Autologous Stem Cell Transplant with Pomalidomide (CC-4047®) Maintenance versus Continuous Clarithromycin / Pomalidomide / Dexamethasone Salvage Therapy in Relapsed or Refractory Multiple Myeloma: A Phase 2 Open-Label Randomized Study by Tristate Consortium

PROTOCOL FACE PAGE FOR
MSKCC THERAPEUTIC/DIAGNOSTIC PROTOCOL

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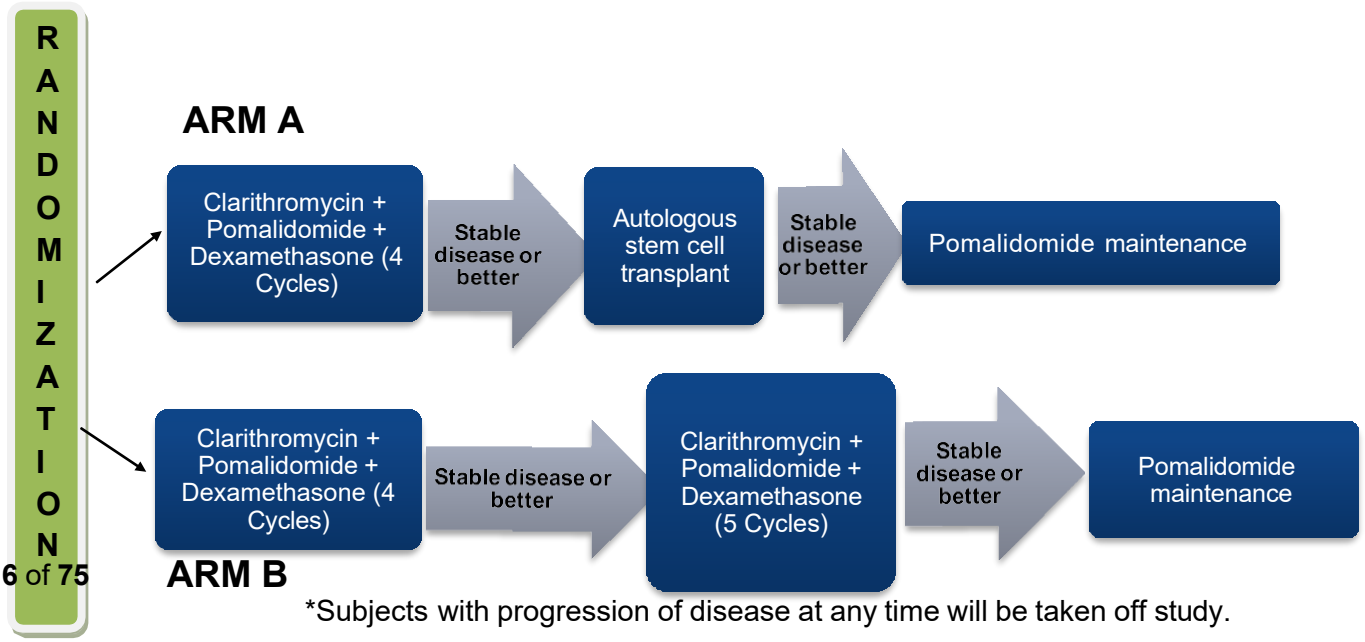
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1.0 PROTOCOL SUMMARY AND/OR SCHEMA

This is a Phase II multicenter, randomized, open label study to determine the effect of autologous Stem Cell Transplant (auto-SCT) with Pomalidomide (CC-4047®) Maintenance versus Continuous Clarithromycin/Pomalidomide/Dexamethasone (ClaPD) Salvage Therapy in Relapsed or Refractory Multiple Myeloma on overall response (Very Good Partial Response or greater).

Eligible patients that will be registered on study will have full restaging evaluation including bone marrow and radiologic survey. Patients will be randomized to autologous Stem Cell Transplant (auto-SCT) (Arm A) versus Clarithromycin/Pomalidomide/Dexamethasone (ClaPD) alone (Arm B) at time of registration (See Study Schema below). All patients will receive 4 cycles of clarithromycin 500mg twice daily on days 1-28, pomalidomide 4 mg daily on days 1 through 21, and dexamethasone orally at a dose of 40 mg daily on days 1, 8, 15, and 22 of each 28-day cycle. Myeloma disease assessment will be done after completion of the 4th cycle and patients with stable disease or better will proceed to additional treatment. Patients randomized to auto-SCT will proceed within 28 days after completion of the 4th cycle of ClaPD to receive melphalan 140mg/m^2 or 200mg/m^2 (as per institutional guidelines) followed by hematopoietic cell infusion. Patients assigned to ClaPD alone will receive 5 additional cycles of ClaPD. Minimum mandatory thromboprophylaxis will be aspirin 325 mg once daily. Disease progression, death or beginning of non protocol therapy will be indications to terminate study therapy. In the transplant arm (Arm A), Pomalidomide maintenance will be given no sooner than 100 days post transplant at a dose of 4mg daily for 21 days of a 28 day cycle and will be continued until 2 years have elapsed from study entry. In the non-transplant arm (Arm B), patients will receive maintenance therapy with pomalidomide at 4 mg orally 21/28 days after the last cycle of ClaPD for up to two years from time of study entry. Serial clinic visits and laboratory measurements will be performed to monitor for treatment response. Treatment response will be determined as per International Myeloma Working Group (IMWG) guidelines (Appendix I).

STUDY SCHEMA



*Subjects with progression of disease at any time will be taken off study.

2.0 OBJECTIVES AND SCIENTIFIC AIMS

Primary Objective

1. Compare the overall response rate (Very Good Partial Responses and higher) at 9 months after start of treatment between the two study arms: 4 cycles of Clarithromycin/Pomalidomide/ Dexamethasone followed by auto-SCT versus 9 cycles of Clarithromycin/Pomalidomide/ Dexamethasone.

Secondary Objectives

1. Determine the feasibility of a salvage auto-SCT after Clarithromycin/Pomalidomide/ Dexamethasone re-induction in relapsed or refractory multiple myeloma.
2. Determine the overall survival and progression free survival for both arms.
3. Compare the time to next treatment on both treatment arms.
4. Determine the safety of maintenance single-agent pomalidomide between both treatment arms.
5. Determine the rates of ≥ Grade 3 toxicities according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 as specified in section 10.0.

3.0 BACKGROUND AND RATIONALE

3.1 Disease

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*)

3.2 Prognosis

Traditionally 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*) Certain chromosomal abnormalities, such as translocations t(4;14) and t(14;16) confer poor prognosis.(*8*)

High dose therapy with auto-SCT has been shown in multiple randomized trials to improve progression free survival (PFS) and in some trials to improve overall survival (OS). (9,10) Maintenance therapy post SCT has also been shown to increase PFS. Thalidomide is an immune-modulatory drug that is relatively inexpensive and has been studied in several randomized trials as post transplant maintenance therapy. Two studies have shown an OS benefit for patients receiving thalidomide.(11-15) Lenalidomide with its better side effect profile was a logical candidate drug to

study as post transplant maintenance therapy. Two randomized trials have been performed and recently reported using lenalidomide. The IFM 2005 reported on 614 patients randomized to receive either lenalidomide or placebo post transplant after 2 cycles of lenalidomide intensification.(16,17) With a median follow up of 34 months the median PFS was 42 months for the lenalidomide arm vs 24 months for the placebo arm ($p<10-8$).(16) At the time of last report no significant difference in overall survival was reported but a significant increased risk of secondary malignancies was seen in the lenalidomide arm (primarily hematologic malignancies). The CALGB 100104 was also presented at the International Myeloma Workshop meeting in Paris. As with the IFM 2005 study there was a significant improvement in time to progression (TTP) for patients receiving lenalidomide maintenance (median 43.6 months vs 21.5 months for placebo). With a median follow up of 18 months, there were significant less deaths in the lenalidomide arm versus placebo (21 vs 37 $p<0.019$) despite the crossover design. Post-hoc analysis suggest that the benefit of lenalidomide maintenance is seen regardless of response to SCT and type of induction therapy.(17)

Bortezomib maintenance has also been demonstrated to reduce the risk of relapse post SCT. Sonneveld et al reported on the outcomes of 626 patients randomized to receive bortezomib during induction in combination with doxorubicin and dexamethasone followed by post transplant bortezomib every other week for 2 years or thalidomide during induction and post transplant. Bortezomib therapy was associated with a higher response rate (60% VGPR or greater vs 40% for thalidomide), on multivariate analysis bortezomib therapy was also associated with improvements in PFS and OS. (18)

3.3 Treatment of Relapsed Myeloma

Patients who have previously been treated for myeloma and have relapsed, or patients that have multiple myeloma that is refractory to therapy, are known to have a worse overall prognosis in terms of survival, likelihood of response to other chemotherapeutics, as well as duration of response to salvage therapies.(19,20)

With the adoption of lenalidomide maintenance post SCT the natural history of and the optimal therapy for patients relapsing on lenalidomide maintenance has not been defined and there is no standard of care. However, the following are potential treatment strategies for these patients:

Multiple potential strategies exist:

a) Aggressive reinduction therapy with triple drug therapy (IMID, proteasome inhibitor, steroids).
b) Less aggressive induction therapy with a more potent IMID (pomalidomide) and dexamethasone.
c) Less aggressive induction therapy with a proteasome inhibitor.
d) Clinical trial of new agents.

This clinical trial explores potential for further treatment. After response to any of the above fore-mentioned strategies the potential role of consolidation with a 2nd course of high dose therapy also needs to be explored.

3.4 High Dose Therapy with Autologous SCT as Salvage Therapy for Myeloma.

Melphalan is commercially available and is the primary agent used for conditioning in auto–SCT for multiple myeloma. It is a derivative of nitrogen mustard and classified as an alkylating agent. Melphalan intercalates within ribonucleic acid base pairs and thus interferes with DNA replication and transcription of RNA, leading to death in actively replicating cells. When used for auto–SCT, it is given intravenously. Melphalan is incompletely and erratically absorbed, has a prolonged plasma half-life, and is excreted largely unchanged in the urine. Intravenous melphalan results in very high plasma levels followed by an initial rapid decay curve (half-life 30-60 minutes). Most of the administered dose is recovered unchanged in the urine and the drug does not need to be metabolized to be active. The peak concentration achieved in the plasma is directly related to creatinine clearance (CrCl) and thus the dose is usually reduced in those patients with a CrCl < 70 cc/min.

The major toxicity of melphalan is myelosuppression, which is dose-related. Other toxicities which may occur at high-doses include nausea and vomiting, mucositis, and diarrhea. Antiemetics are therefore routinely given prior to and after administration, along with oral care to prevent and ameliorate mucositis, and anti-diarrheals as needed. Further details of action and pharmacology can be found in the package insert.

Melphalan's efficacy when used in high doses was pioneered by Mcelwein et al. with high response rates in patients with refractory myeloma, but at the expense of severe myelosuppression. (21,22) The use of autologous stem cell rescue was pioneered by Barlogie et al and its efficacy demonstrated by randomized trials beginning by those performed by Attal et al. (23-*31*)

Autologous stem cell transplantation has also been shown to be an effective salvage therapy for patients with relapsed or refractory multiple myeloma. Mehta et al reported on 42 patients who underwent salvage autologous transplant prior to the era of IMID's and proteasome inhibitors. The complete remission rate was 33% after autologous transplantation. The 3-year probability of event-free survival was 25 ± 8% and overall survival was 54 ± 8% significantly better than for those patients who underwent a salvage allograft (29 ± 9%; P = 0.01). The 1-year probability of transplant-related mortality was 10 ± 5% for autografted patients. (32)

More recently Shah et al reported on 44 myeloma patients who received a second auto-HCT as salvage therapy at The University of Texas MD Anderson Cancer Center. Median time between the first and salvage auto-HCT was 30 months and median number of salvage treatment regimens was 2 (range, 0-5). One patient died within 100 days, for a treatment-related mortality of 2%. Complete response (CR) and near CR were seen in 11% of patients with 79% of patients achieving at least a partial response. Median progression-free survival (PFS) and overall survival (OS) from time of salvage auto-HCT were 12.3 and 31.7 months, respectively with better outcomes for patients with longer time to progression after first auto-HCT and lower number of prior therapies. (33)

Jimenez-Zepeda et al reported on 81 MM patients who received a second ASCT for relapsed MM. The median time to relapse after first transplant was 39 months. All patients received reinduction therapy before the second ASCT. The high-dose regimen given before the second ASCT consisted of melphalan (MEL) alone in the majority. Complete response, very good partial response, and partial response were seen in 7.7%, 39.7%, and 50%, respectively, at day 100 post-ASCT; the median time to relapse after the second ASCT was 19 months. Early deaths occurred in 2.6%. Median progression-free survival (PFS) based on the time to myeloma relapse after first ASCT was 9.83 months (relapse ≤24 months) and 17.3 months (relapse ≥24 months) (P < .05). Median overall

survival (OS) was 28.47 months (relapse ≤24 months) and 71.3 months (relapse >24 months) (P = .006). (34) This second ASCT is a feasible and safe option for salvage therapy in MM. The best outcomes are observed in patients whose time to progression was greater than 24 months after first ASCT, as these patients had a subsequent PFS lasting over 1 year and an OS of almost 6 years. However, the role of this modality in the context of emerging therapies has not been established.

3.5 Investigational Agent: Pomalidomide - CC-4047

The emergence of the immunomodulatory agents, such as thalidomide, lenalidomide and more recently CC-4047 (pomalidomide), as effective therapies has altered the therapeutic paradigm for multiple myeloma (MM). These salvage therapies are associated with response rates of 50-60% with response durations of less than 18 months.

Pomalidomide (CC-4047) is an analogue of thalidomide that, among other anti-tumor properties, on an equimolar basis *in vitro*, displays equivalent anti-angiogenic activity, about 8-fold greater activity in stimulation of apoptosis, at least 10-fold greater activity in inhibition of cellular COX-2 production and over 4,000-fold greater activity in inhibition of cellular TNF-alpha production relative to thalidomide [Data on file: Celgene Corp.; Summit, NJ]. (35). CC-4047 has also been shown to stimulate antibody-dependent cytotoxic T-cell activity (ADCC) [Data on file: Celgene Corp.; Summit, NJ]. At tolerated doses (MTD = 2 mg QD and 5 mg QOD), CC-4047 has been shown to be active in subjects with relapsed or refractory multiple myeloma (MM) (study CC-4047-[Data on file: Celgene Corp.; Summit, NJ].(35) In 45 subjects who received doses of CC-4047 ranging, by cohort, up to 10 mg daily, the most commonly occurring dose-limiting toxicity (DLT) was reversible neutropenia. As with other IMiDs® administered to subjects receiving concomitant systemic steroids, deep vein thrombosis (DVT) was seen (in 1subject each in this study and in its subsequent named patient supply rollover program) [Data on file: Celgene Corp.; Summit, NJ].(35)

Recently, preliminary efficacy and safety data from an ongoing phase II study, led by Martha Lacy, et al, at Mayo Clinic, were published.(36) Sixty patients with relapsed or refractory multiple myeloma were enrolled. Pomalidomide (CC-4047) was given orally at a dose of 2 mg daily on days 1-28 of a 28-day cycle and dexamethasone was given orally at a dose of 40 mg daily on days 1, 8, 15, 22 of each cycle. Patient also received aspirin 325 mg once daily for thromboprophylaxis. The study endpoints were the response rate in patients taking pomalidomide plus dexamethasone including patients with lenalidomide resistant refractory multiple myeloma, and safety of Pomalidomide plus dexamethasone. Responses were recorded using the criteria of the International Myeloma Working Group. Thirty-eight patients achieved objective response (63%) including CR in 3 patients (5%), VGPR in 17 patients (28%), and PR in 18 patients (30%). The CR + VGPR rate was 33%. Grade 3 or 4 hematologic toxicity occurred in 23 patients (38%) and consisted of anemia in three patients (5%), thrombocytopenia in two patients (3%) and neutropenia in 21 (35%). Among those that developed grade 3 or 4 neutropenia, all first experienced the neutropenia in cycle 1-3; no new patients experienced grade 3/4 neutropenia in cycle 4 or later. The most common nonhematologic grade 3/4 toxicities were fatigue (17%) and pneumonia (8%). Other grade 3/4 non-hematological toxicities that occurred in less than 5% included diarrhea, constipation, hyperglycemia, and neuropathy. One patient (1.6%) had a thromboembolic event of deep vein thrombosis.

Lacy et al. have also demonstrated promising clinical activity of pomalidomide in myeloma patients with persistent disease following lenalidomide treatment. (37) CC-4047-MM-002 is a Celgene sponsored phase 1b/2 multi-center, randomized, open-label, dose escalation study that is evaluating the safety and efficacy of oral pomalidomide alone and in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma. (40)

Eligible patients must have received at least 2 prior regimens and all patients must have received prior treatment that includes lenalidomide and bortezomib. This study consists of a phase 1 single agent pomalidomide (maximum tolerated dose [MTD]) segment and phase 2 randomized (pomalidomide plus low-dose dexamethasone versus pomalidomide alone) segment. The MTD was 4 mg 21/28 days (there were 4 drug-related DLTs [grade 4 neutropenia] at 5 mg). Neutropenia and anemia were the most common grade 3/4 toxicities; there was a dose-dependent increase in grade 4 neutropenia. In the phase 2 arm, 221 patients who had all received prior lenalidomide and bortezomib, approximately 65% of who had multiple myeloma that was double-refractory to both lenalidomide and bortezomib (DRMM), were assigned to either pomalidomide 4mg (POM) or pomalidomide plus low dose dexamethasone (POM + LoDex) using the same 21 of 28 day dosing mentioned above . The study population was heavily pretreated, with a median of 5 prior lines of therapy. In preliminary results the response was deeper in the group receiving concurrent steroids with a 34% overall response rate (ORR; ≥ partial response (PR)) and 46% clinical benefit response rate (CBR; ≥ minimal response (MR)) [11]. The median progression free survival (PFS) in the POM + LoDex group was 4.6 months vs 2.6 in the POM alone group, median overall survival(OS) was 16.5 in the POM + LoDEX group vs 13.6 months for POM alone.

In addition, Leleu at al further investigated in a randomized phase II trial two different pomalidomide schedules – 4mg daily on 21/28 days or on 28/28 days – when used with dexamethasone in patients who had at best stable disease following treatment with bortezomib or lenalidomide. Their results showed similar efficacy across arms and that the regimen was well tolerated. This protocol will implement 4mg daily dosing on the 21/28 schedule.(39)

3.6 Clarithromycin (Biaxin®)

Various regimens are being studied combining pomalidomide with other anti-myeloma therapeutics beyond dexamethasone to capitalize on possible synergistic effects for increased potency while maintaining tolerability. Clarithromycin has immunomodulatory activity seen by down regulating IL-6 and activating NK cells, as well as direct pro-apoptotic effect (41-45). These effects overlap with those of pomalidomide providing rationale for possible synergy, this in addition to the efficacy of lenalidomide, clarithromycin and dexamethasone (BiRD) combination in the upfront setting led to the investigation of pomalidomide in combination with clarithromycin and dexamethasone (ClaPD) (46).

In a phase 2 trial 100 patients with relapsed MM who had been previously treated with lenalidomide and bortezomib were treated with ClaPD (47). Among all patients the ORR was 57% and the CBR was 66%. The ORR was not significantly different in patients refractory to lenalidomide (63%) or those with DRMM (54%). At last analysis the median PFS was 8.67 months. The duration of response does not appear to differ between patient with high risk and regular risk cytogenetics. The observed side effects were similar to those seen with pomalidomide and dexamethasone and consisted primarily of grade 3 and 4 hematologic events, there were 4 observed thromboembolic events despite daily low-dose (81mg) aspirin prophylaxis.

3.7 Rationale for Study of Autologous Stem Cell Transplant with Pomalidomide (CC-4047®) Maintenance versus Continuous Clarithromycin / Pomalidomide / Dexamethasone Salvage Therapy

While new anti-myeloma therapies such as bortezomib and immunomodulatory drugs have been developed, multiple myeloma remains an incurable malignancy. The majority of patients will experience relapse or develop disease refractory to currently available treatment, including treatment with thalidomide and lenalidomide. The prognosis and resultant clinical outcomes for myeloma patients who have relapsed or refractory disease is worse than those patients naïve to therapy, with lower response rate and shorter duration of response to each successive line of treatment. Given that achieving another remission will allow patients with relapsed/refractory multiple myeloma to obtain a higher quality of life and longer duration of freedom from disease symptoms, finding new strategies for treatment in this disease setting is imperative. Consolidation with a second course of high dose therapy with autologous or allogeneic stem cell support have been proposed as feasible strategies in this setting to improve long-term disease control. (38) Autologous stem cell transplant in this setting is associated with lower mortality rates and is available to a larger patient pool, but has never been studied in a prospective manner. (32-34)

Great strides have been made in the treatment of multiple myeloma leading to improved overall survival, however the disease remains incurable. As patients relapse after autologous stem cell transplant or become refractory to the novel agents lenalidomide and bortezomib, options for salvage therapy become limited and the optimal treatment strategy remains to be defined. Pomalidomide + Dexamethasone has been shown to have impressive response rates in initial phase 2 trials in both lenalidomide-naïve (overall response rate ~60%) and lenalidomide-refractory (overall response rate-40%) patients, with an overall progression free survival at about 3-6 months. (36,37) The combination of Clarithromycin, Pomalidomide, and Dexamethasone (ClaPD) has compared favorably to Pomalidomide + Dexamethasone alone, with a higher overall response rate and improved progression free survival (48). At this time, it is not known whether auto-SCT is superior to pomalidomide salvage for relapsed/refractory multiple myeloma (RRMM), or whether these therapies may supplement each other to achieve a prolongation of treatment response. The impact of pomalidomide monotherapy as maintenance post-transplant or after prolonged clarithromycin / pomalidomide / dexamethasone induction therapy is also unknown. We hereby propose a study of clarithromycin + pomalidomide + dexamethasone salvage therapy versus auto-SCT followed by pomalidomide maintenance to help answer these important questions and thereby define the roles of these therapies for patients with RRMM. This will be the first trial looking at the role of a second consolidation therapy with autologous stem cell support in the context of relapsed and refractory myeloma responding to novel agents.

4.0 OVERVIEW OF STUDY DESIGN/INTERVENTION

4.1 Design

This multicenter randomized phase II trial will investigate whether auto-SCT following four cycles of Clarithromycin/Pomalidomide/Dexamethasone has a sufficiently promising overall response rate (VGPR or greater) compared to 9 total cycles of Clarithromycin/Pomalidomide/Dexamethasone

therapy to warrant further consideration. The outcome will be assessed at nine months following study entry. A maximum of 36 patients will accrue in each arm. The anticipated duration of the trial is 36 months.

4.2 Intervention

Patients who sign informed consent, complete pretreatment evaluations, and meet all eligibility criteria may undergo computerized randomization into a treatment arm undergoing auto–SCT after 4 cycles of Clarithromycin/Pomalidomide/Dexamethasone treatment arm to be followed by pomalidomide maintenance (ARM A) versus treatment with up to 9 cycles of Clarithromycin/Pomalidomide/Dexamethasone to be followed by pomalidomide maintenance (ARM B). After initial randomization, all patients will receive clarithromycin, pomalidomide, and dexamethasone (ClaPD) in 28-day cycles according to the following schedule:

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

Pomalidomide (CC-4047) will be given orally at a dose of 4 mg daily beginning on day 1 and ending on day 21 of each 28-day cycle. Dosing will be at approximately the same time each day.

Clarithromycin (Biaxin®) will be given orally at a dose of 500 mg twice daily on days 1-28 of each 28-day cycle. The first dose of clarithromycin will be in the morning and the second dose will be in the evening at approximately the same times each day.

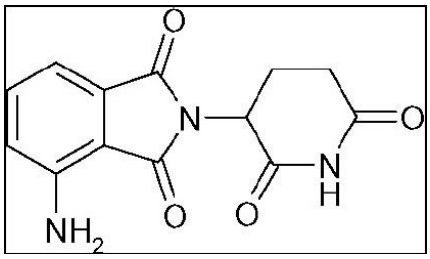
Treatment will be given for 4 complete 28-day cycles. If disease assessment at the end of 4 cycles shows no disease progression, the subjects in Arm A will then move onwards to autologous stem cell transplant, either outpatient or inpatient. Once adequate recovery has been achieved from stem cell transplant for subjects in Arm A, defined by recovery of blood counts to acceptable limits (ANC ≥ 1000 mm^3, platelets ≥ 50,000 /mm^3, and hemoglobin ≥ 8g/dL) and KPS ≥ 70 or ECOG $\leq$ 1, and an elapsed time of no sooner than 100 days post transplant, pomalidomide maintenance will begin. Pomalidomide will be given at a dose of 4mg daily for 21 days of a 28 day cycle. Maintenance therapy will be continued until 2 years have elapsed from study entry, there is progression of disease, or the regimen becomes intolerable for the patient, whichever occurs first.

For subjects in Arm B, if there has been no disease progression after 9 cycles of Clarithromycin/Pomalidomide/Dexamethasone, maintenance pomalidomide will be given at a dose of 4mg daily for 21 days of a 28 day cycle. Maintenance therapy will be continued until 2 years have elapsed from study entry, there is progression of disease, or the regimen becomes intolerable for the patient, whichever occurs first.

5.0 THERAPEUTIC/DIAGNOSTIC AGENTS

5.1. Investigational Agent: Pomalidomide (CC-4047)

Pomalidomide (CC-4047, 4-amino-2-(2,6-dioxo-3-piperidyl)isoindoline-1'-one)-1,3-dione, belongs to the IMiDs class of compounds. The Chemical Abstract Service (CAS) registry number for CC-4047 is 19171-19-8. The chemical structure of the active pharmaceutical ingredient (API) is as follows:



CC-4047 has an asymmetric carbon atom and can therefore exist as the optically active forms S (-) and R (+). CC-4047 is being developed as a racemate.

Clinical Pharmacology of Pomalidomide (CC-4047)

Mechanism of Action:

Pomalidomide is a novel immunomodulatory drug under development for the treatment of MM. Pomalidomide is a member of a class of pharmaceutical compounds known as immunomodulatory drugs (IMiDs). It shares a number of the beneficial pharmacologic properties of thalidomide and lenalidomide, but it is a more potent anti-proliferative immunomodulating agent than either drug. The pharmacodynamic properties of pomalidomide are of potential therapeutic benefit in the treatment of MM.

(CC-4047) is an analogue of thalidomide that, among other anti-tumor properties, on an equimolar basis in vitro, displays equivalent anti-angiogenic activity, about 8-fold greater activity in stimulation of apoptosis, at least 10-fold greater activity in inhibition of cellular COX-2 production and over 4,000-fold greater activity in inhibition of cellular

1. TNF-alpha production relative to thalidomide (Data on file: Celgene Corp.; Summit, NJ.)(*18*) CC-4047 has also been shown to stimulate antibody-dependent cytotoxic T-cell activity (ADCC).(*19*)

Dose and tolerability:

CC-4047 was safe at doses of up to 5 mg in a phase 1 single dose study in normal, healthy male volunteers and up to 5 mg QOD or 2 mg QD in a phase 1 multidose clinical study in subjects with relapsed or refractory multiple myeloma; DLTs seen in subjects receiving higher doses were predominantly hematopoietic (i.e., neutropenia), and lower grade, self-limited neutropenia was also seen in some of the 1 and 2 mg QD and 5 mg QOD recipients. In a multidose, phase 2 clinical study of subjects with prostate cancer, 2 mg QD dosing was well tolerated and, unlike the multiple myeloma subjects who received 1 and 2 mg QD doses, only an overall shift to lower neutrophil counts was noted. No clinically relevant neutropenic AEs were observed, and no grade 3 or 4 neutropenic events occurred. It is, therefore, likely that subjects with solid tumors that do not extensively involve the bone marrow will have a higher CC-4047 MTD than subjects with hematologic malignancies.

Supplier(s) Celgene Corporation will supply POMALYST® (pomalidomide, CC-4047) to study participants at no charge through Celgene's Pomalidomide Risk Evaluation and Mitigation Strategy (POMALYST REMS™).

Dosage form

CC-4047 will be supplied as 1.0 mg, 2.0 mg, 3.0 mg and 4 mg capsules for oral administration.

Packaging

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

Labeling

CC-4047 investigational supplies are dispensed to the patients in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: Caution: New drug - Limited by Federal law to investigational use. CC-4047 should not be handled by FCBP unless wearing gloves.

The study drug label must be clearly visible. Additional labels must not cover the Celgene label.

Receipt of study drug

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received, and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

Storage

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

Unused study drug supplies

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene. Patients will be instructed to return empty bottles or unused capsules to the clinic site.

Drug dispensing requirements

Pomalidomide (POMALYST®) will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers. Pomalidomide will be provided in accordance with the Celgene Corporation's POMALYST REMS™ program. Per the standard **POMALYST REMS™** program requirements, all physicians who prescribe pomalidomide for research subjects enrolled into this trial, and all research subjects enrolled into this trial, must be registered in and must comply with all requirements of the **POMALYST REMS™** program.

Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle. This is in accordance with the POMALYST REMS™ program.

Pregnancy Testing

Patients must follow pregnancy testing requirements as outlined in the POMALYST REMS™ program.

5.2 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.

5.3 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 CNS. Peak serum concentrations within 2 hours with a Tmax of 2-4 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. 500 mg tablets for oral administration will be obtained from the subject's local pharmacy.

5.4 Melphalan (Alkeran®)

Melphalan is commercially available and is the primary agent used for conditioning in autologous stem cell transplantation for multiple myeloma. It is a derivative of nitrogen mustard and classified as an alkylating agent. Melphalan intercalates within ribonucleic acid base pairs and thus interferes with DNA replication and transcription of RNA, leading to death in actively replicating cells. When used for ASCT, it is given intravenously. Melphalan is incompletely and erratically absorbed, has a prolonged plasma half-life, and is excreted largely unchanged in the urine. Intravenous melphalan results in very high plasma levels followed by an initial rapid decay curve (half-life 30-60 minutes). Most of the administered dose is recovered unchanged in the urine and the drug does not need to be metabolized to be active. The peak concentration achieved in the plasma is directly related to creatinine clearance (CrCl) and thus the dose is usually reduced in those patients with a CrCl < 70 cc/min.

5.5 Toxicities and Side Effects

Pomalidomide (CC-4047)

CC-4047 was safe at doses of up to 5 mg in a phase 1 single dose study in normal, healthy male volunteers and up to 5 mg QOD or 2 mg QD in a phase 1 multidose clinical study in subjects with relapsed or refractory multiple myeloma; DLTs seen in subjects receiving higher doses were predominantly hematopoietic (i.e., neutropenia), and lower grade, self-limited neutropenia was also seen in some of the 1 and 2 mg QD and 5 mg QOD recipients. In a multidose, phase 2 clinical study of subjects with prostate cancer, 2 mg QD dosing was well tolerated and, unlike the multiple myeloma subjects who received 1 and 2 mg QD doses, only an overall shift to lower neutrophil counts was noted. No clinically relevant neutropenic AEs were observed, and no grade 3 or 4 neutropenic events occurred. The MTD determined by the phase I/II trial of Pomalidomide in MM has been determined to be 4 mg. The trial is now enrolling to the phase II portion.

Low white blood cell count*, constipation, fatigue, dyspnea, pyrexia, diarrhea, thrombocytopenia*, anemia, nausea, pneumonia*, asthenia, back pain are likely. Dizziness, headache, chest pain, cough, pain in limb/extremity, myalgia, skin rashes, pruritus, peripheral edema, muscle cramps,

arthralgia, dry skin, hypoaesthesia, renal failure*, infection, pulmonary embolism, hypocalcemia, hypercalcemia, epistaxis, hypokalemia, hyperkalemia, tremor, increased sweating including at night, chills, vomiting, abdominal pain, dry mouth, muscle weakness, bone pain, dysgeusia, peripheral neuropathy, somnolence, decreased appetite, hyperglycemia, hyponatremia, dehydration, hypophosphataemia, vision blurred, hypertension, insomnia, confused, anxiety, atrial fibrillation*, depression, dysphonia, and nasal congestion are less likely. Deep vein thrombosis, febrile neutropenia, sepsis, tachycardia, pneumonitis, new cancer, cardiac failure, and hypersensitivity are rare but serious. Medications in the same family of medications of pomalidomide have demonstrated an increased risk of deep vein thrombosis (DVT) and pulmonary embolism (PE).

Dexamethasone (Decadron®)

Increased appetite, weight gain, sleep disturbance, high blood pressure, ankle swelling, bruising, susceptibility to infections, mood changes, slow wound healing, depression, and high blood sugar, which may lead to fatigue, weight loss, excessive thirst and frequent urination are likely. Loss of appetite, muscle twitching, increased thirst, frequent urination, increased sweating, diarrhea, nausea, headache, bone thinning, spinal fracture or fracture of bones, fast heart beats, fungal infections, and anxiety is less likely. Blurred vision, personality changes, decrease in potassium level in blood, swelling and/or redness of skin, allergic skin reactions, itching, hair growth, muscle weakness or loss of muscle mass, rupture of tendons, menstrual cycle disturbances, facial puffiness, leading to the appearance of a “moon face,” hormonal disturbances, hiccups, and high blood sugar are unlikely. Rare but serious effects include, stomach ulcers with bleeding that may cause bleeding, blood in the stool and abdominal pain, bowel perforation, irritation and bleeding of the esophagus, heart failure, allergic reaction that may lead to shortness of breath, abdominal cramps and low blood pressure, seizures, brain swelling, cataracts, glaucoma, pancreatic inflammation, abdominal swelling that may cause abdominal pain, clot in the legs or vessels of the lung, and aseptic necrosis of the hip.

Clarithromycin (Biaxin®)

Headaches, diarrhea, nausea, abnormal taste, heartburn and abdominal pain are common. Irregular blood counts, shortness of breath, hypoglycemia, anxiety, hallucinations, fast heartbeat, and tremors are rare.

Melphalan (Alkeran®)

The major common toxicity of melphalan is myelosuppression, which is dose-related. Other toxicities which occur occasionally at high-doses include nausea and vomiting, mucositis, and diarrhea. Antiemetics are therefore routinely given prior to and after administration, along with oral care to prevent and ameliorate mucositis, and anti-diarrheals as needed. Transient hepatic transaminase elevations are occasionally seen and rarely severe. All of the toxicities associated with melphalan are transient. There is the rare possibility that cataract formation, secondary malignancies, sterility, coronary artery disease, and hypothyroidism may occur.

Autologous Peripheral Blood Stem Cell Transplant

The volume of the peripheral blood stem cell (PBSC) infusate is approximately 800-1000cc for the average adult. Infusions of marrow may produce volume overload and subsequent pulmonary edema which can be prevented and treated by diuretic administration. Stem cell infusion is rarely associated with allergic reactions. Small, subclinical pulmonary emboli may occur, but these rarely if ever require any intervention. Rarely, renal failure due to hemoglobinuria can be seen. Standard pre-medications for blood products may be used before administration of the marrow graft, generally consisting of diphenhydramine or acetaminophen; in some cases, corticosteroids are given, especially if the patient has had allergic reactions to blood products in the past.

In very rare circumstances, an autologous stem cell graft may fail to engraft either as a primary failure to recover marrow function, manifested by failure of early recovery of myeloid and erythroid elements in the marrow, or as an abrupt onset of marrow hypoplasia during the posttransplant period. a) If ANC<0.2 x 10^9 on day 28 of the second transplant the patients will receive GM-CSF (instead of the usually received G-CSF that is given from Day 0 until engraftment) at a dose of 500 ug/m^2/day SC. If ANC <0.5 x 10^9 on day 35, the patient will receive re-infusion of backup stored stem cell product, if available. In addition, the GM-CSF will continue.

Blood Product Infusions

Infusions of fractionated blood products may produce volume overload, which can be managed with diuretics. They may also induce allergic reactions of variable severity, many of which can be prevented or mitigated by premedication with antipyretics, antihistamines, and corticosteroids. These products may also serve as vectors of serious infection [e.g., CMV, hepatitis, HIV]. To circumvent this, prospective blood donors will be screened for evidence of hepatitis B, HIV, HTLV-I/II and CMV infection. CMV will be prevented by WBC depletion. HIV[-] and hepatitis B_sAg[-] and C Ab [-] blood products determined by currently available serologic testing will be used at all times. All blood products are irradiated [3000r,^{137}Cs] to circumvent the risk of GvHD caused by contaminating lymphocytes in the transfused fractions.

Herpes Zoster Prophylaxis – Acyclovir / Valacyclovir

Either acyclovir or valacyclovir will be used for this indication. The serious risks involved with the use of acyclovir include seizure and renal failure, however these are rarely seen. More commonly, acyclovir has been associated with nausea / vomiting, diarrhea, headache, and rash. Valacyclovir has been rarely associated with renal failure, aplastic anemia, anaphylaxis, thrombotic thrombocytopenia purpura / hemolytic-uremic syndrome, psychosis, and seizure. More common side effects of valacyclovir that are seen include nausea / vomiting, abdominal pain, elevated liver function tests, and rash. Any subject sensitive to one of these agents may receive the other or no agent at all, at the discretion of the investigator.

G-CSF (filgrastim)

The only side effect observed frequently is bone pain. Mild hair thinning has been reported but the combination of chemotherapy and radiotherapy of the present program will cause universal alopecia. Splenomegaly has been rarely reported. Flare-up of pre-existing autoimmune diseases and psoriasis have also been reported.

6.0 CRITERIA FOR SUBJECT ELIGIBILITY

6.1 Subject Inclusion Criteria

1. Patients must have histologically or cytologically confirmed relapsed multiple myeloma as defined by the International Myeloma Working Group (IMWG).
2. Patients must have measurable disease as defined by the International Uniform Response Criteria, defined as any of the following:

    - serum M-protein of ≥ 500mg/dL
    - urine M-protein of ≥ 200mg/ 24 hours
    - involved free light chain ≥ 10mg/dL provided serum free light chain ratio is abnormal

3. Patients must have had a previous auto-SCT performed as part of a consolidation of an initial remission and had a remission, defined as a partial response or greater that lasted at least 12 months either on or off maintenance therapy without evidence of progression as defined by IMWG criteria.
4. Patients who are post auto-SCT as primary therapy must have received maintenance therapy with lenalidomide.
5. Patients must be registered within 6 months of last dose of lenalidomide.
6. Minimum of 3 months of maintenance therapy prior to disease progression.
7. Age $\geq$18 years.
8. Life expectancy of $\geq$12 weeks.
9. KPS $\geq$ 70 or ECOG $\leq$ 1 (Appendix IV)
10. Patients must have adequate organ and marrow function as defined below:
    - ANC $\geq$750/μL
    - Platelets $\geq$50,000/μL
    - Total bilirubin $\leq$ 1.5 mg/dL
    - AST(SGOT) $\leq$ 3 X upper limit of normal.
    - ALT(SGPT) $\leq$ 3 X upper limit of normal.
    - Cardiac Ejection Fraction $\geq$ 40%
    - Serum Creatinine $\leq$ 2.0 mg/dL
11. Patients must have an adequate number of CD34+ stem cells collected to allow for transplantation (defined as $\geq 2x10^6$ CD34+ cells / kg body weight). If not previously collected and stored or if previous collection was inadequate, the patient must be willing to undergo stem cell mobilization and collection as per standard practice.
12. Patients who participate in this study must be willing and able to tolerate prophylactic anticoagulation either with aspirin, low-molecular weight heparin (LMWH), or warfarin.
13. Ability to understand and the willingness to sign a written informed consent document.
14. Patient must be determined fit to undergo auto–SCT procedure by a study physician.

Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to prescribing pomalidomide (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 pomalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure.

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

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†

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

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

6.2 Subject Exclusion Criteria

1. Patients who have had myeloma therapy within 14 days prior to entering the study or those who have not recovered from adverse events due to agents administered more than 2 weeks earlier. Patients may have received bisphosphonate therapy or radiation therapy as part of routine myeloma care at any time prior to study entry.
2. Patients may not be receiving any other investigational agents.
3. Any prior use of thalidomide or pomalidomide.
4. History of allergic reactions attributed to compounds of similar chemical or biologic composition to lenalidomide (including thalidomide), clarithromycin, or melphalan.
5. Known prior positivity for active HIV or infectious hepatitis, type B or C.
6. Uncontrolled illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure (See Appendix III), unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
7. Pregnant and lactating women are excluded from the study because the risks to an unborn fetus or potential risks in nursing infants are unknown.
8. History of thrombosis or thromboembolic event within last 30 days prior to study entry.
9. Patients with CNS involvement.

7.0 RECRUITMENT PLAN

The anticipated time for completion of this trial is about 36 months. 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 be enrolled at the following sites in addition to MSKCC: Weill Cornell Medical College, RutgersCancer Institute of New Jersey, SUNY Upstate and North Shore University Hospital. It is expected MSKCC will accrue 24 and 48 amount of patients will be accrued at other centers.

8.0 PRETREATMENT EVALUATION

8.1 Screening (All patients, prior to randomization)

The patient will receive an extensive medical evaluation within 45 days prior to treatment. This evaluation includes:

- Complete medical history, including prior lines of anti-myeloma therapy.
- Physical exam, KPS/ECOG, vital signs, weight
- CBC with differential and platelet count

- Comprehensive metabolic profile (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)
- Serum protein electrophoresis, serum immunofixation, and quant immunoglobulins
- Serum free light chains
- Beta-2 microglobulin
- HIV 1 PCT, quantitative and HIV 1 & 2 antibodiesHepatitis B surface antibody, Hepatitis B core ab (total), Hepatitis B surface antigen, Hepatitis C antibody, and Hepatitis C PCR, quantitative
- 24- hour urine for urine total protein (UTP), urine protein electrophoresis (UPEP), and urine immunofixation (UIF)
- Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). **Pregnancy tests must occur 10 – 14 days and again within 24 hours prior to initiation of pomalidomide.**
- Skeletal survey, spine MRI, or whole body PET/CT scan
- Bone marrow aspirate and biopsy with cytogenetic testing (karyotyping and myeloma FISH panel).
- Concomitant medication review
- Electrocardiogram
- LV ejection fraction by MUGA, echocardiogram, or MRI according to local institutional standards.
- Toxicity assessment

*****Note: Patients randomized to Arm A for auto-SCT will have pre-transplant evaluations as indicated in section 10.2.1.**

9.0 TREATMENT/INTERVENTION PLAN

Patients who sign informed consent, complete pretreatment evaluations, and meet all eligibility criteria will undergo computerized randomization into a treatment arm undergoing autologous stem cell transplant after 4 cycles of ClaPD treatment arm to be followed by pomalidomide maintenance (ARM A) versus treatment with up to 9 cycles of ClaPD to be followed by pomalidomide maintenance (ARM B). Details outlined below.

9.1 Clarithromycin/Pomalidomide/Dexamethasone (ClaPD) Induction (ALL PATIENTS ARM A and B)

After initial randomization, all patients will receive clarithromycin, pomalidomide and dexamethasone (ClaPD) in 28-day cycles (+/- 3 days) according to the following schedule:

Dexamethasone (Decadron®) will be given orally at a dose of 40 mg on days 1, 8, 15, and 22 of each 28 day cycle, supplied as 4 mg tablets.

Pomalidomide (CC-4047) will be given orally at a dose of 4 mg daily beginning on day 1 and ending on day 21 on each 28-day cycle. Dosing will be at approximately the same time each day.

Clarithromycin (Biaxin®) will be given orally at a dose of 500 mg twice daily on days 1-28 of each 28 day cycle, supplied as 500 mg tablets.

Treatment will be given for 4 complete 28-day cycles. If disease assessment at the end of 4 cycles shows no disease progression, the subjects in Arm A will then move onwards to autologous stem cell transplant as described in section 9.2. Subjects in Arm B will continue on ClaPD as described in section 9.3.

Pomalidomide capsules should be swallowed whole, and should not be broken, chewed or opened. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal.

If a dose of pomalidomide 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 pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Day One Dosing Guidelines

On day 1 of therapy, the patient will take Dexamethasone at a dose of 40mg once and Pomalidomide at a dose of 4mg once. Clarithromycin will be taken at a dose of 500mg in the morning and again at a dose of 500mg in the evening. The patient will also be directed to take the following prophylactic medications daily: 1) aspirin at a dose of 325 mg once or per investigator discretion; 2) a proton pump inhibitor (e.g omeprazole).

9.2 Patients Randomized to Arm A

High Dose Melphalan and Autologous Stem Cell Transplant (Arm A)

Two to four weeks after the last dose of cycle 4 of ClaPD, patients in arm A can proceed to autologous SCT as long as they are deemed fit for this procedure by the institutional PI. In no case should a patient with the following conditions proceed to SCT on protocol:

1) Progressive disease
2) Active uncontrolled infection
3) Active uncontrolled arrhythmia or pulmonary dysfunction
4) Creatinine > 2.0 mg/dl

High dose melphalan will be administered at a dose of 140 mg/m^2 or 200 mg/m^2 according to institutional guidelines. Both single dose administration on day -2 or split dose administration on days -2 and -1 prior to stem cell infusion of 70 mg/m^2 or 100mg/m^2 of intravenous melphalan are acceptable. After a period of 24-72 hours has elapsed from the last melphalan dose (designated as Day 0) each patient will receive infusion of at least 2.0 x 10^6/kg of autologous $CD34^+$ stem cells. All patients will be treated according to institutional standard of care autologous stem cell transplant procedures.

All patients will also receive prophylactic antibiotics, antivirals, and antifungals as per usual institutional transplant protocol. Patients will receive full transfusion support at the discretion of the transplant treatment team.

Pomalidomide Maintenance (Arm A)

Once adequate recovery has been achieved from stem cell transplant, defined by recovery of blood counts to acceptable limits (ANC ≥ 1000 mm^3, platelets ≥ 50,000 /mm^3, and hemoglobin ≥ 8g/dL) and KPS ≥ 70 or ECOG $\leq$ 1, and an elapsed time of no sooner than 100 days post transplant, pomalidomide maintenance will begin. Pomalidomide will be given at a dose of 4mg daily for 21 days of a 28 day cycle as depicted in the study schema, section 1.0. Maintenance therapy will be continued until 2 years have elapsed from study entry, there is progression of disease, or the regimen becomes intolerable for the patient, whichever occurs first.

9.3 Patients Randomized to Arm B, No-SCT

Clarithromycin / Pomalidomide / Dexamethasone (ClaPD) induction for 9 cycles (Arm B)

After initial randomization, all patients will receive clarithromycin, pomalidomide, and dexamethasone (ClaPD) in 28-day cycles according to the following schedule:

Dexamethasone (Decadron®) will be given orally at a dose of 40 mg on days 1, 8, 15, and 22 of each 28 day cycle, supplied as 4 mg tablets.

Pomalidomide (CC-4047) will be given orally at a dose of 4 mg daily beginning on day 1 and ending on day 21 on each 28-day cycle. Dosing will be at approximately the same time each day.

Clarithromycin (Biaxin®) will be given orally at a dose of 500 mg twice daily on days 1-28 of each 28 day cycle, supplied as 500 mg tablets.

Treatment will be given for 9 complete 28-day cycles. If disease assessment at the end of 4 cycles shows no disease progression, the subjects in Arm B will then move onwards to receive 5 additional cycles of ClaPD.

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

If a dose of pomalidomide 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 pomalidomide should be instructed to seek emergency medical care if needed and contact study staff immediately.

Patients Randomized to Arm B, No-SCT- Pomalidomide Maintenance:

If there has been no disease progression after 9 cycles of ClaPD, maintenance pomalidomide will be given at a dose of 4mg daily for days 1 through 21 of a 28 day cycle as depicted in the study schema, section 1.0. Maintenance therapy will be continued until 2 years have elapsed from study entry, there is progression of disease, or the regimen becomes intolerable for the patient, whichever occurs first.

9.4 Instructions 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) ≥1000 cells/mm³
- Platelets count ≥ 50,000/mm³
- Any 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. The evaluation will consist of a CBC; this may be done at an outside facility. Once the ANC and Platelet counts result, a member of the clinical staff will review the counts and contact the patient with instructions to either begin treatment or if they need labs the following week.

With the exception of the CBC as indicated above, the Day 1 testing required per protocol does not need to be repeated weekly if a cycle is delayed as long as it was completed on the presumed Day 1

of treatment. If the patient is of childbearing potential the assessments will be altered per the pregnancy testing evaluation per the Pomalyst REMS program.

If the toxicity does not resolve within four weeks, the patient will be taken off the study. If the dosing of pomalidomide or dexamethasone was halted or held during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle.

If the dosing of clarithromycin, pomalidomide, or dexamethasone was omitted or skipped 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 Table 3.

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

9.8 DOSING DELAYS/DOSE MODIFICATIONS

Dose Modification

Doses of study medications will be modified for toxicity as listed below. 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.

9.8.1 Dexamethasone:

Dexamethasone doses will be modified due to toxicity as follows:

- Original dose Level: Dexamethasone 40 mg po on days 1,8,15,and 22.
- Dose level -1: Dexamethasone 20 mg po on days 1,8,15,and 22.
- Dose level -2: Dexamethasone 20 mg po on days 1 and 15.

Table 2: Dose Modification Guidelines for Dexamethasone:

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

Toxicity	**NCI CTCAE 4.0 Toxicity Grade**	**Action**
Dyspepsia	≥ Grade 3	• Hold (interrupt) dexamethasone until ≤ grade 1 • Reduce dexamethasone by 1 dose level and restart
Gastritis, gastric or duodenal ulcer	≥ Grade 3	• Hold (interrupt) dexamethasone until ≤ grade 1 • Reduce dexamethasone by 1 dose level and restart
Edema	≥ Grade 3	• Reduce dexamethasone by 1 dose level

		• Use diuretics as needed
Confusion or mood alternations	≥ Grade 2	• Hold (interrupt) dexamethasone until ≤ grade 1 • Reduce dexamethasone by 1 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 (interrupt) drug(s) attributed to toxicity for remainder of cycle. Reduce drug(s) attributed to toxicity by 1 dose level.
Grade 2 toxicity deemed clinically relevant per the treating physician	Grade 2	• Attribute toxicity to one or more drugs. •Hold (interrupt) dexamethasone until ≤ grade 1 . Restart Clarithromycin at the current dose level.

9.8.2 Pomalidomide

Pomalidomide doses will be modified due to toxicity as follows:

- Original dose level: Pomalidomide 4 mg/day PO
- Dose level -1: Pomalidomide 3 mg/day PO
- Dose level -2: Pomalidomide 2 mg /day PO
- Dose level -3: Pomalidomide 1 mg/day PO

Table 3: Dose Modifications Guidelines for Pomalidomide:		
NCI CTCAE 4.0 Toxicity Grade	**Onset Day 2-14 of Cycle**	**Onset ≥ Day 15 of Cycle**
Grade 3 neutropenia associated with fever	• Hold (interrupt)	• Omit pomalidomide for

Table 3: Dose Modifications Guidelines for Pomalidomide:		
NCI CTCAE 4.0 Toxicity Grade	**Onset Day 2-14 of Cycle**	**Onset ≥ Day 15 of Cycle**
(temperature ≥ 38.5º C) or Grade 4 neutropenia	pomalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the pomalidomide dose maintained	remainder of cycle • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level. If neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the pomalidomide dose maintained for the next cycle at the investigators discretion.
Thrombocytopenia ≥Grade 3 (platelets < 50,000/mm³)	• Hold (interrupt) pomalidomide dose. • Follow CBC weekly. • If thrombocytopenia resolves to ≤ grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle.	• Omit pomalidomide for remainder of cycle • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level.
Non-blistering rash **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) pomalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle. • Discontinue pomalidomide. Remove patient from study.	• Omit pomalidomide for remainder of cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level. • Discontinue pomalidomide. Remove patient from study.
Desquamating (blistering) rash- any Grade	• Discontinue pomalidomide. Remove patient from study.	• Discontinue pomalidomide. Remove patient from study.

Table 3: Dose Modifications Guidelines for Pomalidomide:		
NCI CTCAE 4.0 Toxicity Grade	**Onset Day 2-14 of Cycle**	**Onset ≥ Day 15 of Cycle**
Neuropathy **Grade 3**	• Hold (interrupt) pomalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 (or to baseline at study entry) prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle.	• Omit pomalidomide for the remainder of the cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level.
Grade 4	• Discontinue pomalidomide. Remove patient from study.	• Discontinue pomalidomide. Remove patient from study.
Venous thrombosis/embolism **≥ Grade 3**	• Hold (interrupt) pomalidomide and start anticoagulation; restart pomalidomide at investigator's discretion (maintain dose level).	• Omit pomalidomide for remainder of cycle and start anticoagulation.
other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) pomalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle.	• Omit pomalidomide for remainder of cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level.
Hyperthyroidism or hypothyroidism	• Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level.	• Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level.
Grade 2 toxicity deemed clinically	• Hold (interrupt) pomalidomide dose. Follow	• Omit pomalidomide for

Table 3: Dose Modifications Guidelines for Pomalidomide:		
NCI CTCAE 4.0 Toxicity Grade	**Onset Day 2-14 of Cycle**	**Onset ≥ Day 15 of Cycle**
relevant per the treating physician	at least weekly. • If the toxicity resolves to <grade 2 prior to Day 21, restart pomalidomide at the current dose level	remainder of cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level.

9.8.3 Clarithromycin

Clarithromycin doses will be modified due to toxicity as follows:

- Original dose level: 500mg PO twice daily
- Dose level -1: 250mg PO twice daily
- Dose level -2: 250mg PO once daily
- Dose level -3: 250mg PO on odd days of a 28-day cycle
- Dose level -4: discontinue drug

Table 2: Dose Modification Guidelines for Clarithromycin:

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

Toxicity	**NCI CTCAE 4.0 Toxicity Grade**	**Action**
Dysgeusia	≥ Grade 3	• Hold (interrupt) clarithromycin until ≤ grade 1 • Reduce clarithromycin by 1 dose level and restart
Thrush	≥ Grade 3	• Hold (interrupt) clarithromycin until ≤ grade 1 • Reduce clarithromycin by 1 dose level and restart
Other non-hematologic toxicity assessed as treatment-related	≥ Grade 3	• Attribute toxicity to one or more drugs. Hold (interrupt) drug(s) attributed to toxicity for remainder of cycle. Reduce drug(s) attributed to toxicity by 1 dose level.

Grade 2 toxicity deemed clinically relevant per the treating physician	Grade 2	• Attribute toxicity to one or more drugs. •Hold (interrupt) clarithromycin until ≤ grade 1 . Restart Clarithromycin at the current dose level.

10.0 EVALUATION DURING TREATMENT/INTERVENTION

For Cycle 1, patients will be followed in clinic every week having blood test evaluations and toxicity assessments. In subsequent cycles, patients will be evaluated on Day 1 (+/- 3 days). During scheduled study visits patients will undergo the following evaluations for assessment of response and toxicity (depicted in Table 1 and 2, Schedule of Assessments). Study-related testing may be performed at an outside institution. All records of study-related testing done outside the treating institution must be documented in the patient's medical record.

Pregnancy Testing

Patients must follow pregnancy testing requirements as outlined in the POMALYST REMS™ program.

During the first cycle of treatment, females of childbearing potential (FCBP) must have a pregnancy test with a sensitivity of at least 25 mIU/dL done by the doctor every week for the first 28 days. Thereafter, females of childbearing potential will then have a pregnancy test every 28 days if they have regular or no menstrual cycles or every 14 days if they are irregular FCBP may also need to have a pregnancy test if a period is missed or if there is unusual menstrual bleeding. FCBP will have additional pregnancy tests at discontinuation of study drugs and at Day 28 after discontinuation of study drugs (FCBP with irregular menstrual cycles will also have a pregnancy test at Day 14 after discontinuation of study drugs).

Evaluation of the Primary Endpoint

The primary endpoint, overall response (VGPR or greater) will be evaluated nine months after start of treatment according to International Uniform Response Criteria (Appendix I). This is in accordance with assessments that are complete on a monthly basis (SPEP, IF, quantitative immunoglobulins, serum free light chains, 24-hour urine for UTP, UPEP, and UIF).

Response data will be collected after 4 cycles of treatment and at nine months after start of treatment for both study arms. Patients on Arm A have a +/- 2 week window for overall response assessments due at 9 months. Patients on Arm B will have a +/- 3 day window as indicated in Table 2 Schedule of Assessments. Response will be assessed per Appendix I: Criteria for Response. Once patients are on pomalidomide maintenance, response data will be collected every 3 months (+/- 2 weeks).

Table 1: Schedule of Assessments, ARM A

TEST	Screening (≤ 45 days prior to start date)	Induction Cycle 1, Day 1 (+/- 3 days)	Induction Cycle 1 Day 8, 15, 22 (+/- 3 days)	Induction Cycles 2, 3, 4 Day 1 (+/- 3 days)	≤ 4 weeks prior to the initiation of high-dose melphalan	Day+28 (+/- 4 days), Day + 56 (+/- 4 days) visits (after auto-SCT)	9 Months (+/- 2 weeks)	Maintenance: Cycle 1, Day 1 (+/- 3 days)	Maintenance: Cycle 1 Days 8, 15, 22, (+/- 3 days)	Maintenance: Day 1 all other Cycles, starting Cycle 2 (+/- 3 days)	End of Study
Complete medical history, including prior lines of anti-myeloma therapy	X				X						
Physical exam, history, KPS/ECOG, vital signs, weight	X	X		X	X	X		X		X	X
CBC with differential and platelet count	X	X	X	X	X	X		X	X	X	X
Comprehensive metabolic profile[2]	X	X	X	X	X	X		X	X	X	X
Generate / review new drug diary		X		X				X		X	
Collect / review prior drug diary				X				X		X	X
SPEP, IF, quant immunoglobulins[1] and serum free light chains	X	X		X	X	X	X	X		X	X
HIV 1 PCR, quantitative and HIV 1 & 2 antibodies	X										
Hepatitis B surface antibody, Hepatitis B core ab (total), Hepatitis B surface antigen, Hepatitis C antibody, and Hepatitis C PCR, quantitative	X										
Urinalysis					X						
24-hour urine for UTP, UPEP, UIF[1]	X	X		X	X	X	X	X		X	
β_2M[1]	X[1]										

Pregnancy Testing, education, and counseling[3]	X	X		X	X[7]	X		X	X	X	X
Skeletal survey, spine MRI, or whole body PET/CT scan	X			X[4]						X[4]	
Bone marrow biopsy and aspirate	X			X[4]			X[4]			X[4]	
Concomitant medication review	X	X		X		X		X		X	X
Electrocardiogram	X				X						
Drug dispensation and drug accountability		X		X				X		X	X
Toxicity Assessment[5]	X	X	X[8]	X				X		X	X
LV ejection fraction by MUGA, echocardiogram, or MRI according to local institutional standards	X				X						
Pulmonary function testing, including spirometry and diffusion capacity					X						
Dental clearance					X						
Blood type and screen					X						
Infectious disease testing including hepatitis panel[6]					X						
Coagulation profile					X						
Chest X-Ray					X						
24 hour urine for creatinine clearance					X						
Register to POMALYST REMS™ program	X										

1. 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.
3. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur 10 – 14 days and again within 24 hours prior to initiation of CC-4047. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 28 days while on therapy (including breaks in therapy); at discontinuation of CC-4047 and at Day 28 post the last dose of CC-4047. Females with irregular menstruation must have a pregnancy test weekly for the first 4 weeks and then every 14

days while on therapy (including breaks in therapy), at discontinuation of CC-4047 and at Day 14 and Day 28 post the last dose of CC-4047 Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program.

4. To confirm complete remission or when clinically indicated
5. Toxicity assessments must be completed at least once per cycle, but may be assessed on a continuous basis as clinically indicated. Toxicity assessments must include start date, stop date, grade, and attribution to the study regimen as per CTCAE 4.0. During the induction phase, patients will be assessed for ≥ grade 3 toxicities, except for mood alterations which should be documented ≥ grade 2. Patients randomized to SCT will only have unexpected AEs recorded as per Appendix VIII. Patients on maintenance therapy will be assessed for ≥ grade 3 toxicities, except for mood alterations which should be documented ≥ grade 2.
6. , Hep B Sag, HepB Core Ab, HepC Ab), syphilis, Toxoplasmosis AB, EBV AB, VZV, and HIV 1 & 2 Antibodies, HTLV- I/II antibodies. Cytomegalovirus Ab, HSV.
7. Within 7 days for females of childbearing potential)
8. This may be a nursing visit

Table 2: Schedule of Assessments, ARM B

TEST	Screening (≤ 45 days prior to start date)	Induction: Cycle 1, Day 1 (+/- 3 days)	Induction: Cycle 1 Day 8, 15, 22 (+/- 3 days)	Induction: Cycles 2-9 Day 1 (+/- 3 days)	Maintenance: Cycle 1, Day 1 (+/- 3 days)	Maintenance: Cycle 1 Days 8, 15, 22(+/- 3 days)	Maintenance: Day 1 all other Cycles, starting Cycle 2 (+/- 3 days)	End of Study
Complete medical history, including prior lines of anti-myeloma therapy	X							
Physical exam, history, KPS/ ECOG, vital signs, weight	X	X		X	X		X	X
CBC with differential and platelet count	X	X	X	X	X	X	X	X
Comprehensive metabolic profile[2]	X	X	X	X	X	X	X	X
Generate / review new drug diary		X		X	X		X	
Collect / review prior drug diary				X	X		X	X
SPEP, IF, quant immunoglobulins[1] and serum free light chains	X	X		X	X		X	X
HIV 1 PCR, quantitative and HIV 1 & 2 antibodies	X							
Hepatitis B surface antibody, Hepatitis B core ab (total), Hepatitis B surface antigen, Hepatitis C antibody, and	X							

Hepatitis C PCR, quantitative								
24-hour urine for UTP, UPEP, UIF[1]	X	X		X	X		X	
β_2M[1]	X[1]							
Pregnancy Testing, education, and counseling[3]	X	X		X	X	X	X	X
Skeletal survey, spine MRI, or whole body PET/CT scan	X			X[4]			X[4]	
Bone marrow biopsy and aspirate	X			X[4]			X[4]	
Concomitant medication review	X	X		X	X		X	X
Electrocardiogram	X							
LV ejection fraction by MUGA, echocardiogram, or MRI according to local institutional standards	X							
Drug dispensation and drug accountability		X		X	X		X	X
Toxicity Assessment[5]	X	X	X[6]	X	X		X	X
Register to POMALYST REMS™ program	X							

1. 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.
3. Pregnancy tests for females of childbearing potential. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months). Pregnancy tests must occur 10 – 14 days and again within 24 hours prior to initiation of CC-4047. FCBP with regular or no menstruation must have a pregnancy test weekly for the first 4 weeks and then every 28 days while on therapy (including breaks in therapy); at discontinuation of CC-4047 and at Day 28 post the last dose of CC-4047. Females with irregular menstruation must have a pregnancy test weekly for the first 4 weeks and then every 14 days while on therapy (including breaks in therapy), at discontinuation of CC-4047 and at Day 14 and Day 28 post the last dose of CC-4047 Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program.
4. To confirm complete remission or when clinically indicated
5. Toxicity assessments must be completed at least once per cycle, but may be assessed on a continuous basis as clinically indicated. Toxicity assessments must include start date, stop date, grade, and attribution to the study regimen as per CTCAE 4.0. During the induction phase, patients will be assessed for $\geq$ grade 3 toxicities, except for mood alterations which should be documented $\geq$ grade 2. Patients on maintenance therapy will be assessed for $\geq$ grade 3 toxicities, except for mood alterations which should be documented $\geq$ grade 2.
6. This may be a nursing visit.

10.1 Clarithromycin / Pomalidomide / Dexamethasone Treatment (Arms A and B):

10.1.1 Clarithromycin / Pomalidomide / Dexamethasone Day 1, Cycle 1 (+/- 3 days)

- Physical evaluation: A complete medical evaluation including history and physical, vital signs, ECOG/KPS, and weight.
- Concomitant medication review
- 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, Phosphorus, uric acid, Magnesium)
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulins, and serum free light chains studies.
- Drug diary generated and reviewed with patient
- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program.Toxicity assessment using CTCAE 4.0 (≥ grade 3, except for mood alterations which should be documented ≥ grade 2)

7. 24-hour urine for UTP, UPEP, UIF (UTP = urine total protein; UPEP = urine protein electrophoresis; UIF = urine immunofixation)

10.1.2 Clarithromycin / Pomalidomide / Dexamethasone Days 8, 15, 22, Cycle 1 (+/- 3 days)

- 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, Phosphorus, uric acid, Magnesium)
- Toxicity assessment using CTCAE 4.0 (≥ grade 3, except for mood alterations which should be documented ≥ grade 2)

10.1.3 Clarithromycin / Pomalidomide / Dexamethasone Day 1 (All other cycles, starting Cycle 2), (+/- 3 days)

- Physical evaluation: A complete medical evaluation including history and physical, vital signs, ECOG/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, LDH, Phosphorus, uric acid, Magnesium)

- Prior cycle drug diary will be collected and reviewed. New drug diary will be generated and reviewed with the patient.

- 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.

- Concomitant medication review

- Toxicity assessment using CTCAE 4.0 (≥ grade 3, except for mood alterations which should be documented ≥ grade 2)

- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program.Bone marrow aspiration and biopsy to confirm a CR, or when clinically indicated.

- Skeletal survey, spine MRI or whole body PET/CT scan to confirm a CR or when clinically indicated.

- Response data will be collected after 4 cycles of treatment and at 9 months for both study arms. Patients on Arm A have a +/- 2 week window for overall response assessments due at 9 months. Patients on Arm B will have a +/- 3 day window as indicated in Table 2 Schedule of Assessments. Response will be assessed per Appendix I: Criteria for Response.

10.2 Autologous Stem Cell Transplant (Arm A only):

10.2.1 Evaluation Prior to Autologous Stem Cell Transplant

The following observations must be determined **≤ 4 weeks prior to initiation of high-dose melphalan**.

- EKG
- LV ejection fraction by MUGA, echocardiogram, or MRI according to local institutional standards.
- Pulmonary function testing, including spirometry and diffusion capacity

- Dental clearance (written documentation of dental inspection by dentist indicating no active infections or need for tooth extraction)

- Blood type and screen

- Infectious disease testing including hepatitis panel (, Hep B Sag, HepB Core Ab, HepC Ab), syphilis, Toxoplasmosis AB, EBV AB, HSV, VZV, and HIV 1 & 2 Antibodies, HTLV- I/II antibodies. Cytomegalovirus Ab.
- History, physical examination, performance status (ECOG/KPS), height and weight.
- CBC with differential and platelet count
- Comprehensive metabolic panel (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, Phosphorous, Magnesium)
- Coagulation profile
- Urinalysis
- 24 hour urine for creatinine clearance, UTP, UPEP, UIF
- Chest x-ray
- SPEP, IF, quant immunoglobulins and serum free light chains
- HCG (**within 7 days** for females of childbearing potential)

10.2.2 Day+28 (+/- 4 days) and Day + 56 (+/- 4 days) visits (after autologous stem cell transplant)

- Complete blood count (CBC) with differential and platelets
- 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, Phosphorous, Magnesium)
- 24-hour urine collection for total protein, protein electrophoresis, and immunofixation.
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulins, and serum free light chains studies.
- Physical examination with history, vital signs, and performance status
- Concomitant medication use review
- Serum pregnancy test (for females of childbearing potential)

10.3 Pomalidomide Maintenance Therapy (Arms A and B):

Treatment with maintenance pomalidomide will begin at least 100 days post autologous stem cell transplant and when adequate transplant recovery has been achieved in Arm A or after 9 cycles of Clarithromycin / Pomalidomide / Dexamethasone treatment in Arm B. Maintenance therapy will be continued until 2 years have elapsed from study entry, disease relapse, or intolerability of the regimen, whichever occurs first. Once patients are on pomalidomide maintenance, response data will be collected every 3 months (+/- 2 weeks).

10.3.1 Pomalidomide Maintenance Day 1, Cycle 1

- Physical evaluation: A complete medical evaluation including history and physical, vital signs, ECOG/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, LDH, Phosphorus, uric acid, Magnesium)
- 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.
- Drug diary generated and reviewed with patient
- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program.
- Concurrent medication use review
- Toxicity assessment using CTCAE 4.0 (≥ grade 3, except for mood alterations which should be documented ≥ grade 2)

10.3.2 Pomalidomide Maintenance 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, LDH, Phosphorus, uric acid, Magnesium)
- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program.

10.3.3 Pomalidomide Maintenance Day 1 (All other cycles, starting Cycle 2), (+/- 3 days)

- Physical evaluation: A complete medical evaluation including history and physical, vital signs, ECOG/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, LDH, Phosphorus, uric acid, Magnesium)
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulins, and serum free light chain studies

- Females of reproductive potential must adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program.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.
- Concomitant medication use review
- Toxicity assessment using CTCAE 4.0 (≥ grade 3, except for mood alterations which should be documented ≥ grade 2)
- Skeletal survey, spine MRI, or whole body PET/CT scan may be completed to confirm complete remission or when clinically indicated.
- Bone marrow biopsy and aspirate may be completed to confirm complete remission or when clinically indicated.

10.4 End of Study (Arms A and B), (within 30 days after last study treatment or until treatment related toxicities resolve)

- Physical examination with history, vital signs, KPS/ECOG, and weight
- Complete blood count (CBC) with differential and platelets
- 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, Phosphorous, Magnesium)
- Collect and review prior drug diary
- Serum protein electrophoresis, serum immunofixation, serum quantitative immunoglobulins, and serum free light chains studies.
- Concomitant medication use review
- Serum pregnancy test (for females of childbearing potential)
- Toxicity assessment using CTCAE 4.0 (≥ grade 3, except for mood alterations which should be documented ≥ grade 2)

10.5 Treatment Compliance

At all times, when dispensing study drug, research center personnel will review the instructions with subjects. Subjects will be asked to maintain a diary to record the drug administration. Subjects will be asked to bring any unused study drug to the research center at their next visit. Unused pomalidomide will be returned to the investigational pharmacy.

10.6 Post study follow-up

Patients will be followed until 30 days off treatment or until treatment related toxicities resolve, whichever occurs first.

11.0 TOXICITIES/SIDE EFFECTS

Side effects common to all transplant procedures include:

Likely

- Nausea and vomiting
- Mouth sores
- Diarrhea
- Poor appetite.
- Weight loss
- Low red cell count requiring red cell transfusions
- Low platelet count increasing risk of bleeding and requiring platelet transfusions.
- Weakened immune system with risk of viral, bacteria or fungal infection
- Some degree of graft versus host disease: Graft-versus-host disease (GVHD) is a frequent problem after unrelated donor transplantation. GVHD can cause skin rashes, nausea, vomiting, severe diarrhea and liver problems.
- GVHD can occur as an early (acute form) or late chronic form. Chronic GVHD involves problems with the eyes, mouth, lips, throat and liver.

Possible

- Recurrence of the original malignancy
- Reversible damage to heart, lung, liver and kidney

Unlikely

- Poor graft function and failure of the donor cells to work properly.
- Severe irreversible liver, heart, kidney or lung failure.
- Serious uncontrolled infection.

Infusional Toxicities Include:

Likely

- Changes in heart rate and/or rhythm
- Changes in blood pressure
- Fever
- Chills
- Sweats
- Headache

Unlikely

- Nausea

- Vomiting,
- Diarrhea
- Abdominal cramping

Extremely Rare

- Hemoglobinuria (blood in the urine)
- Acute renal failure
- Allergic reactions
- Respiratory dysfunction

12.0 CRITERIA FOR THERAPEUTIC RESPONSE/OUTCOME ASSESSMENT

Patients' disease status at specific time points will be evaluated based on the International Uniform Response Criteria. All disease responses will be relative to the established baseline disease status at randomization.

International Uniform Response Criteria

Stringent Complete Response (sCR):

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

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

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

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

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

- Serum or urine paraprotein detectable by immunofixation but not on electrophoresis, OR

- Greater than or equal to 90% reduction in serum paraprotein plus urine paraprotein <100 mg/24hrs.

Partial Response (PR) requires one of the following:

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

Stable Disease (SD)

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

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

Increase of $\geq$ 25% from lowest response value in any one or more of the following:

- Serum M-component and/or (the absolute increase must be > 0.5 g/dL)*
- Urine M-component and/or (the absolute increase must be > 200 mg/24 h)

- Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL

- Bone marrow plasma cell percentage; the absolute percentage must be $\geq$ 10%**

- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas

- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

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

* For progressive disease, serum M-component increases of >1 gm/dL are sufficient to define relapse if starting M-component is >5 g/dL.
** Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

13.0 CRITERIA FOR REMOVAL FROM STUDY

If at any time the patient is found to be ineligible for the protocol as designated in the section on Criteria for patient/subject eligibility (e.g. a change in diagnosis), the patient will be removed from the study. Also patients may be removed from the study if requested by the patient. Management will depend on where they are in their treatment course. Such patients will receive appropriate supportive care. The participating site PI may also remove patients from the study for noncompliance.

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

1. Subjects may withdraw consent and stop participation at any time.
2. Any Grade 4 skin toxicity (i.e. Stevens Johnson syndrome) or Grade 4 hypersensitivity (i.e. anaphylaxis)
3. Progression of multiple myeloma, as defined by the International Myeloma Working Group Criteria (Appendix I of the protocol).
4. Subject pregnancy
5. The development of any comorbid condition of excessive toxicity that would make further participation in the protocol unsafe
6. Start of new cycle is delayed more than 4 weeks.
7. Non-compliance or refusal of the patient to continue treatment and/or evaluation.
8. Major violation of the study protocol
9. Any adverse event(s) that, in the judgment of an Investigator, may cause severe or permanent harm if the study medications are continued.
10. At the discretion of the principal investigator and/or Celgene corporation for any reason.

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.).

The National Principal Investigator as well as the Supporters (Celgene Corporation) 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.

14.0 BIOSTATISTICS

This randomized phase II trial will explore two treatment strategies for multiple myeloma patients who have relapsed on lenalidomide maintenance: autologous stem cell transplant (autoSCT) following four cycles of clarithromycin, pomalidomide and dexamethasone (ClaPD and 9 total cycles of ClaPD therapy. The two treatment strategies will be compared based on overall response rate (VGPR or greater) at nine months following study entry. Response categories for multiple myeloma patients are defined in Appendix I. Patients will be randomized across all participating sites to a study arm at entry. The primary analysis will be evaluated in the intent-to-treat (ITT) population. Therefore, the following situations are considered failures for the primary outcome: disease

progression, death, non-protocol therapy, unable to transplant, and graft failure. At the end of the trial, patients in both arms with stable disease or better will be provided pomalidomide maintenance.

Based on previous research, it is estimated that the overall response rate at 9 months will be 57% in the 9-cycle ClaPD arm (48). Using a one-sided type 1 error rate of 20%, a sample size of 36 patients in each treatment arm (72 total) will have 85% power to detect a 23% absolute difference in the overall response rate for the ClaPD + autoSCT arm from 57% to 80%. A significant result would not imply definitive evidence of the superiority of the ClaPD + autoSCT arm due to the high type 1 error; instead, a significant result would provide evidence that testing of this treatment should proceed to a larger comparative study.

In order to reduce patient risk and confirm the feasibility of the ClaPD + autoSCT arm, the study design includes early termination in event that either patients are unable to receive a transplant following four cycles of ClaPD, patients have high rates of graft failure after transplant, or patients have high rates of treatment-related mortality in the ClaPD + autoSCT arm. If Arm A reaches a toxicity or failure boundary, both arms will be stopped and the trial will be reviewed based on the patients who have accrued until that point. The boundaries are based on accrual of 36 patients in the ClaPD + autoSCT arm. The calculations in the table below are based on marginal probabilities.

Failure Type	**# of failures needed to stop the study**	**Failure rate in the population**	**Probability boundary is crossed**
Unable to transplant	3 in the first 8 patients	0.10	0.10
	4 in the first 13 patients		
	5 in the first 19 patients	0.30	0.93
	6 in the first 25 patients		
	7 in the first 32 patients		
	8 in the first 36 patients		
Graft failure	2 in the first 36 patients	0.01	0.10
		0.10	0.90
Treatment Related Mortality	2 in the first 7 patients	0.05	0.10
	3 in the first 17 patients		
	4 in the first 28 patients	0.20	0.91
	5 in the first 36 patients		

In addition to confirming feasibility of the autoSCT arm, other secondary endpoints include minimal residual disease (MRD), progression-free survival (PFS), overall survival (OS), time-to-next treatment, and the safety of the maintenance strategy. In addition to the VGPR or greater serologic assessment, the disease burden will be further assessed by MRD on day 1 of cycle 2 and all subsequent cycles. The overall MRD- negative rate by nine month post-randomization will be calculated and compared across the two treatment groups.

The time-to-event outcomes will be assessed by Kaplan-Meier survival analysis. PFS will be defined as the time from first treatment day until objective or symptomatic progression or death. OS will be defined as the time from first treatment day until death. Time-to-next-treatment is defined as the time from treatment initiation to the first off-protocol therapy.

Data from all subjects who receive any combination of the study drugs will be included in the safety analyses. Subjects will not be included in the safety analysis only when there is confirmation that no study drugs were taken. The frequency of subjects experiencing a specific adverse event will be tabulated overall and by each treatment course. In the by-subject analysis, a subject having the

same event more than once will be counted only once. Adverse events will be summarized by worst NCI CTCAE grade. Laboratory data will be graded according to NCI CTCAE severity grade. The frequencies of the worst severity grade observed during treatment will be displayed in cross - tabulations. For variables for which a NCI CTCAE scale does not exist, the frequency of subjects with values below, within, and above the normal ranges pre and during treatment will be summarized by treatment arm. Exact 95% confidence intervals around the toxicity proportions will be calculated to assess the precision of the obtained estimates.

15.0 RESEARCH PARTICIPANT REGISTRATION AND RANDOMIZATION PROCEDURES

15.1 Research Participant Registration

At MSKCC

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

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

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

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

15.1.1 For Participating Sites:

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

To complete registration and enroll a participant from another institution, the study staff at that site must contact the designated research staff at MSKCC to notify him/her of the participant registration. The site staff then needs to fax or scan registration/eligibility documents to the MSK Study Coordinator at MSKCC **646-227-2482**.

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

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

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

If the eligibility checklist is complete, participant meets all criteria, all source documentation is received, the participating site IRB has granted approval for the protocol, and the site is in good standing with MSKCC, the MSKCC research staff will send the completed registration documents to the MSKCC Protocol Participant Registration (PPR) Office to be enrolled as stated in section 15.1. The participant will be registered.

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

15.2 Randomization

Patients who sign informed consent, complete pretreatment evaluations, and meet all eligibility criteria and are registered with MSKCC PPR office, will undergo computerized randomization into a treatment arm undergoing autologous stem cell transplant after 4 cycles of ClaPD treatment arm to be followed by pomalidomide maintenance (ARM A) versus treatment with up to 9 cycles of ClaPD to be followed by pomalidomide maintenance (ARM B). At the time of registration, after eligibility is confirmed, the patient will be randomized to either ARM A or ARM B. Patients will be registered in MSKCC's Protocol Participant Registration and randomized using the Clinical Research Database. Participating sites will be notified by the MSKCC study coordinator via email the assigned arm.

16.0 DATA MANAGEMENT ISSUES

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

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

16.0.1 Data and Source Documentation for Participating Sites

Data

Electronic Case Report Forms (eCRFs), directions for use and sign off requirements have been generated for this study. The MSKCC Principal Investigator or designee will provide eCRFs to participating sites. The participating site(s) will enter data remotely into the internet based system managed by MSKCC. The site staff will receive training prior to enrollment of the first patient. MSKCC is responsible for providing the site with EDC access and unique

usernames and passwords. The participating Site PI is responsible for ensuring these forms are completed accurately and in a timely manner.

Source Documentation

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

- Baseline measures to assess pre–protocol disease status (ex. Skeletal survey, bone marrow)
- Treatment records
- Grade 2-5 toxicities/adverse events not previously submitted with SAE Reports
- Response designation

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

16.0.2 Data Submission for Participating Sites

The site is responsible for entering data directly into the Electronic Data Capture (EDC) system.

16.0.3 Data and Source Documentation Submission Timelines for Participating Sites

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

Time point	Submission requirement	Source Documentation
Baseline	Eligibility checklist within 24 hours of ICF signature	Required to support all eligibility criteria
Cycle CRFs in EDC	Within 14 days of study visit	Within 14 days of end of cycle
SAE	Must be reported in EDC system within 24 hours/1 business day of event notification (see section 17.2.1 and 17.3); followup as needed	Required to support event within 24 hours/1 business day with SAE report

16.0.4 Data Review and Queries for Participating Site Data

Research staff at MSKCC will review data and source documentation as it is submitted. Data will be monitored against source documentation and discrepancies will be sent as queries to the participating sites. Queries will be sent by MSKCC Research staff twice a month.

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

16.1 Quality Assurance

Weekly registration reports will be generated to monitor patient accruals and completeness of registration data. Routine data quality reports will be generated to assess missing data and inconsistencies. Accrual rates and extent and accuracy of evaluations and follow-up will be monitored periodically throughout the study period and potential problems will be brought to the attention of the study team for discussion and action. Random-sample data quality and protocol compliance audits will be conducted by the study team, at a minimum of two times per year, more frequently if indicated.

Teleconferences will be held approximately once a month to update investigators on the progress with the study and to discuss toxicity observed to date. Frequency of calls may be adjusted as indicated by the study progress. The Principal Investigator and staff will make arrangements with investigators for the teleconferences.

16.1.1 Quality Assurance for Participating Sites

Each site accruing participants to this protocol will be audited by the staff of the MSKCC study team for protocol and regulatory compliance, data verification and source documentation.

Audits will be conducted annually during the study (or more frequently if indicated), and at the end or closeout of the trial. The number of participants audited will be determined by auditor availability and the complexity of the protocol. Each audit will be summarized and a final report will be sent to the PI at the audited participating site within 30 days of the audit.

16.2 Data and Safety Monitoring

The Data and Safety Monitoring (DSM) Plans at Memorial Sloan-Kettering Cancer Center were approved by the National Cancer Institute in September 2001. The plans address the new policies set forth by the NCI in the document entitled “Policy of the National Cancer Institute for Data and Safety Monitoring of Clinical Trials” which can be found at: *http://www.cancer.gov/clinicaltrials/conducting/dsm-guidelines/page1*. The DSM Plans at MSKCC were established and are monitored by the Office of Clinical Research. The MSKCC Data and Safety Monitoring Plans can be found on the MSKCC Intranet at: http://inside2/clinresearch/Documents/MSKCC%20Data%20and%20Safety%20Monitoring%20Plans.pdf

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

During the protocol development and review process, each protocol will be assessed for its level of risk and degree of monitoring required. Every type of protocol (e.g., NIH sponsored,

in-house sponsored, industrial sponsored, NCI cooperative group, etc.) will be addressed and the monitoring procedures will be established at the time of protocol activation.

16.3 Regulatory Documentation

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

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

- Participating Site IRB approval(s) for the protocol, appendices, informed consent form and HIPAA authorization
- Participating Site IRB approved consent form
- Participating Site IRB membership list
- Participating Site IRB's Federal Wide Assurance number and OHRP Registration number
- Curriculum vitae and medical license for each investigator and consenting professional
- Documentation of Human Subject Research Certification training for investigators and key staff members at the Participating Site
- Documentation of Good Clinical Practice (GCP) training for the PI and co-PI at the participating site
- Participating site laboratory certifications and normals

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

16.3.1 Amendments

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

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

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

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

16.3.2 Additional IRB Correspondence

Continuing Review Approval

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

Deviations and Violations

A protocol deviation on this study is defined as a request to treat a research participant who requires alteration in their study plan. If a deviation from this protocol is proposed for a potential or existing participant at MSKCC or a participating site, approval from the MSKCC IRB/PB is required prior to the action. Participating sites should contact the MSKCC PI who will in turn seek approval from the MSKCC IRB/PB. Deviation requests from eligibility criteria will not be permitted for research participants.

A protocol violation is anything that occurs with a participant, which deviated from the protocol without prior approval from the MSKCC IRB/PB. For protocol violations that are identified after they occur, the participating site should report to MSKCC within 14 days of learning of the event. The MSKCC PI will in turn report the violation to the MSKCC IRB/PB.

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

Other correspondence

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

16.3.3 Document maintenance

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

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

A regulatory binder for each site will also be maintained at MSKCC; this binder may be paper or electronic.

After study closure, the participating site will maintain all source documents, study related documents and CRFs for 7 years.

16.4 Noncompliance

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

17.0 PROTECTION OF HUMAN SUBJECTS

This study will explore the potential benefits of clarithromycin/pomalidomide/dexamethasone induction and maintenance and the potential role of high dose melphalan consolidation in

patients with relapsed myeloma. The study was conceived based on prior clinical observations made in relapsed and refractory myeloma patients.

Aside from the known side effects of the agents the potential for an increased risk of 2nd cancers has been identified and addressed in the informed consent document. The potential benefit of a better myeloma response with an increased remission duration for patients undergoing a 2nd autologous SCT justifies the potential risk of this protocol.

This study protects the rights of human subjects because it has carefully devised stopping and safety rules, the consent form clearly specifies the investigational intervention and describes all potential side effects and toxicities. Adverse event reporting follows the current MSKCC guidelines for transplant studies.

Participation in this study is voluntary. All patients will be required to sign a statement of informed consent which conforms to MKSCC IRB guidelines and explains the risks and potential benefits of this study.

The patient's health plan/insurance company will need to pay for all of the costs of treatment in this study except for pomalidomide. Pomalidomide will be provided to patients at no cost. The patient will be responsible for the costs of standard medical care, all hospitalizations and any transplant complications. Pre-authorization for the transplant will be cleared with the health plan/insurance company prior to admission. Patients will not be paid for taking part in this study.

17.1 Privacy

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

17.2 Serious Adverse Event (SAE) Reporting

17.2.1 Serious Event Definition

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

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

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

- Pregnancy (see below, later in this section)

[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.

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 IP, or within (insert time-frame which must be at least 28 days of the subject's last dose of IP), are considered immediately reportable events. IP 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 the IP should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects

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

17.2.2 Procedures for Adverse Event and Drug Reaction reporting

The sponsor-investigator, MSKCC, is responsible for reporting SAEs to Celgene and the MSKCC IRB. Procedures for SAE reporting for participating sites are outlined in section 17.3.

Serious Adverse Event (SAE) Reporting

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

Fields populated from CRDB:

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

Data needing to be entered:

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

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

17.2.3 Celgene Reporting Guidelines (for MSKCC)

Expedited reporting by investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking

number (PO-MM-PI-0036) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the patient records.

Celgene Drug Safety Contact Information:

Celgene Corporation

Global Drug Safety and Risk Management

Connell Corporate Park

300 Connell Dr. Suite 6000

Berkeley Heights, NJ 07922

Fax: (908) 673-9115

E-mail: drugsafety@celgene.com

17.3 Serious Adverse Event (SAE) Reporting for Participating Sites

Responsibility of Participating Sites

- Participating sites are responsible for reporting all SAEs to their local IRB per local guidelines. Local IRB SAE approvals/acknowledgments must be sent to MSK upon receipt.
- Participating sites are responsible for reporting all SAEs to the MSKCC PI via the EDC system within 24 hours of learning of the event.
- Participating sites should notify the MSKCC PI of any grade 5 event immediately.
- Participating sites should report SAEs to the MSKCC PI. The MSKCC PI will be responsible for reporting to Celgene.

SAE contact information for the Coordinating Center is listed below:

EMAIL: **medmctcore@mskcc.org** to the attention of Dr. Sergio Giralt/12-138 Multicenter Trials Core Research Staff at MSKCC

Responsibility of MSKCC

- The MSKCC PI is responsible for submitting all SAEs to the MSKCC IRB/PB as specified in 17.2. The MSKCC PI will report SAEs to the MSKCC IRB prior to Celgene.
- The MSKCC PI is responsible for notifying Celgene of SAEs within 24 hours of the investigator becoming aware of the event. The investigator is defined as all site principal investigators and sub-investigators listed on the face page and delegation logs.
- The MSKCC PI is responsible for informing all participating sites about all deaths and unexpected SAEs that are either possibly, probably, or definitely related to the study intervention within 30 days of receiving the stamped SAE from the MSKCC IRB/PB.

- Any report pertaining to a grade 5 event will be distributed to the participating sites as soon as possible.

17.4 Safety Reports

- Celgene shall notify the Investigator via an IND Safety Report of the following information:
  - Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected.
  - Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.
- MSKCC will distribute outside safety reports to the participating sites immediately upon receipt.
- MSKCC must submit outside safety reports to the MSKCC IRB/PB according to institutional guidelines.
- Participating sites must submit safety reports to their institution's IRBs within 30 days of receipt from MSKCC or per participating site guidelines.

18.0 INFORMED CONSENT PROCEDURES

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

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

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

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

18.1 For Participating Sites

The investigators listed on the Consenting Professionals Lists at each participating site may obtain informed consent and care for the participants according to good clinical practice and protocol guidelines.

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

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

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20.0 APPENDICES

.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 freelight 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:
Increase of ≥ 25% from lowest response value in any one or more of the following: Serum M-component and/or (the absolute increase must be > 0.5 g/dL)* Urine M-component and/or (the absolute increase must be > 200 mg/24 h) Only in patients without measurable serum and urine M-protein levels; the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL

- Bone marrow plasma cell percentage; the absolute percentage must be ≥ 10%**
- Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas
- Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder

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

* For progressive disease, serum M-component increases of >1 gm/dL are sufficient to define relapse if starting M-component is >5 g/dL.
** Relapse from CR has the 5% cut-off versus 10% for other categories of relapse.

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.*

- ***S*almon-Durie Staging System International Staging System (ISS)**

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: 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 IV: 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	

ECOG Performance Status

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

Appendix VIII

Adult and Pediatric BMT Adverse Event Reporting Guide

Version 2.0 dated 29 December 2014

This policy described herein applies to all primary transplant protocols, autologous and allogeneic. The latter includes all sources: peripheral blood progenitor cells, bone marrow, and cord-blood.

1. Definition of Adverse Event

Adverse event (AE) - Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom or disease temporally associated with the use of a medical treatment or procedure regardless of whether it is considered related to the medical treatment or procedure (attribution of definite, probably, possible, unlikely or unrelated)

Life-Threatening Adverse Event – Any adverse event that places the participant, in view of the investigator, at immediate risk of death from the reaction

Serious Adverse Event (SAE) – Any adverse event that results in any of the following outcomes: death, a life threatening adverse event, in-patient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect

Unexpected Adverse Event – Any adverse event, the specificity or severity of which is NOT listed in the study protocol, product inserts or informed consent document

2. Terminology and Grading.

Adverse events are described using the Common Terminology Criteria Adverse Events (CTCAE). CTCAE was developed by the National Cancer Institute (NCI) for use in reporting adverse events. A copy of the current CTCAE guidelines is located at http://ctep.cancer.gov/branches/pio/reporting_guidelines.htm

The CTCAE includes a grading (severity) scale for each adverse event term.

Grade 0:	No adverse event or within normal limits
Grade 1:	Mild adverse event
Grade 2:	Moderate adverse event
Grade 3:	Severe adverse event
Grade 4:	Life-threatening or disabling adverse event
Grade 5:	Fatal adverse event

3. Attribution

The determination of whether an adverse event is related to a medical treatment or procedure. Attribution categories:

Definite	The adverse event is ***clearly related*** to the study drug/device/procedure/ treatment(s).
Probable	The adverse event is ***likely related*** to the study drug/device/procedure/ treatment *The adverse event is not likely to be caused by the subject's underlying medical condition or other concomitant therapy, and the nature of the adverse event or the temporal relationship between the onset of the adverse event and*

	study drug/device/treatment administration lead the investigator to believe that there is a reasonable chance of causal relationship
Possible	The adverse event ***may be related*** to the study drug/device/procedure/ treatment(s). *The adverse event could be attributed to the subject's underlying medical condition or other concomitant therapy, but the nature of the adverse event or the temporal relationship between the onset of the adverse event and study drug/device/treatment administration lead the investigator to believe that there could be a causal relationship*
Unlikely	The adverse event is ***doubtfully related*** to the study drug/device/ procedure/treatment(s)
Unrelated	The adverse event is ***clearly NOT related*** to the study drug/device/ procedure/treatment(s) *The adverse event is most plausibly explained by the subject's underlying medical condition or other concomitant therapy, or the adverse event has no plausible biological relationship to study drug/device/treatment*

4. Adverse Event Reporting

According to MSKCC policy all SAE (unexpected and expected) must be reported to the IRB even if the investigator is unsure whether a relationship exists between the adverse event and the use of the study treatment. However, hematopoietic stem cells transplantation requires the administration of pre-transplant treatments that cause expected SAE. Therefore, this policy defines those expected SAE that do not require reporting; any adverse events not listed in section 4.4 of this document must be reported to the IRB regardless of expectancy.

SAE are reported to the IRB according to procedures and policies defined by the IRB (web site)

4.1. Reporting periods

Active treatment period - Begins once the patient is consented and registered to the protocol and ends 30 days after the last day the patient receives the planned study intervention (drug administration, transplant or cell infusion) as outlined in the protocol. Supportive care and standard forms of post-transplant immunosuppressive therapy are not considered active treatment unless so defined in the protocol

All serious adverse events that occur during the active treatment period must be reported to MSKCC's IRB within 5 calendar days regardless of attribution unless otherwise specified in the protocol

Follow-up period - Is the period of time that begins 31 days after the patient receives the last planned study intervention and continues until the patient is off study as defined by the protocol.

4.2. Reporting Requirements during the Active treatment period

1. All deaths including disease progression

2. Acute GvHD (Grade 3-4) is to be reported
3. Organ failure requiring extensive supportive care (i.e. dialysis, mechanical ventilation)
4. Unexpected Adverse Events regardless of the attribution with the treatment or procedure
5. Any additional SAEs will be reported at the PIs discretion

In addition, patients hospitalized for a total of more than 60 days (starting on day 0 – day of stem cell infusion, not upon initial admission) within the first 100 days post transplant will be reported to the IRB, regardless of duration of the active treatment period

4.3. Reporting Requirements during the Follow-up period

1. Any Serious Adverse Events (SAE) that is assessed as definite, probable or possibly related to the protocol treatment (i.e. death due to progression/relapse of underlying malignancy or disease should not be reported)

4.4. Expected Adverse Events resulting from pretransplantation preparative regimens, graft versus host disease or infections that do not require reporting during the active treatment period are the following:

These expected adverse events occur with at least 80% of the patients transplanted

Not reported during the active treatment period	Reported during active treatment period
Neutrophil count decrease – grade 1-4	--
Platelet count decrease – grade 1-4	--
Anemia – grade 1-3	Anemia – grade 4
Febrile neutropenia – grade 1-3	Febrile neutropenia – grade 4
Fever – grade 1-3	Fever – grade 4
Infections – grade 1-3	Infections – grade 4
Dehydration – grade 1-3	Dehydration – grade 4
Mucositis oral – grade 1-3	Mucositis oral – grade 4
Fatigue – grade 1-3	--
Hematuria – grade 1-3	Hematuria – grade 4
Creatinine increased – grade 1-3	Creatinine increased – grade 4
Alanine aminotransferase increased – grade 1-3	Alanine aminotransferase increased – grade 4
Aspartate aminotransferase increased – grade 1-3	Aspartate aminotransferase increased – grade 4
Alkaline phosphatase increased – grade 1-3	Alkaline phosphatase increased – grade 4
Acute GvHD	Acute GvHD
Conventional and Cord transplants - grade 1-3	Conventional and Cord transplants - grade 4
TCD transplants – grade 1-2	TCD transplants – grade 3-4
Chronic GvHD – mild or moderate	Chronic GvHD – severe
Readmission associated with NCI grade 1-3 toxicity	Readmission associated with NCI grade 4 toxicity

4.5 The following Adverse Events must be reported during the entire study duration regardless of attribution or expectancy

1. Neutrophil count decrease – grade 4 (<500 ANC)
    a. After day 30 for non cord transplants
    b. After day 45 for cord blood transplants

   c. Post initial engraftment requiring stem cell boost or other significant intervention
      i. Grade 4 neutrophil count decrease requiring growth factor alone will not be reported
2. Platelet count decrease – grade 4 (<25,000 or transfusion dependent; defined as ≥ 3 transfusions within 30 days with the exception of transfusions given for diagnostic or therapeutic procedures)
   a. Sustained >7 days post initial engraftment
   b. After day 100 post transplant
3. Acute GvHD
   a. Conventional and Cord transplants – grade 4
   b. TCD transplants – grade 3-4
4. Chronic GvHD – severe
5. All deaths regardless of attribution

NON-TRANSPLANT PHASE 1 and 2 PROTOCOLS

Adverse events occurring in non-transplant protocols are reported according to MSKCC guidelines unless otherwise specified in the protocol

MONITORING AND CAPTURING OF ADVERSE EVENTS (or TOXICITIES) IN CRDB

Tracking and recording requirements

1. All patients on study will have laboratory data collected; this includes all grades I-V hematologic toxicities
2. Unexpected grade 1-4 toxicities
3. Expected grade 3-4 toxicities
4. All SAEs (expected and unexpected) will be tracked and recorded under toxicity in CRDB

Toxicity tracking process

1. RSAs will prepare patient specific toxicity trackers from the rounds meetings and chart review
2. RNs will review the patient trackers and make any necessary changes
3. PI of protocols will review, sign off and attribute all patient toxicities

Appendix IX: Pill Diary

Number of Pills Given:_____ Pill Bottle(s) returned: Circle **Yes** or **No**
Total Daily Dose Pomalidomide:_____ Number of Pills **returned pomalidomide** :_____
Total Daily Dose Clarithromycin: _____
Total Daily Dose Dexamethasone: _____
(To be Completed by RN)

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

CYCLE #: **# of WEEKS**

Day	Date	Number of Pomalidomide capsules taken (please indicate time)	Dexamethasone tablets taken (please indicate time)	Clarithromycin tablets (please indicate times of AM and PM doses)	Aspirin	Proton Pump Inhibitor:
EXAMPLE	*1/1/2012*	*2, 4:00 PM*	*1, 3:00 PM*	*8:00AM, 7:00PM*		
1						
2			***OFF DAY, NO***			
3			***OFF DAY, NO***			
4			***OFF DAY, NO***			
5			***OFF DAY, NO***			
6			***OFF DAY, NO***			
7			***OFF DAY, NO***			
8						
9			***OFF DAY, NO***			
10			***OFF DAY, NO***			
11			***OFF DAY, NO***			
12			***OFF DAY, NO***			
13			***OFF DAY, NO***			
14			***OFF DAY, NO***			
15						
16			***OFF DAY, NO***			
17			***OFF DAY, NO***			
18			***OFF DAY, NO***			
19			***OFF DAY, NO***			
20			***OFF DAY, NO***			
21			***OFF DAY, NO***			
22		***OFF DAY, NO***				
23		***OFF DAY, NO***	***OFF DAY, NO***			
24		***OFF DAY, NO***	***OFF DAY, NO***			
25		***OFF DAY, NO***	***OFF DAY, NO***			
26		***OFF DAY, NO***	***OFF DAY, NO***			
27		***OFF DAY, NO***	***OFF DAY, NO***			
28		***OFF DAY, NO***	***OFF DAY, NO***			

Patient Signature: _____ **Date:** _____

Consenting Professional/Research RN Signature: _____ **Date:** _____
Consenting Professional/Research RN
Comments:_____
_____

Pill Diary: Maintenance Therapy

Number of Pills Given:_____ Pill Bottle(s) returned: Circle **Yes** or **No**
Total Daily Dose Pomalidomide:_____ Number of Pills **returned pomalidomide**:_____
(To be Completed by RN)

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

CYCLE #: **# of WEEKS**

Day	Date	Number of Pomalidomide capsules taken (please indicate time)
EXAMPLE	*1/1/2012*	*2, 4:00 PM*
1		
2		
3		
4		
5		
6		
7		
8		
9		
10		
11		
12		
13		
14		
15		
16		
17		
18		
19		
20		
21		
22		***OFF DAY, NO CAPSULES***
23		***OFF DAY, NO CAPSULES***
24		***OFF DAY, NO CAPSULES***
25		***OFF DAY, NO CAPSULES***
26		***OFF DAY, NO CAPSULES***
27		***OFF DAY, NO CAPSULES***
28		***OFF DAY, NO CAPSULES***

Patient Signature: _____ **Date:** _____

Consenting Professional/Research RN Signature: _____ **Date:** _____
Consenting Professional/Research RN
Comments:_____