutrophil count (ANC) ≥1000 cells/mm3 (1.0 x 10^9/L)
  - Hemoglobin ≥ 7 g/dL
  - Platelet count ≥ 50,000/mm3 (50 x 10^9/L)
  - Serum SGOT/AST <3.0 x upper limits of normal (ULN)
  - Serum SGPT/ALT <3.0 x upper limits of normal (ULN)
  - Serum total bilirubin <2.0 mg/dL (34 μmol/L)
  - Creatinine clearance ≥ 45 cc/min

5.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria are not eligible to participate in this study:

- Subject has immeasurable MM (no measurable monoclonal protein, free light chains in blood or urine, or measurable plasmacytoma on radiologic scanning).
- Subject has a prior history of other malignancies unless disease free for ≥ 5 years, except for basal cell or squamous cell carcinoma of the skin, carcinoma in situ of the cervix or breast, or localized prostate cancer with Gleason score < 7 with stable prostate specific antigen (PSA) levels.
- Subject has had myocardial infarction within 6 months prior to enrollment , or NYHA(New York Hospital Association) Class III or IV heart failure (see APPENDIX VI), Ejection Fraction < 35%, uncontrolled angina, severe uncontrolled ventricular arrhythmias, electrocardiographic evidence of acute ischemia or active conduction system abnormalities.
- Female subject who is pregnant or lactating.
- Subject has known HIV infection
- Subject has known active hepatitis B or hepatitis C infection.
- Subject has active viral or bacterial infections or any coexisting medical problem that would significantly increase the risks of this treatment program.
- Subject is unable to reliably take oral medications
- Subject has known hypersensitivity to dexamethasone, clarithromycin, lenalidomide, or thalidomide
- Subject has a history of thromboembolic event within the past 4 weeks prior to enrollment.
- Subject has any clinically significant medical or psychiatric disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent.
- Subject has previously been treated for multiple myeloma

6.0 PRETREATMENT EVALUATION

6.1 Should be done within four weeks prior to starting treatment, unless otherwise indicated:

6.1.1 Complete medical history and physical exam with particular attention to prior transfusions, prior treatment, and radiotherapy. Vital signs, KPS, weight, and height should be recorded

6.1.2 Complete Blood Count (CBC) with differential and platelet count.

6.1.3 Complete metabolic profile including sodium, potassium, chloride, CO2, calcium, magnesium, phosphorus, blood urea nitrogen (BUN), serum creatinine and calculated creatinine clearance, glucose, albumin, total protein, alkaline phosphate, total bilirubin, SGOT/AST. SGPT/ALT

6.1.4 Lactate dehydrogenase (LDH)

6.1.5 Uric Acid

6.1.6 TSH

6.1.7 Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulins, and free serum light chain studies

6.1.8 24 hour urine collection for total protein, protein electrophoresis, and immunofixation

6.1.9 Beta-2-microglobulin (B2M)

6.1.10 C-reactive protein (CRP)

6.1.11 Urinalysis including microscopic analysis

6.1.12 Serum or urine pregnancy for women in childbearing potential 10 – 14 days and within 24 hours of initiation of treatment

6.2 Within six weeks prior to starting treatment

6.2.1 Complete skeletal survey including all long bones, AP pelvis, C-T-L spine, chest, ribs and lateral skull films OR whole body PET/CT scan.

6.2.2 Unilateral iliac crest bone marrow aspirate for cytological review, cytogenetics, FISH studies, flow cytometry (when available) and core biopsy for immunohistochemistry.

6.2.3 Electrocardiogram

7.0 THERAPUTIC AGENTS

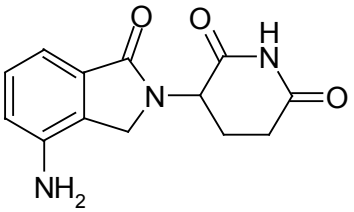
7.1 Clarithromycin (Biaxin®)

Clarithromycin, is a semi-synthetic macrolide antibiotic and is active in vitro against a variety of aerobic and anaerobic gram-positive and gram-negative microorganisms. Biaxin® is indicated for the treatment of mild to moderate infections caused by susceptible strains of microorganisms. It is administered as 500 mg tablets (Abbott Laboratories) to be taken orally. It is rapidly absorbed after oral administration and distributes widely into most body tissue with the exception of the central nervous system. Serum concentrations peak within 2 hours, with a T_{max} of 2 to 4 hours. The elimination half-life is about 3 to 4 hours and has primarily renal excretion, however it is also an inhibitor of cytochrome p450 isozyme CYP3A4. There is potential for drug interaction with other substrates of CYP3A4, as listed in **APPENDIX VII**. The administration of other substrates for CYP3A4 should be avoided if possible. If unavoidable, such drugs should be used with caution. Commercial clarithromycin will be used. Subjects will receive a prescription from the investigator for 500 mg tablets for oral administration, which will be obtained from the subject's local pharmacy. Subjects experiencing adverse event may need study treatment modifications.

7.2 Lenalidomide (Revlimid®)

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

Chemical Structure of Lenalidomide:



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

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

Lenalidomide is an off-white to pale-yellow solid powder. It is soluble in organic solvent/water mixtures, and buffered aqueous solvents. Lenalidomide is more soluble in organic solvents and low pH solutions. Solubility was significantly lower in less acidic buffers, ranging from about 0.4 to 0.5 mg/ml. Lenalidomide has an asymmetric carbon

atom and can exist as the optically active forms S(-) and R(+), and is produced as a racemic mixture with a net optical rotation of zero.

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

7.2.1 Clinical Pharmacology:

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

7.2.2 Pharmacokinetics and Drug Metabolism:

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

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

7.2.3 Pharmacokinetic Parameters:

In vitro (14C)-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

7.2.4 Drug Supply and Dosage: Subjects will obtain commercially available Revlimid® (lenalidomide) as 5 mg and 25 mg capsules for oral administration through Celgene Corporation's 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.

The planned dose of lenalidomide for investigation is 25 mg/day, orally on days 1-21 followed by a 7-day rest period (28 day cycles). Subjects experiencing adverse events may need study treatment modifications.

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.

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

7.2.6 Storage and Special Handling Instructions: Lenalidomide should be stored at room temperature away from direct sunlight and protected from excessive heat and cold. Females of child bearing potential should not handle or administer the clinical dosage forms unless they are wearing gloves.

7.2.7 Prescribing Information: Lenalidomide will be prescribed 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 Celgene's RevAssist® program. Prescriptions must be filled within 14 days unless the patient is a female of childbearing potential, in which case the prescription must be filled within 7 days. **Only enough lenalidomide for one cycle of therapy will be supplied to the patient each cycle.**

7.2.8 Record of Administration: Accurate records will be kept of all study drug administration, including dispensing and dosing, in the source documents.

7.3 Dexamethasone (Decadron®)

Dexamethasone is a synthetic adrenocortical steroid primarily used for its potent anti-inflammatory effects. In addition, it modifies the body's immune response to diverse stimuli. In the treatment of multiple myeloma, dexamethasone has been widely used as a single agent, as well as in combination, for newly diagnosed, relapsed and refractory disease. Pharmacokinetics are characterized by liver metabolism, time to peak serum concentration within 1-2 hours, duration of metabolic effect up to 72 hours and elimination in the urine. Dexamethasone (Decadron®) will be used as 4 mg tablets to be taken orally. Subjects experiencing adverse events may need dosage modification.

8.0 Toxicities and Side Effects

Toxicities and adverse events will be scored using CTCAE version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP homepage (http://ctep.info.nih.gov). All appropriate treatment areas must have access to a copy of the CTCAE version 4.0.

8.1 Clarithromycin (Biaxin®)

Possible common side effects associated with clarithroymycin are headaches, diarrhea, nausea, abnormal taste, heartburn and abdominal pain. Possible rare side effects are irregular blood counts, shortness of breath, hypoglycemia, anxiety, hallucinations, anxiety, fast heartbeat, and tremors.

8.2 Lenalidomide (Revlimid®)

In clinical trials conducted to date, lenalidomide appears to be well tolerated and has an acceptable safety profile. In Phase I/II trials of lenalidomide, the drug was well tolerated and had a manageable side effect profile. Common side effects of lenalidomide include rash, fatigue, itching, diarrhea, fever, constipation, light-headedness, and leg cramps, which generally are very mild. The most common side effects are mostly related to a drop in platelet or neutrophil counts. Severe side effects which include Stevens-Johnson's syndrome, tumor lysis syndrome, and irregular blood counts are rare. These side effects tend to be the dose limiting toxicities when attempting to achieve a full dose. The teratogenic effects of lenalidomide have not been tested in humans. However because lenalidomide is a derivative of thalidomide, all subjects are instructed to use effective contraception prior to study entry and for the duration of study participation.

Secondary Primary Malignancies

Patients treated with lenalidomide (Revlimid) may be at an increased risk of developing secondary primary malignancies than patients who were not treated with lenalidomide. Preliminary data derived from evaluation of outcomes after longer-term exposure to Lenalidomide (Revlimid) and from controlled clinical trials conducted inside and outside the Unites States shows an increased incidence of some second primary malignancies, particularly acute myelogenous leukemia (AML) , myelodysplastic syndromes, B- cell malignancies, and Hodgkin lymphoma when compared to controls.[36]

8.3 Dexamethasone (Decadron®)

Possible common side effects of dexamethasone are fluid retention, weight gain, stomach upset or ulcers, and insomnia and mood changes. Possible side effects of dexamethasone that are less common include hyperglycemia, hypertension, muscle weakness, vertigo, headaches, osteoporosis, manifestation of latent diabetes, increased requirements for insulin or oral hypoglycemic agents in diabetics, cataracts, skin changes, necrosis of the hip, and susceptibility to infections.

8.5 Thrombosis Risk

Lenalidomide and thalidomide increase the risk of thrombotic events in patients who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis. When lenalidomide or thalidomide is combined with other agents such as steroids (e.g. dexamethasone, prednisone), anthracyclines (Doxil, Adriamycin) and erythropoietin the risk of thrombosis is increased. All patients enrolled into this study will take aspirin therapy as outlined in the treatment plan, section 9.1. Concurrent use of recombinant erythropoietin is discouraged due to reports of increased thromboembolic events in patients receiving lenalidomide with erythropoietin. [32] Concurrent use of erythropoietin requires full anticoagulation of patients with therapeutic doses of LMWH or coumadin. Anticoagulation should be held for platelet counts <50,000/mm3. Anti-microbial prophylaxis is not required and is left to the discretion of the treating physician.

9.0 Therapeutic Plan

9.1 Treatment

Patients who sign informed consent will be seen in clinic or in the hospital at New York Presbyterian Hospital-Weill Cornell Medical College, by their physician for pretreatment testing as outlined in section 6.0. All prescribers must be registered in the Celgene RevAssist® program in order to prescribe lenalidomide (Revlimid®). Subjects who complete pretreatment evaluations and meet all eligibility criteria may start treatment. All patients will be started on BiRd in 28-day cycles according to the following schedule:

For all subjects**, Dexamethasone** (Decadron®) will be given orally at a dose of 40 mg on days 1, 8, 15, and 22 for each subsequent cycle

For subjects on the BiRd arm only, **Clarithromycin** (Biaxin®) will be given orally at a dose of 500 mg twice a day, beginning on day 1 of cycle 1.

For all subjects**, Lenalidomide (**Revlimid®) will be given orally at a dose of 25 mg/day beginning on day 3 and ending on day 21 of cycle 1, and on days 1-21 of each subsequent cycle.

Due to the risk of thrombosis (see Section 8.5), all patients will begin thromboembolic prophylaxis with aspirin 81mg daily throughout treatment, starting on cycle 1 day 1. Aspirin-intolerant patients, or patients with a prior history of venous thrombosis, should receive prophylactic doses of daily low molecular weight heparin (LMWH). For patients who are unable to take aspirin or LMWH, other antithrombotic agents may be used at the investigators discretion. If warfarin is used, the INR should be monitored frequently to maintain within the goal range of 2-3. Concurrent use of recombinant erythropoietin to treat anemia is discouraged due to reports of increased thromboembolic events in patients receiving lenalidomide with erythropoietin. Concurrent use of erythropoietin requires full anticoagulation of patients with

therapeutic doses of LMWH or coumadin. Anticoagulation should be held for platelet counts <50,000/mm^3.

Monitoring for Secondary Primary Malignancies

Due to the potential increased risk of developing secondary primary malignancies associated with lenalidomide treatment, patients will be advised to undergo regular cancer screenings as part of standard of care. Monitoring for development of acute leukemia and Hodgkin's lymphoma will be performed by review of regular blood work, chemistry panel, and LDH at each visit including during follow-up. Particular attention will be paid to the complete blood count differential with a low threshold to investigate emerging cytopenias or altered differential with either bone marrow biopsy or PET scanning if clinically indicated. In addition, men and women will be advised to have a yearly skin exam by a dermatologist and regular colonoscopy screening (every 5 years or earlier, depending on GI recommendations). Women will also be advised to have yearly mammograms and regular cervical cancer screening. Men will also be advised to undergo yearly Prostate-Specific Antigen (PSA) testing.

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

Cycles will be repeated every 28 days. Patient will return to clinic every 28 days for evaluation of toxicity and response and will remain on study until progression of disease, toxicities become excessive, or until discontinuation for another reason (see Section 9.2). Doses may be modified due to side effects.

Patients who achieve a resolution of monoclonal gammopathy as detected on serum immunofixation or achieve a plateau of disease (no change in quantitative M-spike or free light chains) for > 2 cycles will be transitioned to maintenance therapy. Maintenance therapy will consist of dexamethasone at a dose of 20mg weekly (given on days 1, 8, 15, and 22 of a 28 day cycle) and lenalidomide at a dose of 25 mg/day on days 1-21 of a 28 day cycle (a dose of 15mg/day days 1-21 of a 28 day cycle will be given to patients with a creatinine clearance of < 60 cc/min).

9.2 Early Termination of Study

Study-terminating events are listed below (to include?):

- *Early death (defined by death within 30 days of beginning therapy) deemed to be related to study treatment of more than 1 of the first 10 subjects.*
- *Early need for hospitalization (defined by hospitalization within 30 days of beginning therapy) of more than 5 of the first 10 subjects.*
- *If there is an unacceptable rate of Grade 4 toxicities (according to CTCAE version 4.0), as deemed by the research team, Celgene, or the Data Safety Monitoring Board.*

- *If >5% of patients develop a secondary primary malignancy on maintenance lenalidomide, the study will be halted and reviewed by the Investigator and Data Safety Monitoring Board before a decision will be made to proceed.*

9.3 Supportive Care and Concurrent Treatments

9.3.1 Treatments: Prophylactic medications should be routinely administered in combination with Dexamethasone. Individualization is required, as some patients require no prophylaxis therapy, while other patients require intensive therapy. The particular choice of prophylactic therapy will be at the discretion of the treating physician investigator. We recommend patients receive omeprazole 20 mg once daily as gastritis prophylaxis, docusate 100mg tablet twice daily for constipation prophylaxis, Bactrim DS 1 tablet once daily for *Pneumocystis carinni* pneumonia prophylaxis beginning with cycle 2 of either BiRd or Rd therapy, and mycelex troches 10mg four to five times daily as needed for oral thrush prophylaxis. See Section 9.1 for thromboembolic prophylaxis using aspirin, warfarin or coumadin.

9.3.2 Lytic Bone Lesions: Patients with lytic bone lesions, if able to, should receive standard of care treatment in routine multiple myeloma management, such as IV bisphosphonates, as determined by the investigator. It is preferred that investigators use the same route of bisphosphonate therapy for all subjects at their sites (if applicable).

9.3.3 Hematopoeitic support: Thrombocytopenia should be treated conservatively. In the absence of bleeding, platelet transfusions should only be given for a platelet count below 10,000. If the patient develops bleeding, platelet transfusions should be administered in accordance with standard of practice, usually maintaining a platelet count $\geq 50{,}000/mm^3$. Febrile neutropenia is a life-threatening complication requiring hospitalization and urgent broad-spectrum antibiotics. Hematopoietic growth factors may be used according to Table 2: Dose Modification Instructions. Such cases will be evaluated individually to determine the toxicity grade. Symptomatic anemia should be treated with appropriate red blood cell support and transfusion is recommended if the hemoglobin falls below 8 g/dl. Recombinant erythropoietin may be used with concurrent anticoagulation, as described above in section 9.1, if desired by the patient's local physician.

9.3.4 Radiotherapy: Patients who require localized external beam radiotherapy or surgery at the time of protocol screening should receive it before study entry. Patients may receive radiotherapy or surgery during the study if required to treat a pathological fracture, cord compression, or associated pain that was present prior to study entry. Patients who require radiotherapy or surgery to treat pathological fractures related to a new growth of myeloma, cord compression, or associated pain will be considered to have progression of disease and will be removed from study. Patients may receive radiation therapy or surgery for the treatment of a plasmacytoma that was present prior to study entry only if the plasmacytoma is not considered a target lesion to assess response.

9.3.5 Prohibited Concomitant Therapy: Concomitant use of sargramostim (GM-CSF), other anti-cancer therapies, or other investigational agents is not permitted while subjects

are receiving study drug during the treatment phase of the study. Agents that alter the QTc will be discouraged particularly in patients receiving clarithromycin. See Appendix VII

9.4 Day One Dosing Guidelines

A new cycle of treatment may begin on a scheduled Day 1 if any therapy related adverse events have resolved to an acceptable grade (see Section 9.3, Dose Modifications). If not, the patient should be evaluated at least at weekly intervals until resolution of toxicities. If start of new cycle is delayed more than 4 weeks, the patient will be removed from the protocol. The patient will also be directed to take the following prophylactic medicines: 1) omeprazole at a dose of 20mg once daily; 2) Bactrim at a dose of one DS tab once daily (or equivalent *Pneumocystis jiroveci* prophylaxis; patients may start at cycle 2 if preferred by treating physician); 3) aspirin at a dose of 81 mg once daily (or other equivalent anti-thrombotic therapy).

9.5 Instruction for initiation of a new cycle

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

- Absolute neutrophil count (ANC) ≥750 cells/mm³
- Platelets count ≥ 50,000/mm³
- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If the toxicity does not resolve within four weeks, the patient will be taken off the study. If the dosing of clarithromycin, lenalidomide or dexamethasone was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose will be initiated on Day 1 of the new cycle. If the dosing of clarithromycin, lenalidomide or dexamethasone was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with dose modifications as described in Section 9.6 and Table 2.

If the start of a new cycle is delayed more than 4 weeks, the patient will be removed from the protocol.

9.6 Dose Modification

Doses of study medications will be modified for toxicity as listed below in Tables 1, 2a, and 2b. Doses must be adjusted for adverse events deemed related to study drug by the investigator. Doses may be adjusted for adverse events related to study medications not listed below at the discretion of the investigator.

Unless otherwise noted, other drugs in the regimen should be continued when the dosing of one or more drugs is delayed due to toxicity.

During BiRd therapy, if toxicity occurs that would indicate an interruption in treatment, the toxicity should be attributed to one or more drugs in the BiRD regimen and dose modifications instituted as instructed in the "Action" column of the table below based on attribution. During maintenance therapy, if toxicity occurs that would indicate a lenalidomide dose modification, toxicity should be attributed to lenalidomide and dose modifications instituted as instructed in the "Action" column of the table below based on attribution.

Table 1: Dose Reduction Steps:	
Lenalidomide Dose Reduction	
Starting Dose	Lenalidomide PO 25mg/day on days 1-21 of a 28 day cycle
Dose Level -1	Lenalidomide PO 15mg/day on days 1-21 of a 28 day cycle
Dose Level -2	Lenalidomide PO 10 mg/day on days 1-21 of a 28 day cycle
Dose Level -3	Lenalidomide PO 5 mg/day on days 1-21 of a 28 day cycle
Dose Level -4	Lenalidomide PO 5 mg every other day for on days 1-21 of a 28 day cycle
Dexamethasone Dose Reduction	
Starting Dose	40 mg PO on days 1, 8, 15 and 22 of a 28 day cycle
Dose Level -1	20 mg PO on days 1, 8, 15 and 22 of a 28 day cycle
Dose Level -2	8 mg PO on days 1, 8, 15 and 22 of a 28 day cycle
Dose Level -3	8 mg PO on days 1 and 15 of a 28 day cycle
Dose Level -4	4 mg PO on days 1 and 15 of a 28 day cycle
Clarithromycin Dose Reduction	
Starting Dose	500 mg BID PO days 1-28 of a 28 day cycle
Dose Level -1	250 mg BID PO days 1-28 of a 28 day cycle

Dose Level -2	250 mg PO daily on days 1-28 of a 28 day cycle
Dose Level -3	250 mg PO daily on days odd days of a 28 day cycle
Dose Level -4	Discontinue drug

Table 2a: RD Dose Modification Instructions

Toxicity	*NCI Toxicity Grade*	*Action*
Neutropenia	≥ Grade 3 with fever (temperature ≥ 38.5º C)	• Hold (interrupt) lenalidomide. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue through Day 21. **If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.**
Neutropenia	Grade 4	• Hold (interrupt) lenalidomide. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue through Day 21. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.
Thrombocytopenia	≥ Grade 3 (platelet count < 50,000/mm³)	• Hold (interrupt) lenalidomide and anti-coagulation dosing. • Follow CBC weekly. • If thrombocytopenia has resolved to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and restart anti-coagulation.

Toxicity	*NCI Toxicity Grade*	*Action*
Rash (non-blistering)	≥ Grade 3	• Hold (interrupt) lenalidomide for remainder of cycle • Reduce lenalidomide by 1 dose level and restart next cycle.
Rash	Grade 4 non-blistering or desquamating (blistering) any Grade	• Discontinue lenalidomide and take patient off study
Erythema multiforme	≥ Grade 3	• Discontinue lenalidomide and take patient off study
Hyperthyroidism or Hypothyroidism	Any grade	• Omit lenalidomide remainder of cycle • Evaluate etiology and initiate appropriate therapy • Restart lenalidomide at same dose level.
Sinus bradycardia/ other cardiac arrhythmia	Grade ≥ 2	• Hold (interrupt) lenalidomide for remainder of cycle. Follow at least weekly. • Reduce lenalidomide by 1 dose level and restart next cycle.
Sinus bradycardia/ other cardiac arrhythmia	≥ Grade 3	• Discontinue lenalidomide and take patient off study
Allergic reaction or hypersensitivity	≥ Grade 2	• Hold (interrupt) lenalidomide for remainder of cycle. Follow at least weekly. • Reduce lenalidomide by 1 dose level and restart next cycle.
Allergic reaction or hypersensitivity	≥ Grade 3	• Discontinue lenalidomide and take patient off study
Venous thrombosis/embolism	≥ Grade 3	• Hold (interrupt) lenalidomide and Start anticoagulation; restart lenalidomide at investigator's discretion (maintain dose level).
Gastritis, gastric or duodenal ulcer	≥ Grade 3	• Hold (interrupt) dexamethasone until ≤ grade 1 • Reduce dexamethasone by 1 dose level and restart

Toxicity	*NCI Toxicity Grade*	*Action*
Edema	≥ Grade 3	• Reduce dexamethasone by 1 dose level • Use diuretics as needed
Confusion or mood alternations	≥ Grade 2	• Hold (interrupt) dexamethasone until ≤ grade 1 • Reduce dexamethasone by 1 dose level and restart
Muscle weakness	≥ Grade 3	• Reduce dexamethasone by 1 dose level • If symptoms persist continue to reduce dexamethasone by 1 dose level as needed.
Hyperglycemia	≥ Grade 3	• Reduce dexamethasone by 1 dose level • Treat with insulin or oral hypoglycemics as needed
Acute pancreatitis	≥ Grade 3	• Discontinue dexamethasone and patient off study.
Other non-hematologic toxicity assessed as treatment-related	≥ Grade 3	• Attribute toxicity to one or more drugs. Hold drug(s) attributed to toxicity for remainder of cycle. Reduce drug(s) attributed to toxicity by 1 dose level.*

Table 2b: BiRD Dose Modification Instructions

Toxicity	*NCI Toxicity Grade*	*Action*
Neutropenia	≥ Grade 3 with fever (temperature ≥ 38.5° C)	• Hold (interrupt) lenalidomide. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue through Day 21. **If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.**

Toxicity	*NCI Toxicity Grade*	*Action*
Neutropenia	Grade 4	• Hold (interrupt) lenalidomide. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and continue through Day 21. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the lenalidomide dose maintained.
Thrombocytopenia	≥ Grade 3 (platelet count < 50,000/mm^3)	• Hold (interrupt) lenalidomide and anti-coagulation dosing. • Follow CBC weekly. • If thrombocytopenia has resolved to ≤ grade 2 prior to Day 21, restart lenalidomide at next lower dose level and restart anti-coagulation.
Rash (non-blistering)	≥ Grade 3	• Hold (interrupt) lenalidomide for remainder of cycle • Reduce lenalidomide by 1 dose level and restart next cycle.
Rash	Grade 4 non-blistering or desquamating (blistering) any Grade	• Discontinue lenalidomide and take patient off study
Erythema multiforme	≥ Grade 3	• Discontinue lenalidomide and take patient off study
Hyperthyroidism or Hypothyroidism	Any grade	• Omit lenalidomide remainder of cycle • Evaluate etiology and initiate appropriate therapy • Restart lenalidomide at same dose level.
Sinus bradycardia/ other cardiac arrhythmia	Grade ≥ 2	• Hold (interrupt) lenalidomide for remainder of cycle. Follow at least weekly. • Reduce lenalidomide by 1 dose level and restart next cycle.
Sinus bradycardia/ other cardiac arrhythmia	≥ Grade 3	• Discontinue lenalidomide and take patient off study

Toxicity	*NCI Toxicity Grade*	*Action*
Allergic reaction or hypersensitivity	≥ Grade 2	• Hold (interrupt) lenalidomide for remainder of cycle. Follow at least weekly. • Reduce lenalidomide by 1 dose level and restart next cycle.
Allergic reaction or hypersensitivity	≥ Grade 3	• Discontinue lenalidomide and take patient off study
Venous thrombosis/embolism	≥ Grade 3	• Hold (interrupt) lenalidomide and Start anticoagulation; restart lenalidomide at investigator's discretion (maintain dose level).
Diarrhea	≥ Grade 3	• Hold (interrupt) clarithromycin until ≤ grade 1, then reduce dose to 250 mg twice daily
Dyspepsia	≥ Grade 3	• Hold (interrupt) clarithromycin and dexamethasone dosing until ≤ grade 1 • Reduce dexamethasone OR clarithromycin by 1 dose level based on attribution and restart dexamethasone and clarithromycin
Anaphylaxis or Hepatic failure	≥ Grade 3	• Discontinue clarithromycin and patient is off study
Loss of appetite or Nausea	≥ Grade 3	• Hold (interrupt) clarithromycin until ≤ grade 1, then reduce dose to 250 mg twice daily
Gastritis, gastric or duodenal ulcer	≥ Grade 3	• Hold (interrupt) dexamethasone until ≤ grade 1 • Reduce dexamethasone by 1 dose level and restart
Edema	≥ Grade 3	• Reduce dexamethasone by 1 dose level • Use diuretics as needed
Confusion or mood alternations	≥ Grade 2	• Hold (interrupt) dexamethasone until ≤ grade 1 • Reduce dexamethasone by 1 dose level and restart
Muscle weakness	≥ Grade 3	• Reduce dexamethasone by 1 dose level • If symptoms persist continue to reduce dexamethasone by 1 dose level as needed.

Toxicity	*NCI Toxicity Grade*	*Action*
Hyperglycemia	≥ Grade 3	• Reduce dexamethasone by 1 dose level • Treat with insulin or oral hypoglycemics as needed
Acute pancreatitis	≥ Grade 3	• Discontinue dexamethasone and patient off study.
Other non-hematologic toxicity assessed as treatment-related	≥ Grade 3	• Attribute toxicity to one or more drugs. Hold drug(s) attributed to toxicity for remainder of cycle. Reduce drug(s) attributed to toxicity by 1 dose level.*

10.0 STUDY EVALUATIONS

Patients will be followed in clinic every week for the first cycle and on Day 1 (+/- 7 days) for subsequent cycles. Females of childbearing potential (FCBP) must have a pregnancy test done by the doctor as outlined in Appendix III prior to and during lenalidomide-containing cycles. During scheduled study visits patients will undergo the following evaluations for assessment of response and toxicity (depicted in Table 1, section 1.0):

10.1 Day 1, Cycle 1

- Physical evaluation: A complete medical evaluation including medical history, concomitant medications, physical exam, vital signs, KPS, height and weight.
- Complete Blood Count (CBC) with differential and platelet count
- Complete metabolic profile (including sodium, potassium, chloride, CO2, calcium, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT/AST, and SGPT/ALT)
- Lactate dehydrogenase (LDH)
- Uric Acid
- Magnesium
- Phosphorus
- Drug diary generated and reviewed with patient (See Appendix VIII)
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulins
- Serum free light chain studies
- 24-hour urine collection for total protein, protein electrophoresis, and immunofixation
- Serum pregnancy test, if applicable
- Quality of Life Assessment (See Appendix IX)

10.2 Days 8, 15, 22 Cycle 1

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

10.3 Day 1 (starting cycle 2) and End of Study

- Physical evaluation: A complete medical evaluation including medical history, adverse events, concomitant medications, physical exam, vital signs, KPS, height and weight.
- Complete Blood Count (CBC) with differential and platelet count.
- Complete metabolic profile (including sodium, potassium, chloride, CO2, calcium, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT/AST, SGPT/ALT
- LDH
- Uric Acid
- TSH every 3 months beginning with cycle 4 (more often if clinically indicated)
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulins
- Serum free light chains studies
- 24-hour urine collection for total protein, protein electrophoresis, and immunofixation.
- Prior cycle drug diary will be collected. New drug diary will be generated and reviewed with the patient.
- Serum pregnancy test, if applicable
- Bone marrow aspiration and biopsy to confirm a CR, or when clinically indicated.
- Skeletal survey, MRI, or whole body PET/CT scan when clinically indicated (i.e., to evaluate for disease response in non-secretory myeloma or to investigate for disease progression).
- All subjects will be followed for survival. Cause of death is to be recorded in the subject's medical record.
- Quality of Life assessment (Appendix IX)
- Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of adverse events throughout the course of the study.

10.4 Post Study Follow-up

All attempts will be made to follow patients until progression or death. Subjects who have been discontinued from study will still be followed in a clinic setting to the fullest extent possible on a monthly to bi-monthly basis. Those who choose not to resume regular clinic follow-up will be contacted every 6 months by telephone or electronically

to collect post study information. The post-study collection information will consist of a telephone interview between the clinical investigator and the discontinued patient. The information requested will be current disease status including information about the development of secondary primary malignancies, current treatment use, and physical status of the patient.

10.5 Treatment Compliance

At all times research center personnel will review the dosing instructions with subjects. Subjects will be asked to maintain a drug diary to record the drug administration. If doses of clarithromycin or lenalidomide are missed, the dose should be taken as soon as possible on the same day. If the dose is missed for the entire day, it should not be made up. Missed doses of dexamethasone will not be made up. Vomited doses of clarithromycin, lenalidomide and dexamethasone will not be made up. Patients who take more than the prescribed dose of clarithromycin, lenalidomide or dexamethasone should be instructed to seek emergency medical care if needed and contact study staff immediately. Subjects will be asked to bring any unused study drug to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules at each visit.

10.11 Criteria for removal from study

Rules for termination of the study for the individual subject are listed below:

- Subjects may withdraw consent and stop participation at any time.
- Any Grade 4 skin toxicity (i.e. Stevens Johnson syndrome) or Grade 4 hypersensitivity (i.e. anaphylaxis).
- Progression of multiple myeloma, as defined by the International Myeloma Working Group Criteria (Appendix 1 of the protocol).
- Development of any co-morbid condition or excessive toxicity that would make further participation in the protocol unsafe.
- The development of any comorbid condition of excessive toxicity that would make further participation in the protocol unsafe.
- Non-compliance or refusal of the patient to continue treatment and/or evaluation.
- Major violation of the study protocol.
- Any adverse event(s) that, in the judgment of an Investigator, may cause severe or permanent harm if the study medications are continued.
- At the discretion of the principal investigator and/or Celgene Pharmaceuticals, Inc. for any reason.
- Loss to follow up.
- Death of patient

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

10.11.2 The responsible Clinical Investigator as well as Celgene Pharmacuticals, Inc. 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.

11.0 ADVERSE EVENTS GRADING AND REPORTING

11.1 Adverse Events

An adverse event is any sign, symptoms, illness, or diagnosis (either observed or volunteered) that appears or worsens during the course of the study. Toxicity will be scored using CTCAE version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP homepage http://ctep.info.nih.gov. All appropriate treatment areas must have access to a copy of the CTCAE version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the patients, must be recorded with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the patient's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

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

11.2 Serious Adverse Events (SAE)

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

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

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

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

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

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment arm the subject is in. This includes any second primary malignancy, regardless of causal relationship to any of the study drugs, occurring at any time for the duration of the study, from the time of signing the informed consent up to the time all patients have been followed for at least 5 years from randomization or have died. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF and subject's source documents.

Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (eg., any confirmatory histology or cytology results, X-rays, CT scans, etc.).

11.2.1 Pregnancies:

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

The Investigator will follow the female subject until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the

pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 1 business day of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to lenalidomide should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 1 business day of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

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

11.2.2 Celgene Drug Safety Contact Information for Pregnancy Reporting:

Celgene Corporation
Drug Safety
86 Morris Avenue
Summit, NJ 07901

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

11.3 Investigator Reporting Responsibilities:

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

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 "unexpected" as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

11.3.1 Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined in Section 11.2 above. The investigator should inform Celgene Pharmaceuticals, Inc. of any SAE within 1 business day of being aware of the event. The date of awareness should be noted on the report. This must be documented on the Onyx Therapeutics, Inc. SAE forms or a FDA 3500 or MEDWATCH form. This form must be completed and supplied to Onyx Therapeutics, Inc. within 24 hours / 1 business day at the latest on the following working day. The initial report must be as complete as possible, including details of the current illness and (serious) adverse event, and an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up MEDWATCH. A final report to document resolution of the SAE is required. The Celgene protocol number should be included on the SAE reports. 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.

Celgene Drug Safety Contact Information
Celgene Corporation
Drug Safety
86 Morris Avenue
Summit, NJ 07901

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

11.3.2 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.

11.3.3 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 Dr. Ruben Niesvizky (the principal sponsor-investigator). A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

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

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

The address of the FDA is: FDA
Division of Oncology
HFD-150
1451 Rockville Pike
Rockville, MD 20852-1448

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

Please ask to speak with the Division of Oncology.

11.3.4 Reporting of Secondary Primary Malignancies

Secondary primary malignancies will be reported to the FDA, Celgene Pharmaceuticals, and the Weill Cornell Medical College Data Safety Monitoring Board at the time of annual renewal. Additional information regarding secondary primary malignancies listed in Section 11.2.

11.4 Adverse event updates/IND safety reports

Celgene Pharmaceuticals, Inc. 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 15.4 for records retention information).

11.5 Provisions for Adverse Events

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

12.0 PROTOCOL AMENDMENTS AND DEVIATIONS

12.1 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 Celgene Pharmaceuticals, Inc. review. Written verification of IRB/EC approval will be obtained before any amendment, which affects subject safety or efficacy, is implemented. Amendments that are administrative in nature do not require IRB/EC approval but will be submitted to the IRB/EC for information purposes.

12.2 Protocol Deviations

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

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

13.0 DATA MANAGEMENT

13.1 Analyses and Reporting

This study will be conducted at The New York Presbyterian Hospital at the Weill Cornell Medical College. Clinical data will be collected under the supervision of one of the study investigators. Clinical data will be organized and recorded with the help of data managers located at the Cornell campus. Study design and data analysis will be implemented in collaboration with our biostatistician at Weill Cornell Medical College and data will be collected and tabulated on a monthly basis.

13.2 Data Safety Monitoring Board.

The Data Safety Monitoring Board (DSMB) at Weill-Cornell Medical Center will be composed of medical and statistical independent reviewers and will meet to review the efficacy and safety data and determine a risk/benefit analysis in this subject population. The purpose of the DSMB is to advise on serious safety considerations, lack of efficacy and any other considerations within the charge to the Committee. The DSMB may request additional meetings or safety reports as deemed necessary upon discussion with Celgene and its representatives. The PI, Dr. Jorge Monge, will be the safety contact for all DSMB related analysis outcomes.

Dr. Monge's office is located at: NYPH-WCMC
425 East 61st Street, Suite 800
New York, NY 10065

The phone number to Dr. Monge's office is: +1-646-962-6500

The DSMB may stop the study following review of results from each interim analysis. The first interim analysis will take place 3 months after the study begins subject accrual or after 10 patients have been enrolled, whichever occurs first, and will examine only safety information. A subsequent interim analysis will take place 6 months after the study begins subject accrual, and every six months thereafter, and will examine both safety and efficacy. The DSMB will also review the study after 66 PFS events have occurred across both arms for futility, (as outlined in the Statistical Considerations Section 14) including toxicity data, protocol adherence, and protocol deviations and enforce stopping rules if necessary. Efficacy and safety data summaries will be provided to the DSMB after each interim analysis.

"13.3 Study Monitoring and Auditing

13.3.1 Investigator Responsibilities

Investigator responsibilities are set out in the ICH guideline for Good Clinical Practice (GCP) and in the US Code of Federal Regulations. Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related monitoring visits and audits by Celgene Corporation or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

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

14.0 STATISTICAL CONSIDERATIONS

14.1 Study Design/Primary Endpoint

The study is a randomized phase III design, and the primary endpoint in both treatment arms is median PFS. PFS will be defined as the time from randomization day until objective progression or death from any cause. The PFS distributions of the two treatment arms will be estimated by Kaplan-Meier survival analysis and the PFS distributions will be compared by an unstratified log-rank test. Ninety-five percent confidence intervals for the Kaplan-Meier PFS estimates will be calculated using

Greenwood's formulae. The primary comparison will be made using the intent-to-treat (ITT) patient population. Patients will be analyzed based on their randomization assignments, regardless of therapy initiation or compliance. A secondary analysis will be performed comparing "evaluable" patients as patients who met eligibility requirements, have initiated therapy, and were not removed from the study for non-compliance or patient withdrawal.

The median PFS for MM patients receiving Revlimid /dexamethasone chemotherapy (Rd) (Arm A) is expected to be approximately 25.5 months, as reported in the MM-010 study of continuous Rd vs Rd for 18 months (Facon T, Dimopoulos M, Dispenzieri A, et al: Initial phase 3 results of the FIRST trial in newly diagnosed multiple myeloma patients ineligible for stem cell transplant. 2013 ASH Annual Meeting. Abstract 2. Presented December 8, 2013.). Therefore, the target median PFS for patients receiving Revlimid/dexamethasone/Clarithromycin (BiRd) (Arm B) is hypothesized to be 44.6 months (target hazard ratio = 1.75).

14.2 Sample Size/Accrual Rate

To achieve 90% power to detect a 75% increase in median PFS (44.6 vs. 25.5 months), at the two-sided 0.05 significance level, will require 306 patients total, accrued over approximately 3.0 years (assuming an accrual rate of approximately 9 patients/month), with an additional 12 months of follow-up subsequent to termination of accrual.

When the sample size in each group is 153 patients, with a total number of PFS events required of 133, an exponential maximum likelihood test of equality of survival curves with a 0.05 two-sided significance level will have 90% power to detect the difference between an Arm A (Rd) median PFS of 25.5 months and an Arm B (BiRd) median PFS of 44.6 months (a constant hazard ratio of 1.75); this assumes an accrual period of 3.0 years, a maximum follow-up time of 4.0 years, and no dropouts. The exponential assumption is for planning purposes only, actual analysis will employ nonparametric methods for estimation and testing of survival distributions. Assuming a 10% dropout rate, approximately 337 patients will be accrued to the study.

A futility analysis will be conducted after 50% of the total PFS events required for final analysis has occurred (i.e., 66 of the 133 required PFS events). No accrual suspension is required to conduct the futility analysis. If at this point (i.e., after accumulation of 66 PFS events) the hazard ratio of the control arm over the experimental arm is 1.0 or less, the study will be stopped for futility.

14.3 Analysis of Progression-Free Survival

Because the analysis of PFS can be difficult, especially in the presence of missing data and lost-to-follow-up, sensitivity analyses can be helpful in determining whether the PFS analysis is robust. As suggested by the alternative PFS definitions recommended in the FDA's Guidance for Industry, "Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics (May, 2007), the following three types of PFS analyses will be

conducted:

Table A. PFS #1 (includes documented progression only) (Primary PFS Analysis):

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Earliest of: • Date of hematological assessment showing progression; or • Date of radiological assessment showing progression; or • Date of urine assessment showing progression	Progressed
No progression	Date of last hematological, radiological, or urine assessment	Censored
Treatment discontinuation for undocumented progression	Date of last hematological, radiological, or urine assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last hematological, radiological, or urine assessment	Censored
New anticancer treatment started	Date of last hematological, radiological, or urine assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	If progression: • Date of hematological assessment showing progression; or • Date of radiological assessment showing progression; or • Date of urine assessment showing progression OR, if not progression: Date of last hematological, radiological, or urine assessment	Censored

Table A represents the primary PFS analysis that only includes well-documented and verifiable progression events. Other data are censored. In Table A, the progression dates are 1) based only on radiological assessments verified by an IRC (clinical progression will not be considered a progression endpoint), 2) assigned to the first time when disease progression is noted, and 3) the date of death when the patient is closely followed. However, deaths occurring after two or missed visits will be censored at the last visit.

Table B. PFS #2 (uniform progression and assessment dates) (PFS Sensitivity Analysis #1):

Situation	Date of Progression or Censoring	Outcome
No baseline tumor assessments	Randomization	Censored
Progression documented between scheduled visits	Date of next scheduled visit	Progressed
No progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for undocumented progression	Date of last visit with adequate assessment	Censored
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censored
New anticancer treatment started	Date of last visit with adequate assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
Death or progression after more than one missed visit	Date of last visit with adequate assessment	Censored

Table B presents a sensitivity analysis for PFS that helps to correct for potential bias in follow-up schedules for tumor assessment by assigning the dates of censoring and events only at scheduled visit dates. This approach can introduce bias if the progression occurred closer to the last visit, particularly in an open-label study.

Table C. PFS #3 (includes investigator claims) (PFS Sensitivity Analysis #2):

Situation	Date of Progression or Censoring	Outcome
No baseline assessment	Randomization	Censored
Progression documented between scheduled visits	Next scheduled visit	Progressed
No progression	Date of last visit with adequate assessment	Censored
Investigator claim of clinical progression	Scheduled visit (or next scheduled visit if between visits)	Progressed
Treatment discontinuation for toxicity or other reason	Date of last visit with adequate assessment	Censored
New anticancer treatment started with no claim of progression	Date of last visit with adequate assessment	Censored
Death before first PD assessment	Date of death	Progressed
Death between adequate assessment visits or after patient misses one assessment visit	Date of death	Progressed
Death after an extended lost-to-follow-up time (two or more missed assessments)	Last visit with adequate assessment	Censored

Table C presents a sensitivity analysis for PFS that evaluates PFS according to the investigator's assessment. This approach can introduce bias if the progression occurred closer to the last visit, particularly in an open-label study.

Although the above PFS analyses will initially censor patients who died or progressed after more than one missed visit (Tables A/B/C), these analyses will also be redone to classify the patients as progression events, and the date of death will be used as the date of progression. Counting such deaths as progression events may overestimate PFS, but also minimizes bias.

Lastly, a comparison of the adequacy of follow-up and the number of scheduled assessments in each treatment arm will be performed to evaluate potential bias resulting from missing data. Because the trial is unblinded, there is always the potential for bias (i.e., evaluation-time bias) between the treatment arms because of the subjective aspects of the progression endpoint. To evaluate the impact of any evaluation-time bias in the assessment of PFS, we will use the approach of Freidlin and Korn when comparing PFS between the two treatment arms (Freidlin B, Korn EL, Hunsberger S, Gray R, Saxman S, Zujewski J. Proposal for the use of progression-free survival in unblinded randomized trials. Journal of Clinical Oncology. 2007;25:2122-2126). The method of Freidlin and Korn will not be the primary analysis. The primary analysis will be performed as discussed in section 14.2, first two paragraphs. The Freidlin/Korn method will be performed to assess the extent of any evaluation-time bias that may have resulted from comparison of the two treatment arms in the primary analysis (i.e., primary analysis using the actual reported progression times; progression-free survival curves).

14.3 Stratification Factors

Patients will be stratified based on enrolling institution.

Blocked randomization will be performed at all participating sites. A series of randomized blocks will be generated for each participating site with a 1:1 allocation ratio. This will provide assurance that there will be an equal patient allocation to both treatment arms at any given participating site.

14.4 Analysis of Secondary Endpoints

Secondary endpoints include objective response rate (CR+PR) and complete response rate (CR) (estimated via binomial proportions), and Kaplan-Meier overall survival. Overall survival will be defined as the time from randomization day until death. Ninety-five percent confidence intervals will be calculated for the objective response proportion in each group via binomial proportions. Comparison of the objective response rate and complete response rate between the treatment groups will be performed by the chi-square test. The comparison of the overall survival distributions between the treatment groups will be performed by the log-rank test. Analysis of these three secondary endpoints will

be considered hypothesis-generating only and will be adjusted for multiplicity of outcomes by the Bonferroni method. In the event that no significant result is observed for the primary endpoint (PFS), significant findings for the secondary endpoints (even after correction for multiplicity of outcomes) will not result in efficacy claims for labeling purposes. Similarly, if a significant finding is observed for the primary endpoint, significant findings for the secondary endpoints will still not result in efficacy claims for labeling purposes. All other secondary endpoints (i.e., event-free survival, duration of response, time to progression, progression-free survival 2, and quality of life measures) will only be descriptively presented for each treatment group and no formal statistical comparison will be made between treatment arms. Confidence intervals for the secondary endpoints of objective response rate, complete response rate, and overall survival will be Bonferroni-corrected. The frequency of subjects experiencing toxicities will be tabulated. Toxicities will be assessed and graded according to CTCAE v. 4.0 terminology. Exact 95% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates.

All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. P-values will be Bonferroni-corrected for the secondary endpoints of objective response rate, complete response rate, and overall survival. All analyses will be performed in SAS Version 9.4 (SAS Institute, Inc. Cary, NC) and Stata Version 14.0 (StataCorp, College Station, TX).

15.0 REGULATORY CONSIDERATIONS

15.1 Institutional Review Board/Ethics Committee approval

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

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

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

Any amendments to the protocol after receipt of IRB/EC approval must be submitted for approval by the Investigator to the IRB/EC. 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.

15.2 Informed Consent Procedures

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

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

15.3 Protecting Privacy and Confidentiality

Confidentiality will be maintained within the limits of the law. Patient names or any other identifying information will not be used in reports or publications resulting from this study. Only qualified staff from New York Presbyterian Hospital, Weill Medical College of Cornell University, the Food and Drug Administration, or other study support such as the National Cancer Institute will be able to review patient medical records.

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

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

15.4 Study records requirements

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

needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

15.5 Protection of Human Rights

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

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

15.6 Premature Discontinuation of Study

The responsible local clinical investigator, as well as Celgene, has 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.

15.6.1 Study as a whole

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

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

15.7 Benefits of the Protocol

The potential benefit of this study is the development of a safe and effective treatment program for newly diagnosed MM patients. Knowledge will be acquired about this treatment program, its tolerability, and the effectiveness of clarithromycin (Biaxin®), lenalidomide (Revlimid®), and dexamethasone (Decadron®) in the treatment of newly diagnosed MM. If effective, this treatment plan may improve remission rates in newly diagnosed MM patients and hopefully prolong the disease survival.

15.8 Risks in Relation to Anticipated Benefit

The risks associated with participation in this trial are commensurate with the expected risks of other potential therapies and are reasonable given the potential benefit to patients

with newly diagnosed MM. If the combination of Car-BiRD is as effective against newly diagnosed MM as anticipated, this regimen could become standard of care leading to improved survival.

15.8 Alternative Treatments

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

15.9 Incentives

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

15.10 Costs

Patients and/or their medical insurance coverage will be responsible for paying for their hospitalization, doctor visits, diagnostic tests, chemotherapy drugs, and other medicines used in their care directly. Patients and/or their medical insurance coverage will also be responsible for payment for clarithromycin and dexamethasone as used in this study and are freely available in local pharmacies. These costs are expected to be equivalent to those of standard treatment. Commercially available Lenalidomide (Revlimid®) will be prescribed to research subjects for the duration of their participation in this trial in accordance with the RevAssist® program. Lenalidomide will be shipped directly to patients.

References

1. Munshi, N., Tricot, G. & Barlogie, B. in *Principles and Practice of Oncology* (eds DeVita, J., VT., Hellman, S. & Rosenberg, S. A.) 2465-2499 (Lippincott Williams & Wilkons, Philadelphia, PA, 2001).
2. Siegel, R., Naishadham, D. & Jemal, A. Cancer statistics, 2012. *CA Cancer J Clin* **62**, 10-29 (2012).
3. Riedel, D. A. & Pottern, L. M. The epidemiology of multiple myeloma. *Hematol Oncol Clin North Am* **6**, 225-247 (1992).
4. Greipp, P. R. et al. International staging system for multiple myeloma. *J Clin Oncol* **23**, 3412-3420 (2005).
5. Durie, B. G. et al. Prognostic value of pretreatment serum beta 2 microglobulin in myeloma: a Southwest Oncology Group Study. *Blood* **75**, 823-830 (1990).
6. Dimopoulos, M. A., Barlogie, B., Smith, T. L. & Alexanian, R. High serum lactate dehydrogenase level as a marker for drug resistance and short survival in multiple myeloma. *Ann Intern Med* **115**, 931-935 (1991).
7. Fonseca, R. et al. International Myeloma Working Group molecular classification of multiple myeloma: spotlight review. *Leukemia* **23**, 2210-2221 (2009).
8. Chang, H. et al. The t(4;14) is associated with poor prognosis in myeloma patients undergoing autologous stem cell transplant. *Br J Haematol* **125**, 64-68 (2004).
9. Niesvizky, R. et al. Impact of early response to sequential high-dose chemotherapy on outcome of patients with advanced myeloma and poor prognostic features. *Leuk Lymphoma* **43**, 607-612 (2002).
10. Niesvizky, R. et al. The relationship between quality of response and clinical benefit for patients treated on the bortezomib arm of the international, randomized, phase 3 APEX trial in relapsed multiple myeloma. *Br J Haematol* (2008).
11. Kyle, R. A. Long-term survival in multiple myeloma. *N Engl J Med* **308**, 314-316 (1983).
12. Attal, M. et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Francais du Myelome. *N Engl J Med* **335**, 91-97 (1996).
13. Michaeli, J., Choy, C. G. & Zhang, X. The biological features of multiple myeloma. *Cancer Invest* **15**, 76-84 (1997).
14. Zervas, K. et al. Comparison of vincristine, carmustine, melphalan, cyclophosphamide, prednisone (VBMCP) and interferon-alpha with melphalan and prednisone (MP) and interferon-alpha (IFN-alpha) in patients with good-prognosis multiple myeloma: a prospective randomized study. Greek Myeloma Study Group. *Eur J Haematol* **66**, 18-23 (2001).
15. Alexanian, R., Barlogie, B. & Tucker, S. VAD-based regimens as primary treatment for multiple myeloma. *Am J Hematol* **33**, 86-89 (1990).
16. MacLennan, I. C., Chapman, C., Dunn, J. & Kelly, K. Combined chemotherapy with ABCM versus melphalan for treatment of myelomatosis. The Medical Research Council Working Party for Leukaemia in Adults. *Lancet* **339**, 200-205 (1992).
17. Boccadoro, M. et al. Multiple myeloma: VMCP/VBAP alternating combination chemotherapy is not superior to melphalan and prednisone even in high-risk patients. *J Clin Oncol* **9**, 444-448 (1991).

18. Kumar, S. K. et al. Improved survival in multiple myeloma and the impact of novel therapies. *Blood* **111**, 2516-2520 (2008).
19. Gandhi, A. K. et al. Dexamethasone synergizes with lenalidomide to inhibit multiple myeloma tumor growth, but reduces lenalidomide-induced immunomodulation of T and NK cell function. *Curr Cancer Drug Targets* **10**, 155-167 (2010).
20. Segeren, C. M. et al. Vincristine, doxorubicin and dexamethasone (VAD) administered as rapid intravenous infusion for first-line treatment in untreated multiple myeloma. *Br J Haematol* **105**, 127-130 (1999).
21. Matsuoka, N. et al. Inhibitory effect of clarithromycin on costimulatory molecule expression and cytokine production by synovial fibroblast-like cells. *Clin Exp Immunol* **104**, 501-508 (1996).
22. Fost, D. A. et al. Inhibition of methylprednisolone elimination in the presence of clarithromycin therapy. *J Allergy Clin Immunol* **103**, 1031-1035 (1999).
23. Durie, B. G., Villarete, L. & Farvard, M. Clarithromycin (Biaxin®) as primary treatment for myeloma. *Blood* **90**, 579a (1997).
24. Stewart, A. K., Trudel, S., Al-Berouti, B. M., Sutton, D. M. & Meharchand, J. Lack of response to short-term use of clarithromycin (BIAXIN) in multiple myeloma. *Blood* **93(12)**, 4441 (1999).
25. Coleman, M. et al. BLT-D (clarithromycin [Biaxin], low-dose thalidomide, and dexamethasone) for the treatment of myeloma and Waldenstrom's macroglobulinemia. *Leuk Lymphoma* **43**, 1777-1782 (2002).
26. Anderson, K. C. Moving disease biology from the lab to the clinic. *Cancer* **97**, 796-801 (2003).
27. Richardson, P. G. et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. *Blood* **100**, 3063-3067 (2002).
28. Richardson, P. G. et al. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood* **108**, 3458-3464 (2006).
29. Weber, D. M. et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med* **357**, 2133-2142 (2007).
30. Niesvizky, R. et al. BiRD (Biaxin [clarithromycin]/Revlimid [lenalidomide]/dexamethasone) combination therapy results in high complete- and overall-response rates in treatment-naive symptomatic multiple myeloma. *Blood* **111**, 1101-1109 (2008).
31. Gay, F. et al. Clarithromycin (Biaxin)-lenalidomide-low-dose dexamethasone (BiRd) versus lenalidomide-low-dose dexamethasone (Rd) for newly diagnosed myeloma. *Am J Hematol* **85**, 664-669 (2010).
32. Knight, R., DeLap, R. J. & Zeldis, J. B. Lenalidomide and venous thrombosis in multiple myeloma. *N Engl J Med* **354(19)**, 2079-2080 (2006).
33. Rajkumar, S Vincent et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. *The Lancet Oncology* 15(12), e538 - e548 (2014).

APPENDIX I: Criteria for Response

Table 1: Criteria for Response, Disease plateau, and Disease Relapse as adopted from the EBMT and the international uniform response criteria[35]

Stringent Complete Response (sCR) requires all of the following:
❑ All of the criteria of complete response ❑ Normal serum free light chain ratio ❑ Absence of monoclonal cells on bone marrow aspirate by immunohistochemistry or immunofluorescence
Complete Response (CR) requires all of the following:
❑ Absence of the original monoclonal protein in serum and urine by immunofixation. The presence of oligoclononal bands consistent with oligoclonal immune reconstitution does not exclude CR. ❑ ≤5% plasma in a bone marrow aspirate and also on trephine bone biopsy, if biopsy is performed. If absence of monoclonal protein is sustained for 6 weeks it is not necessary to repeat the bone marrow, except in patients with non-secretory myeloma where the marrow examination must be repeated after an interval of at least 6 weeks to confirm CR. ❑ No increase in size or number of lytic bone lesions (development of a compression fracture does not exclude response) ❑ Disappearance of soft tissue plasmacytoma.
Very Good Partial Response (VGPR) requires all of the following:
❑ Negative serum and urine protein electrophoeresis with persistence of monoclonal protein detectable on immunofixation OR ❑ ≤90% reduction in serum monoclonal protein level with urine monoclonal protein level < 100mg in 24 hour collection.
Partial Response (PR) requires all of the following:
❑ ≥50% reduction in the level of the serum monoclonal paraprotein. ❑ Reduction in 24h urinary light chain excretion either by ≥90% or to <200mg. ❑ For patents with light chain only disease, then a 50% reduction in the difference between the involved and uninvolved free light chain level may be substituted for the M-protein measurement. ❑ For patients with non-secretory myeloma only, ≥50% reduction in plasma cells in a bone marrow aspirate and on trephine bone biopsy, if biopsy is performed. ❑ ≥50% reduction in the size of soft tissue plasmacytomas (by radiography or clinical examination). ❑ No increase if size or number of lytic bone lesion (development of a compression fracture does not exclude response)
Stable Disease (SD) requires the following:
❑ Not meeting the criteria stringent complete response (sCR), complete response (CR), very good partial response (VGPR), or partial response (PR)
Plateau:
❑ Stable values (within 25% above or below value at the time response is addressed) Patients in which no significant change (<50% decrease or <25% increase from baseline) in the production rate of the monoclonal serum protein or Bence-Jones protein excretion and no new lytic lesions and/or plasmacytomas are detected.
Relapse from CR requires at least one of the following:

- Reappearance of serum or urinary paraprotein on immunofixation or routine electrophoresis, confirmed by at least one further investigation and excluding oligoclonal immune reconstitution.
- ≥5% plasma in a bone marrow aspirate or trephine bone biopsy.
- Development of new lytic lesions of soft tissue plasmacytomas or definite increase in the size of residual bone lesions (development of a compression fracture does not exclude continued response and may not indicate progression).
- Development of hypercalcemia (corrected serum calcium >11.5mg/dl or 2.8 mmol/l) not attributable to any other cause.

Progressive disease (PD) for patients not in CR requires one or more of the following:

- >25 increase in the level of the serum monoclonal paraprotein, which must also be an absolute increase of at least 5g/L and confirmed by at least one repeated investigation.
- >25 increase in the 24h urinary light chain excretion, which must also be an absolute increase of at least 200mg/24h and confirmed by at least one repeated investigation.
- >25% increase in plasma cells in a bone marrow aspirate and on trephine bone biopsy, which must also be an absolute increase of at least 10%.
- Definite increase in the size of excisting bone lesions or soft tissue plasmacytomas.
- Development of new bone lesions or soft tissue plasmacytomas (development of a compression fracture does not exclude continued response and may not indicate progression).
- Development of hypercalcemia (corrected serum calcium >11.5mg/dl or 2.8 mmol/l) not attributable to any other cause.

Appendix II: Diagnostic and Staging Criteria for Multiple Myeloma[33]

International Myeloma Working Group (IMWG) Guidelines for the diagnosis of Multiple Myeloma

Definition of multiple myeloma

Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma* and any one or more of the following myeloma defining events:

- Myeloma defining events:
  - Evidence of end organ damage that can be attributed to the underlying plasma cell proliferative disorder, specifically:
    - Hypercalcaemia: serum calcium >0.25 mmol/L (>1 mg/dL) higher than the upper limit of normal or >2.75 mmol/L (>11 mg/dL)
    - Renal insufficiency: creatinine clearance <40 mL per min † or serum creatinine >177 μ mol/L (>2 mg/dL)
    - Anaemia: haemoglobin value of >20 g/L below the lower limit of normal, or a haemoglobin value <100 g/L
    - Bone lesions: one or more osteolytic lesions on skeletal radiography, CT, or PET-CT ‡
  - Any one or more of the following biomarkers of malignancy:
    - Clonal bone marrow plasma cell percentage* ≥60%
    - Involved:uninvolved serum free light chain ratio§ ≥100
    - >1 focal lesions on MRI studies¶

Definition of smoldering multiple myeloma

Both criteria must be met:

- Serum monoclonal protein (IgG or IgA) ≥30 g/L or urinary monoclonal protein ≥500 mg per 24 h and/or clonal bone marrow plasma cells 10–60%
- Absence of myeloma defining events or amyloidosis

PET-CT=18F-fluorodeoxyglucose PET with CT. *Clonality should be established by showing κ / λ -light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used. † Measured or estimated by validated equations. ‡ If bone marrow has less than 10% clonal plasma cells, more than one bone lesion is required to distinguish from solitary plasmacytoma with minimal marrow involvement. §These values are based on the serum Freelite assay (The Binding Site Group, Birmingham, UK). The involved free light chain must be ≥100 mg/L. ¶Each focal lesion must be 5 mm or more in size.

Diagnosis	Diagnostic Criteria: All Three Required
Symptomatic multiple myeloma[a]	• Monoclonal plasma cells in the bone marrow >/=10% and/or presence of a biopsy-proven plasmacytoma • Monoclonal protein present in the serum and/or urine[b] • Myeloma-related organ dysfunction (>/=1)[c] [C] Calcium elevation in the blood (serum calcium >10.5 mg/l or upper limit of normal [R] Renal insufficiency (serum creatinine >2mg per 100 ml) [A] Anemia (hemoglobin <10 g per 100 ml or 2 g <normal) [B] Lytic bone lesions or osteoporosis[d]
Monoclonal gammopathy of undetermined significance (MGUS)	• Serum monoclonal protein low[e] • Monoclonal bone marrow plasma cells <10% • No evidence of end-organ damage attributable to the clonal plasma cell disorder: o Normal serum calcium, hemoglobin level and serum creatinine o No bone lesions on full skeletal X-ray survey and/or other imaging if performed o No clinical or laboratory features of amyloidosis or light chain deposition disease
Smoldering or indolent myeloma[f]	• Monoclonal protein present in the serum 3 g per 100 ml or higher or • Monoclonal plasma cells 10% or greater present in the bone marrow and/or a tissue biopsy • No evidence of end-organ damage attributable to the clonal plasma cell disorder: o Normal serum calcium, haemoglobin level and serum creatinine o No bone lesions on full skeletal X-ray survey and/or other imaging if performed

	○ No clinical or laboratory features of amyloidosis or light chain deposition disease
Solitary plasmacytoma of bone	• Biopsy-proven plasmacytoma of bone in a single site only. X-rays and magnetic resonance imaging and/or • FDG PET imaging (if performed) must be negative outside the primary site. • The primary lesion may be associated with a low serum and/or urine M-component • The bone marrow contains no monoclonal plasma cells • No other myeloma-related organ dysfunction

Adapted with permission from Kyle and Rajkumar, Criteria for diagnosis, staging, risk stratification and response assessment of multiple myeloma..*Leukemia* 2009; 23: 3–9.
[a]These criteria identify Stage IB and Stages II and III A/B myeloma by Durie/Salmon stage. Stage IA becomes smoldering or indolent myeloma.
[b]If no monoclonal protein is detected (non-secretory disease), then >/= 30% monoclonal bone marrow plasma cells and/or a biopsy-proven plasmacytoma required.
[c]A variety of other types of end-organ dysfunctions can occasionally occur and lead to a need for therapy. Such dysfunction is sufficient to support classification as myeloma if proven to be myeloma related.
[d]If a solitary (biopsy-proven) plasmacytoma or osteoporosis alone (without fractures) is the sole defining criteria, then >/= 30% plasma cells are required in the bone marrow.
[e]Low is defined as serum M protein <3.0 g per 100 ml.
[f]These criteria identify Stage IA myeloma by Durie/Salmon stage.

Salmon-Durie Staging System

Stage	Criteria
I	All of the following present:
	Hemoglobin > 10 g/dL
	Serum IgG < 5 g/dL
	Serum IgA < 3 g/dL
	Normal serum calcium
	Urine monoclonal protein excretion < 4 g/day
	No lytic bone lesions
II	Fulfills neither stage I nor stage III criteria
III	One of more of the following present
	Hgb < 8.5 g/dL
	Serum IgG > 7g/dL
	Serum IgA > 5 g/dL
	Serum calcium > 12mg/dL (3mmol/L)

	Urine monoclonal protein excretion > 12g/day
	Multiple lytic bone lesions
Subcategory	
A	Serum creatinine < 2mg/dL (177 µmol/L)
B	Serum creatinine ≥ 2mg/dL

International Staging System (ISS)

Stage	**Criteria**
I	β2-microglobulin < 3.5 mg/dL
	Serum albumin ≥ 3.5 g/dL
II	Neither stage I nor stage II
III	β2-microglobulin ≥ 5.5 mg/dL

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

Risks Associated with Pregnancy

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

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

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

Counseling

For a female of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 4 weeks before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures

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

- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

The investigator must ensure that for females of childbearing potential:

- Complies with the conditions for pregnancy risk minimization, including confirmation that she has an adequate level of understanding
- Acknowledge the aforementioned requirements

For a female NOT of childbearing potential, lenalidomide is contraindicated unless all of the following are met (i.e., all females NOT of childbearing potential must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- She acknowledges that she understands the hazards and necessary precautions associated with the use of lenalidomide

Traces of lenalidomide have been found in semen. Male patients taking lenalidomide must meet the following conditions (i.e., all males must be counseled concerning the following risks and requirements prior to the start of lenalidomide study therapy):

- Understand the potential teratogenic risk if engaged in sexual activity with a pregnant female or a female of childbearing potential
- Understand the need for the use of a condom even if he has had a vasectomy, if engaged in sexual activity with a pregnant female or a female of childbearing potential.

<u>Contraception</u>

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 contact during the following time periods related to this study: 1) for at least 28 days before starting study drug; 2) while participating in the study; 3) dose interruptions; and 4) for at least 28 days after study treatment 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 to 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 25 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 study drug:

Female Subjects:

- FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to prescribing lenalidomide. The first pregnancy test must be performed within 10-14 days prior to prescribing lenalidomide and the second pregnancy test must be performed within 24 hours prior to prescribing lenalidomide (prescriptions must be filled within 7 days). The subject may not receive study drug until the Investigator has verified that the results of these pregnancy tests are negative.

Male Subjects:

- Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

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

All Subjects:

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

Female Subjects:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following discontinuation from the study. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following discontinuation from the study.
- In addition to the required pregnancy testing, the Investigator must confirm with FCBP that she is continuing to use two reliable methods of birth control at each visit.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.
- Pregnancy testing and counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days and must be performed if a subject misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Subjects:

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

- Counseling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to lenalidomide must be conducted at a minimum of every 28 days.
- 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 this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.

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

APPENDIX IV: Karnofsky Performance Status (KPS) Scale

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

APPENDIX V

WCMC IRB SAE Reporting Forms

http://www.med.cornell.edu/research/for_pol/ins_rev_boa.html

APPENDIX VI: New York State Association Classification of Cardiac Disease

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

APPENDIX VII: P450 Substrates and Inhibitors

The following table presents a list of drugs that may interfere with the metabolism of clarithromycin. The drugs that are metabolized through CYP3A4 should be avoided if possible. If not possible use with caution.

	P450 isozyme					
Function	CYP1A2	CYP2C19	CYP2C9	CYP2D6	CYP2E1	CYP3A4
Substrates of isozyme:	caffeine clozapine cyclobenzaprine fluvoxamine imipramine mexiletine olanzapine pimozide propranolol tacrine theophylline warfarin	amitriptyline citalopam clomipramine cyclophosphamide diazepam imipramine lansoprazole nelfinavir omeprazole phenytoin	amitriptyline *(demethylation)* celecoxib diclofenac flurbiprofen ibuprofen losartan *(not candesartan)* naproxen phenytoin piroxicam sulfamethoxazole tolbutamide warfarin	amitriptyline clomipramine codeine desipramine dextromethorphan imipramine metoprolol nortriptyline oxycodone paroxetine propafenone risperidone thioridazine timolol tramadol venflaxine	acetaminophen chlorzoxazone dapsone enflurane ethanol halothane isoflurane isoniazid	alprazolam astemizole buspirone calcium channel blockers carbamazepine cisapride cyclosporine doxorubicin erythromycin etoposide felodipine fentanyl HIV protease inhibitors ifosphamide lovastatin *(not pravastatin)* midazolam nifedipine pimozide quinidine quinine simvastatin tacrolimus terfenadine triazolam
Inhibitors of isozyme:	cimetidine ciprofloxacin citalopram diltiazem enoxacin erythromycin fluvoxamine mexiletine ofloxacin tacrine ticlopidine	cimetidine felbamate fluoxetine fluvoxamine ketoconazole lansoprazole omeprazole paroxetine ticlopidine	amiodarone fluconazole fluoxetine fluvastatin isoniazid metronidazole paroxetine phenylbutazone sulfamethoxazole/ trimethoprim sulfaphenazole ticlopidine	amiodarone chlorpheniramine fluoxetine haloperidol indinavir paroxetine propafenone quinidine ritonavir sertraline thioridazine ticlopidine	disulfiram water cress	amiodarone cimetidine cyclosporine danazol diltiazem fluconazole *(large doses)* grapefruit juice HIV protease inhibitors itraconazole ketoconazole macrolides *(not azithromycin)* miconazole nefazadone omeprazole quinidine ritonavir verapamil
Inducers of isozyme:	carbamazepine tobacco	carbamazepine norethindrone *(not phenobarb.)*	phenobarbital rifampin secobarbital		chronic ethanol isoniazid tobacco	carbamazepine rifabutin rifampin ritonavir

*Table compiled from references 1, 2, 4, 8.

APPENDIX VIII: Example Drug Diaries

Arm: BiRd	Patient NAME _____	Cycle #

REVLIMID® (Lenalidomide): Take **25 mg** each morning on the dates marked on calendar;
DECADRON® (Dexamethasone): Take **ten 4mg** pills once weekly on the dates marked on calendar;
BIAXIN® (Clarithromycin): Take **one 500mg** pill a day on the dates marked on calendar.
ASPIRIN: Take **81mg** daily on the dates marked on your calendar;
BACTRIM® (Trimethoprim/Sulfamethoxasole): Take **one DS** pill daily on the dates marked on calendar;
PRILOSEC® (Omeprazole): Take **one 20mg** pill once a day on the dates marked on calendar.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		Day 1 mm/dd/yy	**Day 2** mm/dd/yy	**Day 3** mm/dd/yy	**Day 4** mm/dd/yy	**Day 5** mm/dd/yy
		Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
		Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )
		Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )
		Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )
		Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron ( )				
Day 6 mm/dd/yy	**Day 7** mm/dd/yy	**Day 8** mm/dd/yy	**Day 9** mm/dd/yy	**Day 10** mm/dd/yy	**Day 11** mm/dd/yy	**Day 12** mm/dd/yy
Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )
Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )
Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )
Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron ( )				
Day 13 mm/dd/yy	**Day 14** mm/dd/yy	**Day 15** mm/dd/yy	**Day 16** mm/dd/yy	**Day 17** mm/dd/yy	**Day 18** mm/dd/yy	**Day 19** mm/dd/yy
Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )
Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )

Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )
Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron ( )				
Day 20 mm/dd/yy	**Day 21** mm/dd/yy	**Day 22** mm/dd/yy	**Day 23** mm/dd/yy	**Day 24** mm/dd/yy	**Day 25** mm/dd/yy	**Day 26** mm/dd/yy
Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
Revlimid ( )	Revlimid ( )					
Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )	Biaxin ( )( )
Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )
Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron ( )				
Day 27 mm/dd/yy	**Day 28*** mm/dd/yy	**Day 1** mm/dd/yy	**Day 2** mm/dd/yy	**Day 3** mm/dd/yy		
Bactrim ( )	Bactrim ( )				***On Day 28:** See Dr. _____ Bring this calendar, your empty medication bottles, and 24-hour urine collection to your appointment.	
Biaxin ( )( )	Biaxin ( )( )					
Aspirin ( )	Aspirin ( )					
Prilosec ( )	Prilosec ( )					

Arm: Rd	Patient NAME _____	Cycle #

REVLIMID® (Lenalidomide): Take **25 mg** each morning on the dates marked on calendar;
DECADRON® (Dexamethasone): Take **ten 4mg** pills once weekly on the dates marked on calendar;
ASPIRIN: Take **81mg** daily on the dates marked on your calendar;
BACTRIM® (Trimethoprim/Sulfamethoxasole): Take **one DS** pill daily on the dates marked on calendar;
PRILOSEC® (Omeprazole): Take **one 20mg** pill once a day on the dates marked on calendar.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
		Day 1 mm/dd/yy	**Day 2** mm/dd/yy	**Day 3** mm/dd/yy	**Day 4** mm/dd/yy	**Day 5** mm/dd/yy
		Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
		Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )
		Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )
		Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron ( )				
Day 6 mm/dd/yy	**Day 7** mm/dd/yy	**Day 8** mm/dd/yy	**Day 9** mm/dd/yy	**Day 10** mm/dd/yy	**Day 11** mm/dd/yy	**Day 12** mm/dd/yy
Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )
Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )
Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron ( )				
Day 13 mm/dd/yy	**Day 14** mm/dd/yy	**Day 15** mm/dd/yy	**Day 16** mm/dd/yy	**Day 17** mm/dd/yy	**Day 18** mm/dd/yy	**Day 19** mm/dd/yy
Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )
Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )
Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron ( )				

Day 20 mm/dd/yy	**Day 21** mm/dd/yy	**Day 22** mm/dd/yy	**Day 23** mm/dd/yy	**Day 24** mm/dd/yy	**Day 25** mm/dd/yy	**Day 26** mm/dd/yy
Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
Revlimid ( )	Revlimid ( )					
Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )	Aspirin ( )
Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron ( )				
Day 27 mm/dd/yy	**Day 28*** mm/dd/yy	**Day 1** mm/dd/yy	**Day 2** mm/dd/yy	**Day 3** mm/dd/yy		
Bactrim ( )	Bactrim ( )				***On Day 28:** See Dr. _____ Bring this calendar, your empty medication bottles, and 24-hour urine collection to your appointment.	
Aspirin ( )	Aspirin ( )					
Prilosec ( )	Prilosec ( )					

APPENDIX IX: Quality of Life

FACIT Fatigue Scale (Version 4)

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

		Not at all	A little bit	Some-what	Quite a bit	Very much
HI7	I feel fatigued	0	1	2	3	4
HI12	I feel weak all over	0	1	2	3	4
An1	I feel listless ("washed out")	0	1	2	3	4
An2	I feel tired	0	1	2	3	4
An3	I have trouble <u>starting</u> things because I am tired	0	1	2	3	4
An4	I have trouble <u>finishing</u> things because I am tired	0	1	2	3	4
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
An8	I need to sleep during the day	0	1	2	3	4
An12	I am too tired to eat	0	1	2	3	4
An14	I need help doing my usual activities	0	1	2	3	4
An15	I am frustrated by being too tired to do the things I want to do	0	1	2	3	4

An16	I have to limit my social activity because I am tired	0	1	2	3	4