TITLE: A PHASE II STUDY OF SEQUENTIAL CARFILZOMIB, CLARITHROMYCIN (BIAXIN®), LENALIDOMIDE (REVLIMID®), AND DEXAMETHASONE (DECADRON®) [Car-BiRD] THERAPY FOR SUBJECTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

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NEW YORK PRESBYTERIAN HOSPITAL
WEILL CORNELL MEDICINE

A PHASE II STUDY OF SEQUENTIAL CARFILZOMIB, CLARITHROMYCIN (BIAXIN®), LENALIDOMIDE (REVLIMID®), AND DEXAMETHASONE (DECADRON®) [Car-BiRD] THERAPY FOR SUBJECTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA

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1.0 PROTOCOL SCHEMA

Figure 1: Protocol Schema

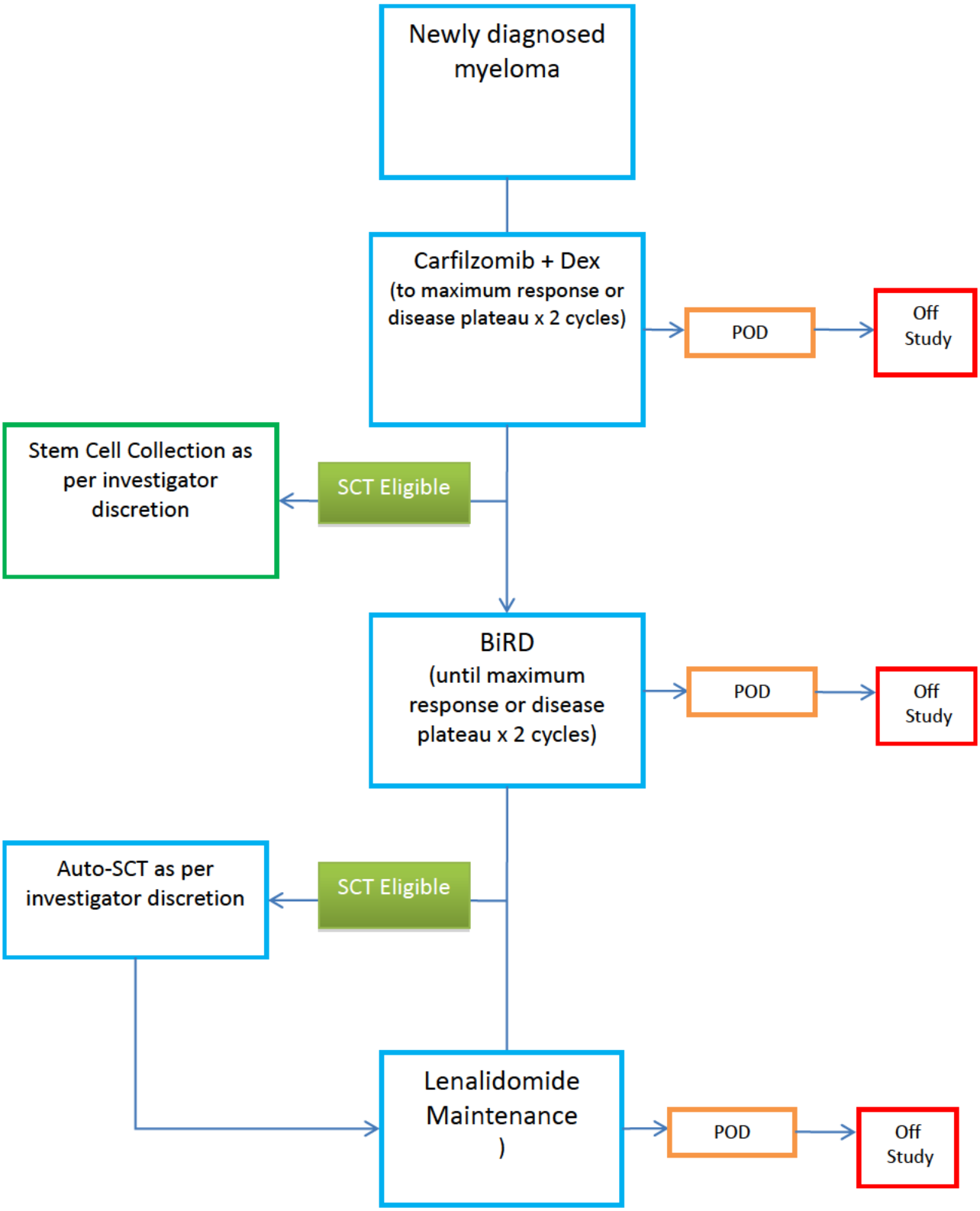
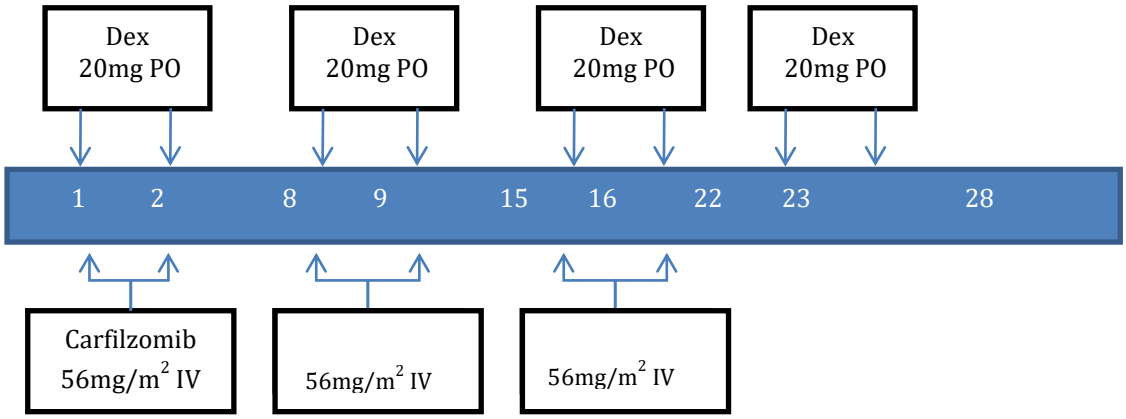
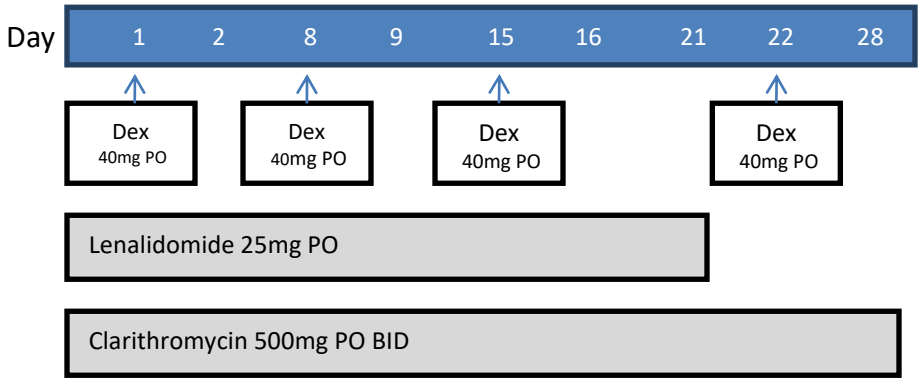


Figure 2: Carfilzomib + Dexamethasone medication schedule (one cycle)*



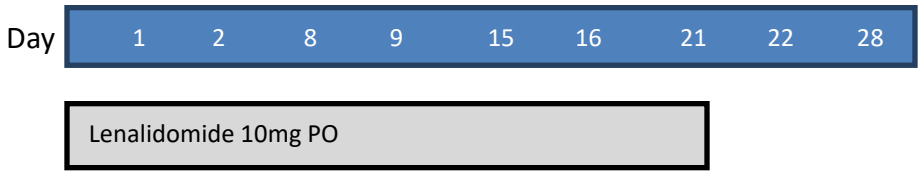
(For Cycle 1 only, Carfilzomib will be dosed on 20mg/m^2 IV on Days 1 and 2).

Figure 3: BiRD medication schedule (one cycle)*



* All patients must receive prophylactic anti-coagulation as described in Section 9.1.
(Lenalidomide will be given for days 1-21 followed by a 7 day rest period for each 28-day cycle)

Figure 4: Lenalidomide maintenance medication schedule (one cycle)*



(Lenalidomide will be given for days 1-21 followed by a 7 day rest period for each 28-day cycle)

* All patients must receive prophylactic anti-coagulation as described in Section 9.1.

Table 1: Schedule of Assessments

	Screening (<42 days prior to start date)	Cycle 1 Day 1	Cycle 1 Day 8, 15, 22	All Other Cycles Day 1	All Other Cycles Days 8, 15, 22	End of Study
Complete medical history	X	X		X		X
Physical exam, KPS, vital signs, height and weight	X	X		X		X
CBC[1]	X[1]	X	X	X	X	X
Complete metabolic profile[1,2]	X[1,2]	X[2]	X[2]	X[2]	X	X[2]
Generate / review new drug diary		X		X		
Collect / review prior drug diary				X		
SPEP, IF, quant immunoglobulins[1]	X[1]	X		X		X
Serum free light chains[1]	X[1]	X		X		X
24-hour urine for UTP, UPEP, UIF[1]	X[1]	X		X		
β_2M[1]	X[1]					
CRP[1]	X[1]					
Urinalysis[1]	X[1]					
Serum pregnancy test[3]	X[3]	X[3]		X[3]		X[3]
Register patient into Revlimid REMS® program[4]	X					
Skeletal survey or whole body PET/CT scan[1]	X[1]			X[7]		
MRI	X					X
Bone marrow biopsy and aspirate	X			X[5]		
Concurrent medication use survey	X	X		X		
Electrocardiogram	X					
ECHO/MUGA (research imaging)	X					
Quality of Life Questionnaires[9]	X	X		X[9]		X
Drug dispensation[6]		Continuous				
Adverse event monitoring		Continuous				
Assessment of Second Primary Malignancy[8]		Continuous				
Obtain Follow-Up anti-cancer treatments after study discontinuation for a period of two years		See Section 10.10 of protocol				
Obtain Follow-Up survival information after study discontinuation		See Section 10.10 of protocol				

1. Within 4 weeks prior to starting treatment. UTP = urine total protein; UPEP = urine protein electrophoresis; UIF = urine immunofixation; SPEP = serum protein electrophoresis; IF = serum immunofixation; β_2M = beta-2 microglobulin.
2. Includes sodium, potassium, chloride, CO_2, calcium, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase, total bilirubin, SGOT/AST, SGPT/ALT, LDH, uric acid, phosphorus, magnesium. LDH, uric acid, phosphorus and magnesium are performed at screening, Cycle 1, Day 1 of Carfilzomib+Dexamethasone, Cycle 1, Day 1 of BiRD, and End of Study
3. 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 and thalidomide (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 or thalidomide (whichever comes later) and at Day 28 post the last dose of lenalidomide or thalidomide (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 or thalidomide (whichever comes later) and at Day 14 and Day 28 post the last dose of lenalidomide or thalidomide (whichever comes later) (see Appendix III: Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods.

4. Lenalidomide must be prescribed through and in compliance with Celgene's Revlimid REMS® program. Prescriptions of lenalidomide must be filled within 7 days.
5. To confirm complete remission or when clinically indicated
6. An additional safety assessment will be done 30 days (+/- 7 days) following the last dose of study drug.
7. When clinically indicated
8. 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 the drugs being studied, occurring at any time for the duration of the study, from the time of signing the ICF 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 (e.g., any confirmatory histology or cytology results, X-rays, CT scans, etc.).
9. FACIT Fatigue Scale (Version 4), EORTC QLQ-C30 and EORTC MY-20 will be completed by subjects at baseline, the start of each new phase of the study (Carfilzomib+Dexamethasone, BiRD therapy and Lenalidomide Maintenance) and at the End of Study

2.0 OBJECTIVES AND SCIENTIFIC AIMS

2.1 Study Objectives

2.1.1 Evaluate the efficacy of the combination of carfilzomib plus dexamethasone (Decadron®) as an induction therapy for patients with newly diagnosed multiple myeloma (MM).

2.1.2 Evaluate the efficacy of subsequent treatment with clarithromycin (Biaxin), lenalidomide (Revlimid®) and dexamethasone (Decadron®) combination therapy (BiRD) as a method to increase the complete remission rate for patients with newly diagnosed multiple myeloma.

2.1.3 Evaluate the safety of the combination of carfilzomib plus dexamethasone induction therapy followed by BiRD consolidation with subsequent lenalidomide maintenance therapy for patients with newly diagnosed MM.

2.1.4 Determine the progression free survival (PFS) of the Car-BiRD regimen

2.1.5 Evaluate the quality of life at four time points 1) study entry; 2) after carfilzomib + dexamethasone induction therapy; 3) 3 months after consolidation with either autologous stem cell transplant (auto-SCT); 4) after 6 months of maintenance lenalidomide monotherapy

2.1.6 Determine the event-free survival and overall survival of the Car-BiRD regimen

2.1.7 Evaluate the impact of carfilzomib on $CD34^+$ hematopoietic stem cell collection yield

2.1.8 Evaluate role of whole body bone marrow MRI in evaluation of multiple myeloma

2.1.9 Evaluate minimal residual disease following therapy with Car-BiRd regimen

2.2 Study Endpoints

- Response rate by IMWG criteria (see Appendix I)
- Progression free survival
- 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
- Stem cell yield (only for patients electing to undergo autologous stem cell collection).
- Quality of life
- 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). It is estimated that 19,000 new cases of myeloma are diagnosed in the US each year[1], accounting for approximately 1% of all cancers and 10-15% of all hematological malignancies.[2] The disease is twice as common in blacks as whites.[3] MM usually occurs in older individuals with a median age of 69 years old.

3.2 Prognosis

The overall median survival for patients with MM is 36 months, with 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] An elevated serum lactate dehydrogenase (LDH) predicts an aggressive course with lymphoma like features.[7] Chromosomal abnormalities, such as translocations t(4;14) and t(14;16) confer poor prognosis.[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 on high-dose chemotherapy.[12] Based on those observations, the goal of achieving an early CR 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, were seen in approximately 30-60% of patients. Duration of response to these agents is generally 1 1/2 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),[14] vincristine, doxorubicin, and dexamethasone (VAD),[15] doxorubicin, carmustine, cyclophosphamide, and melphalan (ABCM),[16] vincristine, melphalan, cyclophosphamide, and prednisone alternating with vincristine, carmustine, doxorubicin, and prednisone (VMCP VBAP),[17] amongst other regimens. Although these regimens may produce higher response rates and in some cases more rapid tumor mass reduction, a survival advantage has not been demonstrated.

3.4 Dexamethasone

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 an overall response rate of 68% when VAD was administered as an IV push and dexamethasone was given at 40 mg PO QD x 4 only.[18] 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.[19] These results indicate that the intensification of dexamethasone is an important factor in determining responses. Thus, the data provide compelling evidence that dexamethasone is by far the most important component in this combination. Thus, pulse high dose dexamethasone is an effective and relatively well-tolerated induction therapy for patients with advanced stage MM. Dexamethasone has also proven to be an integral part of salvage therapies for multiple myeloma patients as well.

3.5 Carfilzomib®

Carfilzomib is a proteasome inhibitor that specifically binds the chemotrypsin-like subunit of the proteasome, inhibiting its catalytic activity.[20] This agent has recently been studied in both Phase 1 and Phase 2 clinical trials.[21,22] The aims of these studies were to determine the safety profile (MTD, DLTs), pharmacokinetics and objective response rates in patients with relapsed and refractory MM. Single agent therapy in these subjects has demonstrated an objective partial response in patients with refractory relapsed multiple myeloma at doses ranging from 15-56mg/m^2.[21] Responses were seen in patients that had been on a median of 5 prior therapies and in patients who had relapsed after therapy with bortezomib, an agent that targets a different enzymatic domain of the proteasome. The responses were rapid in onset and sustainable from 90-280 days. Stable disease has also been seen subjects for up to 409 days.[22] Major toxicities are thrombocytopenia and reversible acute kidney injury. Thrombocytopenia is reversible and thought secondary to a defect in megakaryocyte budding rather than cytotoxic mechanisms. The mechanism of kidney injury is still under investigation. Tumor lysis syndrome has also been documented and prophylaxis is warranted with allopurinol. A recent phase 1b/2 study of Carfilzomib explored in combination with dexamethasone and lenalidomide as frontline therapy in treatment-naïve patients with multiple myeloma achieved a maximal tolerated dose of 56mg/m^2 and overall response rates of close to 60% in patients who had a relapsed after a median of 4.5 prior lines of therapy (Abstract #2930, PX-171-007 study, American Society of Hematology Meeting 2011). Given this data, we have elected to use carfilzomib at a dose of 20mg/m2 for the first week of treatment and thereafter dose at 56 mg/m^2 in order to limit the risk of tumor lysis and deliver the maximal effective dose possible.

3.6 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 immunomodulatory properties mediated in part by suppression of Interleukin-6 and other cytokines.[23] 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.[24] 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.[25] 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.[26,27]

3.7 Biaxin®, Low-dose Thalidomide and Dexamethasone

Preliminary studies 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 extraordinary results.[28] Of 40 evaluable patients, 37 (93%) have 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 (results not yet published). 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).

3.8 Lenalidomide (Revlimid®)

Lenalidomide (Revlimid®) is an 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.[29]

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.[30] 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.[31]

Thus, early studies suggest that lenalidomide is active against advanced multiple myeloma and is well tolerated. A randomized, phase III study is currently being conducted to investigate the effectiveness and safety of lenalidomide at 25 mg combined with high-dose dexamethasone compared to high-dose dexamethasone to treat patients with relapsed or refractory multiple myeloma.[32] An interim analysis of the results of this study revealed 59.4% of heavily pretreated patients with relapsed / refractory multiple myeloma responded to the combination of 25mg lenalidomide and high-dose dexamethasone compared to a 21.1% response rate to high-dose dexamethasone alone. This preliminary data led to the approval of lenalidomide in combination with dexamethasone in patients with relapsed / refractory multiple myeloma in 2006.

3.9 BiRD Combination in Multiple Myeloma

The recent studies discussed above have shown that lenalidomide has different anti-myeloma activity than thalidomide with a toxicity profile that is entirely distinct from its analog agent, thalidomide. A phase II study of clarithromycin (500mg twice daily), lenalidomide (25mg daily for 21 days out of a 28 day cycle), and dexamethasone (40mg weekly) called the BiRD regimen was conducted at this institution.[33] By replacing thalidomide with lenalidomide into our former BLTD treatment platform, we achieved an overall response rate of 91%, and a higher CR rate compared with the earlier BLTD data, 30% vs. 13%. The BiRD study evaluated the efficacy of the combination of Biaxin®, lenalidomide (Revlimid®), and Dexamethasone in treatment naïve multiple myeloma patients and proved to be a powerful regimen.

3.10 Car-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.

The robust overall response rate of 91% with the BiRD regimen for patients with newly diagnosed multiple myeloma is encouraging and we believe that by adding carfilzomib the

overall response rate and CR rate can be improved. As carfilzomib has proven efficacy in myeloma and in patient's who have relapsed on bortezomib, we anticipate that it will synergize with the previous BiRD regimen to induce greater reduction of tumor burden overall.

This study is intended to investigate the efficacy of combination therapy with an induction phase utilizing a combination of carfilzomib® and dexamethasone and subsequent consolidation therapy with clarithromycin (Biaxin®), lenalidomide (Revlimid®), dexamethasone (Decadron®), in multiple myeloma patients who are newly diagnosed and require treatment. The primary endpoints include best response rate, toxicities, progression free survival, event free survival, and overall survival. In those patients who are eligible for autologous stem cell transplantation, we will also study the effect of carfilzomib on CD 34^+ stem cell yield following mobilization.

3.11 Lenalidomide Maintenance in Multiple Myeloma

Due to mounting evidence on the efficacy and safety of continuous lenalidomide therapy, lenalidomide maintenance will be initiated to patients who plateau on BiRD, and will continue until patients are removed from the study due to progression of disease, unacceptable toxicity, or one of the other reasons listed in Section 10.11. In the non-transplant setting, it has been shown that continuous lenalidomide use is effective and safe. Palumbo et al 2012 demonstrated MPR-R (melphalalan-prednisone-lenalidomide followed by lenalidomide maintenance) was an effective treatment for transplant ineligible newly diagnosed patients, with lenalidomide maintenance significantly extending progression free survival. In that study, 459 patients were assigned to receive MPR-R, MPR (melphalan-prednisone-lenalidomide), or MP (melphalan-prednisone-); lenalidomide maintenance significantly extended PFS when compared to the placebo groups (median 26 months and 7 months, respectively). It was well tolerated , with similar frequencies of second primary malignancies seen across all groups (3 year rate of invasive second primary tumors was 7% with MPR-R vs 7% with MPR vs 3% with MP; solid tumors of heterogenous types occurred in 5 patients in the MPR-R group, 4 in the MPR group, and 3 in the MP group). These results provide confirmation of the benefits of continuous lenalidomide maintenance therapy with respect to PFS, without increase in cumulative toxic effects or incidence of secondary primary malignancies.

4.0 INVESTIGATIONAL PLAN

4.1 Study Design

This phase II study is a treatment program for patients with newly diagnosed multiple myeloma. Up to 72 patients will be enrolled. Patients who sign consent and fulfill all eligibility criteria will be enrolled to receive the following treatment plan:

4.1.1 Carfilzomib-Dexamethasone Therapy:

Induction Therapy

- Carfilzomib 56mg/m^2 IV will be infused over 30 minutes on days 1, 2, 8, 9, 15, 16 (+/- 2 days) of a 28-day cycle. Anticipated delays greater than +/- 2 days must be discussed with the study doctor. For cycle 1, days 1 and 2 only, Carfilzomib

will be dosed at 20mg/m^2 IV over 30 minutes to better assess tolerability and limit tumor-lysis syndrome.

- Dexamethasone 20 mg PO will be given on days 1, 2, 8, 9, 15, 16, 22, 23 of a 28-day cycle. Missed or vomited doses will not be made up.
- Cycles of Carfilzomib-Dexamethasone will continue until there is confirmed complete remission (as defined by the criteria listed in Appendix I) or disease plateau defined as no significant (>25%) change in M-spike, no significant change in involved serum free light chain level, no new development or worsening of myeloma-related end organ dysfunction (defined by hypercalcemia, new anemia, new renal insufficiency, or a new lytic bone lesion), no new or worsening growth or appearance of a soft-tissue based plasma cell collection (i.e., plasmacytoma) for 2 consecutive cycles (also defined in Appendix I).
- After achievement of maximum response to therapy with carfilzomib + dexamethasone, autologous stem cell transplant eligible patients (in general, patients with KPS > 60 and < 70 years of age with adequate organ function) can then elect to undergo stem cell collection as per institutional guidelines. Once stem cell collection is complete, they will begin BiRD therapy as described below. Stem cell ineligible patients will move on directly to BiRD therapy as described below.
- Prophylactic medications, such as medication for thrombosis and tumor lysis syndrome risk, will be given as outlined in Sections 9.1 and 9.3.1 and will be continued at the discretion of the investigator.
- Patients who demonstrate progression of disease at any time will be taken off study.

4.1.2 BiRD Therapy

BiRD therapy will be given after maximum response has been achieved with Carfilzomib+Dexamethasone, and will consist of the following:

- 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. 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.
- Patients will continue on BiRD therapy until complete remission or stable disease plateau for 2 cycles
- Patients who demonstrate progression of disease on BiRD therapy will be taken off study
- At maximum response or stable disease plateau patients will then transition to lenalidomide maintenance therapy
- Prophylactic medications, such as medication for thrombosis and tumor

lysis syndrome risk, will be given as outlined in Sections 9.1 and 9.3.1 and will be continued at the discretion of the investigator.

4.1.3 Lenalidomide maintenance therapy:

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 as detected on serum immunofixation) for > 2 cycles after sequential therapy of carfilzomib+ dexamethasone followed by BiRD will be transitioned to maintenance therapy. Maintenance therapy will be comprised of:

- Lenalidomide 10 mg PO daily for days 1-21 of every 28-day 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.
- Prophylactic medications, such as medication for thrombosis and tumor lysis syndrome risk, will be given as outlined in Sections 9.1 and 9.3.1 and will be continued at the discretion of the investigator.
- Patients will continue on lenalidomide maintenance for 24 cycles or until there is evidence of progression of disease (as defined by the criteria listed in Appendix I) or the patient experiences intolerability
- Patients who demonstrate progression of disease on Lenalidomide maintenance will be taken off study

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. Patients who achieve a stable plateau and are on either BiRD or lenalidomide maintenance therapy may be taken off study if eligible to proceed to high dose chemotherapy and autologous stem cell transplantation to be followed by return to maintenance lenalidomide therapy, as outlined in the treatment schema **(Figure 1)**. Once on lenalidomide maintenance therapy, patients will be taken off study after 24 cycles (approximately 2 years) unless they have an adequate response, in which case they will remain on study until they are removed at the discretion of the investigator.

4.2 Recruitment Plan

A reasonable estimate for accrual of patients for this study is 1-4 patients per month. The anticipated time for completion of this trial is about 2 years. We plan to initially recruit 35 patients in stage I of the study. If 12 or fewer objective tumor complete responses are observed in the first 35 evaluable patients then the study will be terminated. If 13 or more objective complete responses are observed then the study will expand to enroll 22 more patients. (Full details are

outlined in the statistical considerations section below). 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 ≥18 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 had no anti-myeloma 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 must have LVEF ≥ 40%, determined by 2-D transthoracic echocardiogram (ECHO) is the preferred method of evaluation. Multigated Acquisition Scan (MUGA) is acceptable if ECHO is not available.
- Subject has a Karnofsky performance status ≥60% (>50% if due to bony involvement of myeloma (see Appendix VI).
- 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 Revlimid REMS® program, and is willing and able to comply with the requirements of Revlimid REMS® 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

[†] 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).

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 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) ≥750 cells/mm3 (1.0 x 109/L)
  - Hemoglobin ≥ 7 g/dL
  - Platelet count ≥ 30,000/mm3 (75 x 109/L)
  - Serum SGOT/AST <3.0 x upper limits of normal (ULN)
  - Serum SGPT/ALT <3.0 x upper limits of normal (ULN)
  - Serum creatinine <2.5 mg/dL (221 µmol/L)
  - Serum total bilirubin <2.0 mg/dL (34 µmol/L)

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 measureable 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 IV), Ejection Fraction < 40%, 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 has known hypersensitivity to dexamethasone, clarithromycin, lenalidomide, thalidomide, allopurinol, or carfilzomib.
- 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.

6.0 PRETREATMENT EVALUATION

Screening assessments and all on-study scheduled visits and assessments are outlined in Table 1.0 Schedule of Assessments.

7.0 THERAPUTIC AGENTS

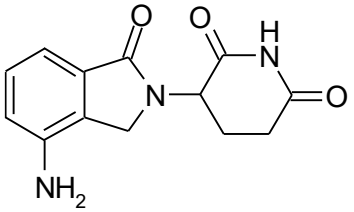
7.1 Clarithromycin (Biaxin®)

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. 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 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 Revlimid REMS® 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 Revlimid REMS® 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 Revlimid REMS® program of Celgene Corporation. Per standard Revlimid REMS® 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 Revlimid REMS® 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.

7.4 Carfilzomib®

Carfilzomib is a synthetic small molecule peptide bearing the chemical name (2S)-N-((S)-1-((S)-4-methyl-1-((R)-2-methyloxiran-2-yl)-1-oxopentan-2-ylcarbamoyl)-2- phenylethyl)-2-((S)-2-(2-morpholinoacetamido)-4-phenylbutanamido)-4- methylpentanamide. The molecular formula is $C_{40}H_{57}N_5O_7$ and the molecular weight is 719.91. It specifically functions as an inhibitor of the chymotrypsin-like activity of the 20s proteasome which leads to the accumulation of protein substrates within the cell and induction of apoptosis.

7.4.1 Formulation

Carfilzomib for Injection will be provided as a lyophilized powder containing for administration as an IV push. The reconstituted lyophilized product consists of 2 mg/mL solution of carfilzomib Free Base in 10 mM sodium citrate buffer (pH 3.5) containing 10% (w/v) sulfobutylether-β-cyclodextrin (SBE-β-CD, Captisol®).

7.4.2 Storage Conditions

Lyophilized carfilzomib for injection must be stored at 2ºC to 8ºC under the conditions outlined in the pharmacy manual "Instructions for Storage and Use of Lyophilized Carfilzomib for Injection," in a securely locked area to which access is limited to appropriate study personnel.

7.4.3 Accountability for Carfilzomib

Onyx Therapeutics, Inc. and the Investigator will maintain records of each shipment of investigational product. The records will document shipment dates, method of shipment, batch numbers, and quantity of vials contained in the shipment. Upon receipt of the investigational product, the designated recipient at the study site will inspect the shipment, verify the number and condition of the vials, and prepare an inventory or drug accountability record.

Drug accountability records must be readily available for inspection by representatives of Onyx Therapeutics, Inc. and by regulatory authorities.

Empty and partially used vials should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures. Drug destruction records must be readily available for inspection by representatives of Onyx and by regulatory authorities. The study monitor, along with the site, will be responsible for returning the unused supply of investigational product to the Sponsor designated distribution center as described in the pharmacy instruction manual. Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

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 clarithromycin are headaches, diarrhea, nausea, abnormal taste, heartburn and abdominal pain. Possible rare side effects are irregular blood counts, shortness of breath, hypoglycemia, anxiety, hallucinations, 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, 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 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.

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.

8.4 Carfilzomib®

Clinical trials to date show that carfilzomib is well tolerated. Major side effects are mainly limited to acute kidney injury and thrombocytopenia both of which are rapidly reversible. The mechanism is still currently under investigation. Thrombocytopenia is thought to be secondary defective budding of megakaryocytes rather than direct cytotoxicity. Other side effects such as fevers, chills and rigors have been reported during initial infusion. Upon repeat challenge these side effects are diminished and negligible. The reaction is thought to be secondary to direct tumor cytoxicity as tumor lysis syndrome has also been documented and should be prophylaxed against. Subjects in this study will receive allopurinol prophylaxis.

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.[34] 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 Revlimid REMS® 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 Car-BiRD therapy which includes subsequent 28-day cycles of carfilzomib plus dexamethasone to maximum response, followed by 28-day cycles of BiRD which includes clarithromycin, lenalidomide, and dexamethasone to maximum response, followed by lenalidomide maintenance in 28-day cycles according to the following schedule (also depicted in Figures 2 and 3, Section 1.0):

Carfilzomib + Dexamethasone:
Carfilzomib will be given at a dose of 56mg/m^2 IV over 30 minutes on days 1, 2, 8, 9, 15, 16 (+/- 2 days) of a 28-day cycle. For Cycle 1, Days 1 and 2 only, carfilzomib will be given at a dose of 20mg/m^2 over 30 minutes.

Dexamethasone (Decadron®) will be given orally at a dose of 20 mg on days 1, 2, 8, 9, 15,16 and days 22, 23 of a 28-day cycle.

BiRD:
Clarithromycin (Biaxin®) will be given orally at a dose of 500 mg twice a day on days 1-28 of a 28-day cycle.

Dexamethasone (Decadron®) will be given orally at a dose of 40 mg on days 1, 8, 15 and 22 of a 28-day cycle.

Lenalidomide (Revlimid®) will be given orally at a dose of 25 mg/day on days 1-21 of a 28-day cycle.

Maintenance Lenalidomide:
Lenalidomide (Revlimid®) will be given as a maintenance medication at a dose of 10 mg/day on days 1-21 of a 28-day cycle.

Due to the risk of thrombosis (see Section 8.2.1), all patients will begin thromboembolic prophylaxis with aspirin 81mg daily throughout treatment with BiRD. 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
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 bloodwork, 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. After completion of carfilzomib plus dexamethasone therapy, depending on response, patients may either proceed immediately to (or undergo stem cell collection followed by) consolidation therapy with BiRD therapy. After completion of BiRD therapy, patients may undergo stem cell transplant to be followed by, or go on directly to maintenance therapy (see Section 4.1 for details on carfilzomib plus dexamethasone, BiRD and maintenance therapy, also see Figure 1).

Maintenance therapy will be prescribed to patients who achieve a negative serum immunofixation status or disease plateau as defined by Appendix I after BiRD therapy. Maintenance therapy is shown in Section 1.0, Figure 3, and Section 4.1.3 and consists of lenalidomide 10mg by mouth daily for days 1-21 of a 28-day cycle. Maintenance therapy will be continued until there is progression of disease or the patient experiences excessive toxicity. At each of these time points, the patient will be taken off study.

9.2 Early Termination of Study

Study-terminating events are listed below:

- Early death (defined by death within 30 days of beginning therapy) 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, Onyx Pharmaceuticals, 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.

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).
- Subject pregnancy.
- 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 Onyx Therapeutics, Inc. for any reason.

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, and mycelex troches 10mg four to five times daily as needed for oral thrush prophylaxis. Allopurinol at a dose of 300mg twice daily is recommended in the 24 hours prior to the first dose of Carfilzomib for tumor-lysis prophylaxis and thereafter may be discontinued. See Section 9.1 for thromboembolic prophylaxis using aspirin, warfarin or Coumadin.

9.3.2 Hematopoietic 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 ≥ 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.

9.3.3 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.

9.3.4 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.

9.4 Day One Dosing Guidelines

On day 1 of therapy during Carfilzomib and dexamethasone (induction) therapy, the patient will take Carfilzomib at a dose of 56mg/m^2 IV once and Dexamethasone at a dose of 40mg once. Patients will take 20 mg/m^2 of Carfilzomib and 40mg of Dexamethasone on day 1 of cycle 1. The patient will also be directed to take the following prophylactic medicines, which may be modified at the discretion of the treating physician: 1) allopurinol at a dose of a 300mg tablet twice daily starting 24 hours before the first dose of carfilzomib only; 2) omeprazole at a dose of 20mg once daily; 3) Bactrim at a dose of one DS tab once daily.

On day 1 of therapy during BiRD (consolidation therapy) the patient will take Lenalidomide at a dose of 25mg once, Dexamethasone at a dose of 40mg once, and Clarithromycin at a dose of 500mg once in the morning and once at night. The patient will also be directed to take the following prophylactic medications during BiRD therapy: 1) aspirin at a dose of 81 mg once daily (or other equivalent anti-thrombotic therapy); 2) omeprazole at a dose of 20mg once daily; 3) Bactrim at a dose of one DS tab once daily.

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 drug-related somnolence, rash, peripheral neuropathy, sinus bradycardia/ other cardiac arrhythmia, allergic reaction/hypersensitivity, diarrhea, dyspepsia, loss of appetite, nausea, gastritis, gastric or duodenal ulcer or confusion or mood alterations that may have occurred has resolved to ≤ grade 2 severity;
- Any other drug-related adverse events that may have occurred have resolved to ≤ grade 2 severity.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of 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 carfilzomib, 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 carfilzomib, 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 Table 1. 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.

Table 1: Dose Reduction Steps:	
Carfilzomib Dose Reduction	
Starting Dose	Carfilzomib IV 56mg/m^2 on days 1,2,8,9,15,16 of a 28-day cycle
Dose Level -1	Carfilzomib IV 45mg/m^2 on days 1,2,8,9,15,16 of a 28-day cycle
Dose Level -2	Carfilzomib IV 36mg/m^2 on days 1,2,8,9,15,16 of a 28-day cycle
Dose Level -3	Carfilzomib IV 27mg/m^2 on days 1,2,8,9,15,16 of a 28-day cycle
Lenalidomide Dose Reduction	
Starting Dose	Lenalidomide PO 25mg/day on days 1-21 of a 28 day cycle
Dose Level -1	Lenalidomide PO 20mg/day on days 1-21 of a 28 day cycle
Dose Level -2	Lenalidomide PO 15 mg/day on days 1-21 of a 28

	day cycle
Dose Level -3	Lenalidomide PO 10 mg/day on days 1-21 of a 28 day cycle
Dose Level -4	Lenalidomide PO 5 mg/day on days 1-21 of a 28 day cycle
Dexamethasone Dose Reduction	
Starting Dose for Car-Dex	20 mg PO on days 1,2,8,9,15,16,22,23 of a 28 day cycle
Dose Level -1 Car-Dex	12 mg PO on days 1,2,8,9,15,16,22,23 of a 28 day cycle
Dose Level -2 Car-Dex	8 mg PO on days 1,2,8,9,15,16,22,23 of a 28 day cycle
Dose Level -3 Car-Dex	4 mg PO on days 1,2,8,9,15,16, 22,23 of a 28 day cycle
Dose Level -4 Car-Dex	4 mg PO on days 1,8,15,22 of a 28 day cycle
Starting Dose for BiRD	40 mg PO on days 1, 8, 15 and 22 of a 28 day cycle
Dose Level -1 BiRD	20 mg PO on days 1, 8, 15 and 22 of a 28 day cycle
Dose Level -2 BiRD	8 mg PO on days 1, 8, 15 and 22 of a 28 day cycle
Dose Level -3 BiRD	8 mg PO on days 1 and 15 of a 28 day cycle
Dose Level -4 BiRD	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
Lenalidomide Maintenance Dose Reduction	
Starting Dose	Lenalidomide PO 10 mg/day on days 1-21 of a 28-day cycle
Dose Level -1	Lenalidomide PO 5 mg/day on days 1-21 of a 28 day cycle
Dose Level -2	Lenalidomide PO 5 mg every other day on days 1-21 of a 28 day cycle

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 2a: Carfilzomib / Dexamethasone Dose Modification Instructions

Toxicity	*NCI Toxicity Grade*	*Action*
Neutropenia	≥ Grade 3	• Hold (interrupt) Carfilzomib dose • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 15, restart carfilzomib at next lower dose level and continue through Day 23. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the carfilzomib dose maintained.
Thrombocytopenia	≥ Grade 3 (platelet count < 50,000/mm^3)	• Hold (interrupt) carfilzomib • Follow CBC weekly. • If thrombocytopenia has resolved to ≤ grade 2 prior to Day 15, restart carfilzomib at next lower dose level and continue through Day 23.
Rash (non-blistering)	≥ Grade 3	• Hold (interrupt) carfilzomib for the remainder of cycle • Reduce carfilzomib by 1 dose level and restart next cycle.
Rash	Grade 4 non-blistering or desquamating (blistering) any Grade	• Discontinue carfilzomib and take patient off study
Erythema multiforme	≥ Grade 3	• Discontinue carfilzomib and take patient off study
Peripheral Neuropathy	≥ Grade 3 or Grade 2 with pain	• Hold carfilzomib for remainder of cycle • Reduce carfilzomib by 1 dose level and restart next cycle. If there is recurrence, carfilzomib will be discontinued and the patient taken off study.

Toxicity	*NCI Toxicity Grade*	*Action*
Allergic reaction or hypersensitivity	≤ Grade 2	• Hold (interrupt) carfilzomib for remainder of cycle. Follow at least weekly. • Reduce carfilzomib by 1 dose level and restart next cycle. If recurs, take patient off study.
Allergic reaction or hypersensitivity	≥ Grade 3	• Discontinue carfilzomib and take patient off study
Any 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 ≥ 38.5º 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).
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

Toxicity	*NCI Toxicity Grade*	*Action*
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.
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.*

* See Section 9.5 for Instructions for Initiation of a New Cycle

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 Carfilzomib-Dexamethasone: 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 V)
- 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

10.2 Carfilzomib-Dexamethasone: 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)

10.3 Carfilzomib-Dexamethasone: Day 1 of each cycle (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
- 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.

10.4 Carfilzomib-Dexamethasone: Days 8, 15, 22 (Starting Cycle 2) and End of Study

- 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

10.5 BiRD: Day 1, 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, SGPT/ALT
- LDH
- Uric Acid
- Magnesium
- Phosphorus
- Drug diary generated and reviewed with patient (See Appendix V)
- Pregnancy test for females of childbearing potential as outlined in Appendix III.

10.6 BiRD: 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, SGPT/ALT

10.7 BiRD: Day 1 of each cycle (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, 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
- Serum or urine β-HCG (with a sensitivity of 50mIU/mL) pregnancy testing for females of childbearing potential (FCBP) (See Appendix III for complete pregnancy testing, birth control and counseling) every 28 days for females with regular or no menstruation, or every 14 days for females with irregular menstruation. FCBP will have another pregnancy test at discontinuation of lenalidomide. FCBP with regular or no menstruation will have a pregnancy test at Day 28 post last dose of lenalidomide and FCBP with irregular menstruation will have a pregnancy test at Day 14 and 28 post last dose of lenalidomide.
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulins, and 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.
- 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.

10.8 Lenalidomide maintenance: Day 1 of each cycle and End of Study

- Physical evaluation: A complete medical evaluation including medical history, adverse events, concomitant medications, physical exam, vital signs, KPS, 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
- Serum or urine β-HCG (with a sensitivity of 50mIU/mL) pregnancy testing for females of childbearing potential (FCBP) (See Appendix III for complete pregnancy testing, birth control and counseling) every 28 days for females with regular or no menstruation, or every 14 days for females with irregular menstruation. FCBP will have another pregnancy test at discontinuation of lenalidomide. FCBP with regular or no menstruation will have a pregnancy test at Day 28 post last dose of lenalidomide and FCBP with irregular menstruation will have a pregnancy test at Day 14 and 28 post last dose of lenalidomide.
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulins, and 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.
- 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).
- Adverse Events will be monitored continuously as specified in the Schedule of Assessment (Table 1).
- 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.
- All subjects will be followed for survival. Cause of death is to be recorded in the subject's medical record.

10.9 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.

10.10 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.

10.11 Criteria for removal from study

10.11.1 Patients will be removed from study when any of the following occurs:

- Progressive disease
- Adverse event(s) that, in the judgment of an Investigator, may cause severe or permanent harm or which rule out continuation of study drug
- Major violation of the study protocol
- Withdrawal of consent
- Patient is lost to follow-up
- Death
- Suspected or confirmed pregnancy

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 Onyx Therapeutics, 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 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.

11.2 Adverse Event and Drug Reaction reporting

Toxicity will be scored using CTCAE version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE version 4.0 can be downloaded from the CTEP homepage http://ctep.info.nih.gov. All appropriate treatment areas 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.

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 (e.g. 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 (insert time-frame which must be 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 24 hours 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 24 hours 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 as defined above are present. The investigator is responsible for reporting adverse events to Celgene as described below.

11.3.1 SAE Reporting by Investigator-sponsor to Onyx

Serious adverse events (SAE) are defined in Section 11.1 above. The investigator at each site should inform Dr. Ruben Niesvizky (the principal sponsor-investigator) and Onyx Therapeutics, Inc. of any SAE within 24 hours of being aware of the event. The date of awareness should be noted on the report. The Investigator-sponsor is responsible for notifying the appropriate health authorities (HAs), ethics committees (ECs), and investigators, of any expedited, annual, or other periodic safety reports in accordance with applicable regulations. Any safety report submission will cross reference the Onyx investigational new drug (IND) or clinical trial approval (CTA) number. The Investigator is also responsible for notifying the local ECs in accordance with local regulations.

The Investigator-sponsor must inform Onyx in writing by e-mail or fax at the contact information listed below for all SUSARs that are judged as reasonably related to the Onyx study drug. Site will transmit the final CIOMS of that event to Onyx within twenty-four (24) hours of submitting the report to the applicable regulatory authority.

For regulatory reporting purposes, an event of "Death, Cause Unknown" from the study shall be processed as a SUSAR. All forms must be completed and provided to Onyx in English.

The Individual Case Safety Report (ICSR) may be referred to as an individual safety report or SAE Report, including Pregnancy Exposure Reports and Follow up Reports. The ICSR must be as complete as possible, at a minimum including event reference number, protocol name and number, investigator contact information, specific patient identifiers (e.g., initials, patient number, date of birth or age, or gender), the name of the suspect Study Drug, the date and

dosage(s) of exposure, event, the date(s) of event, country of event, "Serious" Criteria, Relationship/causality of Study Drug, Hospitalization history for the event, Event status/outcome, Relevant history (including diagnostics, laboratory values, radiographs, concomitant medications, and event treatment, and narrative summary.

Sponsor shall be responsible for collecting all SAEs and Pregnancy and Lactation Exposure Reports and will exercise commercially reasonable due diligence to obtain follow-up information on incomplete SAE or Pregnancy and Lactation Exposure Reports. In the event that the Company requires clarification or further information on individual SAE or Pregnancy and Lactation Exposure Reports, Company will not contact non-party investigators directly, but will route all such inquiries through Site for forwarding to such investigator(s). Site will be responsible to ensure such inquiries are completed and timely provided to Company.

Information not available at the time of the initial report (e.g., an end date for the SAE, discharge summaries, lot numbers, relevant laboratory values, scan data and autopsy reports) which are received after the initial report must be documented on a follow-up form, and submitted to Onyx in the same timelines as outlined above. Sponsor shall be responsible for obtaining follow-up information for the SAEs and demonstrate diligence in attempting to obtain such information by, among other things, maintaining written records of such attempts.

Other aggregate analysis including reports containing safety data generated during the course of the study is to be submitted to Onyx at the time the sponsor ISS submits to anybody governing research conduct i.e. RA, IRB etc. Final study report including unblinding data when applicable and reports of unauthorized use of a marketed product to be submitted to Onyx at the time the sponsor ISS submits to anybody governing research conduct i.e. RA, IRB etc. but not later than one calendar year of study completion.

Sponsor will provide an annual IND report to Onyx. Reports containing safety data generated during the course of the study is to be submitted to Onyx at the time the sponsor submits to anybody governing research conduct, i.e. regulatory authorities and IRBs. Sponsor will support reconciliation of all ICSRs at the end of the study at a minimum.

Pregnancy Reporting by Investigator-sponsor to Onyx

Report Pregnancy and potential infant exposure including Lactation, within ten (10) calendar days of Sponsor awareness. Provide to Onyx the SAE reports associated with pregnancy. SUSARs are to be reported within twenty-four (24) hours of submitting the report to the applicable regulatory authority.

Onyx Drug Safety and Pharmacovigilance Contact Information:

- Drug Safety Reporting Fax
- Toll-free US 888-814-8653
- Toll US 805-480-9205

Drug Safety Reporting by secure e-mail can be established upon request.

11.3.2 Report of Adverse Events to the Institutional Review Board

Each Investigator is required to notify his/her Institutional Review Board (IRB) by facsimile within 7 calendar days of observing or learning of a serious and unexpected adverse event. A mailed hard copy to the IRB must be submitted within 15 calendar days of observing or learning of the event.

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, Onyx Therapeutics, and the Weill Cornell Medical College Data Safety Monitoring Board at the time of annual renewal.

The Investigator must keep copies of all AE information, including correspondence with Onyx Therapeutics, Inc. and the IRB/EC, on file (see Section 15.4 for records retention information).

11.4 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 Onyx Therapeutics, Inc. Amendments should only be submitted to IRB/EC after consideration of Onyx Therapeutics, 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, Dr. Ruben Niesvizky.

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 or Onyx and its representatives. The PI, Dr. Ruben Niesvizky, will be the safety contact for all DSMB related analysis outcomes.

Dr. Niesvizky's office is located at: NYPH-WCMC
428 East 61st Street, 8th Floor
New York, NY 11101

The phone number to Dr. Niesvizky's office is: 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 at the end of the first stage of accrual (before proceeding on to stage 2, as outlined in the miniMax design in the Statistical Considerations Section 14 below) including toxicity data, protocol adherence, and protocol deviations. 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, Onyx Therapeutics, Inc., 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 Onyx Therapeutics, Inc. representative so that the accuracy and completeness may be checked.

14.0 STATISTICAL CONSIDERATIONS

14.1 Datasets To Be Analyzed

The primary efficacy analyses will be performed on the Intent-to-treat (ITT) population, which will include all subjects who have been enrolled for the study.

14.2 Statistical Methodology

Sample Size:

Sample size recommendations for the phase II design are determined according to Simon's two-stage design [as per: Simon R (1989): Optimal Two-Stage Designs for Phase II Clinical Trials, Controlled Clinical Trials, 10:1-10.]. The primary endpoint in the study is the maximum objective complete remission proportion following maintenance lenalidomide monotherapy (either directly following BiRD or an autologous stem cell transplant). Objective complete remission will be measured with standard IMWG criteria as well as via PET/CT scanning and molecularly with PCR.

We project an objective complete remission proportion (CR) of 40%, below which the response will be unacceptable, and an objective complete remission proportion of 55%, above which the regimen will be considered worthy of further exploration. The null hypothesis that the objective complete remission proportion is less than or equal to 40% will be tested against the alternative hypothesis that the objective complete remission proportion is greater than or equal to 55%.

The sample size computations were performed assuming a 10% level of significance and 90% power. In the first stage, 43 patients will enter the study. If 18 or fewer patients fail to achieve at least a partial remission within the first 6 cycles of therapy, then it is very unlikely that they will achieve a complete remission at any future time. If this is the case, the study will be terminated early and declared to have a negative result. If 19 or more attain a partial remission within the first 6 cycles of therapy, enrollment will be extended to 72 patients. At Stage 2, the treatment will be declared effective and worthy of further testing if 34 or more patients continue to respond towards a complete remission among the 72 patients entered. This two-stage design yields a ≥ 0.90 probability of a positive result if the true percentage of objective complete remission responders is $\geq 55\%$. It yields a ≥ 0.90 probability of a negative result if the true percentage of objective complete remission responders is $\leq 40\%$.

Table A. Numbers of objective complete remission responders required to accept or reject H_0 at each stage. Under this design, H_0 will not be rejected at Stage 1

	N	Accept H_0	Reject H_0
Stage 1	43	≤ 18	---
Stage 2	72	≤ 33	≥ 34

Analysis Plan for Endpoints:

Primary Endpoint:

The primary endpoint of objective complete remission proportion (CR) will be estimated and a 95% confidence interval will be estimated via binomial proportions. The CR proportion will be estimated at: 1) after Carfilzomib/Dexamethasone induction; 2) at maximum response after

consolidation therapy with BiRD therapy; and 3) at maximum response on maintenance lenalidomide monotherapy (either directly following BiRD or an autologous stem cell transplant). The latter (final) assessment reflects the primary endpoint of this study.

Secondary Clinical Endpoints:

With adequate follow-up time, progression-free survival (PFS) and overall survival (OS) will be assessed by Kaplan-Meier survival analysis and 95% confidence intervals will be calculated using Greenwood's formulae. PFS will be defined as the time from first treatment day until objective or symptomatic progression or death (or until date of last follow-up if no progression/death). OS will be defined as the time from first treatment day until death (or until date of last follow-up if no death).

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.

Descriptive analyses of quality of life parameters will be performed at: 1) study entry; 2) after Carfilzomib+dexamethasone induction; 3) at 3 months after consolidation with BiRD therapy; and 4) after 6 months of maintenance lenalidomide monotherapy.

All p-values will be two-sided with statistical significance evaluated at the 0.05 alpha level. Ninety-five percent confidence intervals will be calculated to assess the precision of the obtained CR proportions. All analyses will be performed in SAS Version 9.2 (SAS Institute, Inc., Cary, NC).

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, the Onyx Therapeutics, Inc., or other study support such as the National Cancer Institute will be able to review patient medical records.

Onyx Therapeutics, Inc. affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Onyx Therapeutics, Inc. requires the Investigator to permit Onyx'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 Onyx Therapeutics, 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.

15.6.1 Study as a whole

Onyx Therapeutics, Inc. 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 carfilzomib, 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. (See sections 3.5 and 3.8). 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. Carfilzomib will be provided to research subjects for the duration of their participation in this trial by the Onyx Therapeutics, Inc. at no charge to them and will be dispensed through the hospital investigational pharmacy. Commercially available Lenalidomide (Revlimid®) will be prescribed to research subjects for the duration of their participation in this trial in accordance with the Revlimid REMS® program. Lenalidomide will be shipped directly to patients.

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 electrophoresis 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 existing 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

World Health Organization (WHO) Criteria for the diagnosis of Multiple Myeloma

Major Criteria
Bone marrow plasmacytosis > 30 percent
Biopsy-proven plasmacytomas
Presence of monoclonal protein in the serum or urine
Serum IgG > 3.5g/dL or
Serum IgA > 2g/dL or
Urine Bence-Jones protein > 1g/24 hours
Minor Criteria
Bone marrow plasmacytosis of 10 – 30 percent
Presence of monoclonal protein less than major criteria values
Presence of lytic bone lesions
Reduced immunoglobulin levels to < 50 percent of normal
IgG < 600mg / dL
IgA < 100 mg/dL
IgM < 50 mg/dL

For the diagnosis of multiple myeloma to be made, the patient must fulfill a minimum of one major and one minor criterion, or three minor criterion which must include bone marrow plasmacytosis of 10 – 30 percent and the presence of monoclonal protein.

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 Revlimid REMS® program, and be willing and able to comply with the requirements of Revlimid REMS®.

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: 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 V: Example Drug Diaries

1) Carfilzomib-Dexamethasone:

Protocol: Carfilzomib-Dexamethasone	**Patient NAME**	**Cycle #**

Carfilzomib: This will be given to you in the infusion center.

DECADRON® (Dexamethasone): Take **five 4mg** pills twice weekly as marked on calendar – this will be given to you in the infusion center.

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.

Allopurinol: Take 300 mg two times per day prior to the first dose of Carfilzomib.

Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
	Allopurinol 300mg ()() Cycle 1 only	**5/1/07 Day 1**	**5/2/07 Day 2**	**5/3/07 Day 3**	**5/4/07 Day 4**	**5/5/07 Day 5**
		Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
		Carfilzomib( )	Carfilzomib( )			
		Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron( )	Decadron( )			
5/6/07 Day 6	**5/7/07 Day 7**	**5/8/07 Day 8**	**5/9/07 Day 9**	**5/10/07 Day 10**	**5/11/07 Day 11**	**5/11/07 Day 12**
Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
		Carfilzomib( )	Carfilzomib( )			
Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron( )	Decadron( )			
5/12/07 Day 13	**5/13/07 Day 14**	**5/14/07 Day 15**	**5/15/07 Day 16**	**5/16/07 Day 17**	**5/18/07 Day 18**	**5/19/07 Day 19**
Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
		Carfilzomib( )	Carfilzomib( )			
Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron( )	Decadron( )			
5/20/07 Day 20	**5/21/07 Day 21**	**5/22/07 Day 22**	**5/23/07 Day 23**	**5/24/07 Day 24**	**5/25/07 Day 25**	**5/26/07 Day 26**
Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )	Bactrim ( )
		Carfilzomib( )	Carfilzomib( )			
Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )	Prilosec ( )
		Decadron( )	Decadron( )			
5/27/07 Day 27	**5/28/07 Day 28***	**5/29/07 Day 1**	**5/30/07 Day 2**	**5/31/07 Day 3**		
Bactrim ( )	Bactrim ( )				***On Day 28:** See Dr. X Bring this calendar, your empty medication bottles, and 24-hour urine collection to your appointment.	
Prilosec ( )	Prilosec ( )					

2) BiRD

Protocol: 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
		5/1/07 Day 1	**5/2/07 Day 2**	**5/3/07 Day 3**	**5/4/07 Day 4**	**5/5/07 Day 5**
		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( )				
5/6/07 Day 6	**5/7/07 Day 7**	**5/8/07 Day 8**	**5/9/07 Day 9**	**5/10/07 Day 10**	**5/11/07 Day 11**	**5/11/07 Day 12**
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( )				
5/12/07 Day 13	**5/13/07 Day 14**	**5/14/07 Day 15**	**5/15/07 Day 16**	**5/16/07 Day 17**	**5/18/07 Day 18**	**5/19/07 Day 19**
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( )				
5/20/07 Day 20	**5/21/07 Day 21**	**5/22/07 Day 22**	**5/23/07 Day 23**	**5/24/07 Day 24**	**5/25/07 Day 25**	**5/26/07 Day 26**
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( )				
5/27/07 Day 27	**5/28/07 Day 28***	**5/29/07 Day 1**	**5/30/07 Day 2**	**5/31/07 Day 3**		
Bactrim ( )	Bactrim ( )				***On Day 28:** See Dr. X Bring this calendar, your empty medication bottles, and 24-hour urine collection to your appointment.	
Biaxin( )( )	Biaxin( )( )					
Aspirin ( )	Aspirin ( )					
Prilosec ( )	Prilosec ( )					

3) Lenalidomide Maintenance:

Protocol: BiRD		**Patient NAME**				**Cycle #**
REVLIMID® (Lenalidomide): Take **10 mg** each morning on the dates marked on calendar;						
Sunday	**Monday**	**Tuesday**	**Wednesday**	**Thursday**	**Friday**	**Saturday**
		5/1/07 Day 1	**5/2/07 Day 2**	**5/3/07 Day 3**	**5/4/07 Day 4**	**5/5/07 Day 5**
		Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )
5/6/07 Day 6	**5/7/07 Day 7**	**5/8/07 Day 8**	**5/9/07 Day 9**	**5/10/07 Day 10**	**5/11/07 Day 11**	**5/11/07 Day 12**
Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )
5/12/07 Day 13	**5/13/07 Day 14**	**5/14/07 Day 15**	**5/15/07 Day 16**	**5/16/07 Day 17**	**5/18/07 Day 18**	**5/19/07 Day 19**
Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )	Revlimid ( )
5/20/07 Day 20	**5/21/07 Day 21**	**5/22/07 Day 22**	**5/23/07 Day 23**	**5/24/07 Day 24**	**5/25/07 Day 25**	**5/26/07 Day 26**
Revlimid ( )	Revlimid ( )					
5/27/07 Day 27	**5/28/07 Day 28***	**5/29/07 Day 1**	**5/30/07 Day 2**	**5/31/07 Day 3**		
					***On Day 28:** See Dr. X Bring this calendar, your empty medication bottles, and 24-hour urine collection to your appointment.	
		Revlimid ( )				

APPENDIX VI: Karnofsky Performance Status (KPS) Scale

Patient Performance Status	KPS %	Care Needs
Normal, no complaints, no evidence of disease	100	Able to carry on normal activity and work; no special needs required
Able to carry on normal activity, minor signs / symptoms of disease	90	
Normal activity with effort; some signs or symptoms of disease	80	
Cares for self; unable to carry on normal activity or to active work	70	Unable to work; able to care for most of self-care needs at home; varying amounts of assistance needed
Requires occasional assistance, but is able to care for most of personal needs	60	
Requires considerable assistance / frequent medical care	50	
Disabled; requires special care and assistance	40	Unable to care for self; requires institutional or hospital-level care; disease may be progressing rapidly
Severely disabled; hospital admission is indicated although death not imminent	30	
Very sick; hospital admission necessary; active supportive treatment necessary	20	
Moribund; fatal processes progressing rapidly	10	
Dead	0	

APPENDIX VII: REFERENCES

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