

Mayo Clinic Cancer Center

A Phase I/II Trial of Pomalidomide (CC-4047), Bortezomib and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma

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Drug Availability

Commercial Agent: Bortezomib and Dexamethasone

Drug Company Supplied: Pomalidomide (CC-4047)

√Study contributor(s) not responsible for patient care.

October 25, 2011

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Protocol Resources

| Questions: | Contact Name: |
|--|--|
| Patient eligibility*, test schedule, treatment delays/interruptions/adjustments, dose modifications, adverse events, forms completion and submission | <div style="background-color: black; width: 100px; height: 15px; margin-bottom: 5px;"></div> Phone: <div style="background-color: black; width: 100px; height: 15px; display: inline-block;"></div> E-mail: <div style="background-color: black; width: 150px; height: 15px; display: inline-block;"></div> |
| Drug administration, infusion pumps, nursing guidelines | <div style="background-color: black; width: 100%; height: 100%;"></div> |
| Forms completion and submission | <div style="background-color: black; width: 100%; height: 100%;"></div> |
| Protocol document, consent form, regulatory issues | <div style="background-color: black; width: 100%; height: 100%;"></div> |
| Biospecimens | <div style="background-color: black; width: 100%; height: 100%;"></div> |
| Adverse Events (AdEERS, MedWatch, Non-AER, AML/MDS) | <div style="background-color: black; width: 100%; height: 100%;"></div> |

***No waivers of eligibility per NCI**

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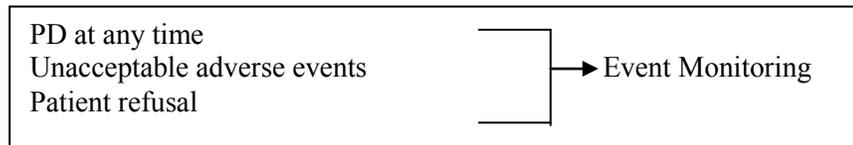
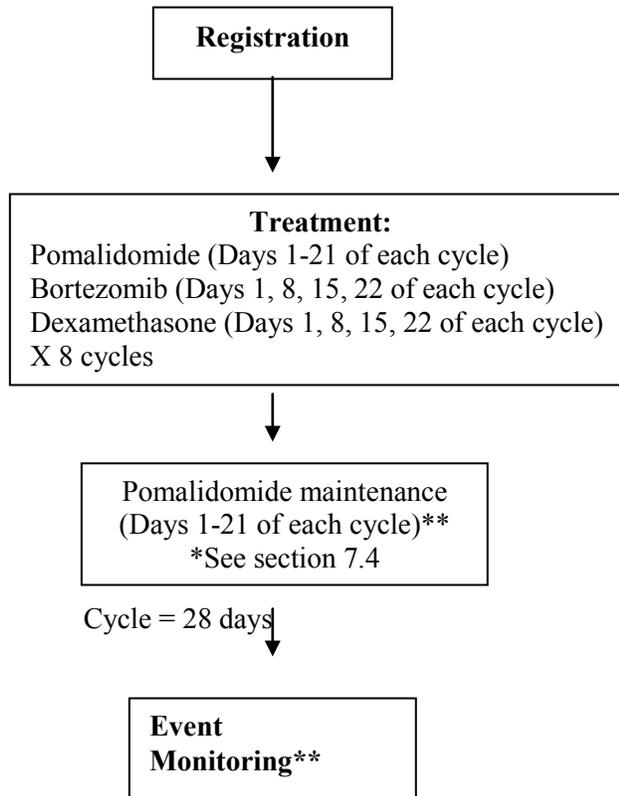
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Schema

**MTD(Bortezomib 1.3 mg/m²) reached in Phase I and permanently closed 11/13/2012
Phase II opened 01/10/2013**



** As of Addendum 6, patients in active treatment and in event monitoring will be removed from the study.

Mayo Drug Names/Abbreviations

| | | |
|--|--|---|
| Generic name: Pomalidomide (CC-4047) Brand name: NA Mayo abbreviation: CC4047 Availability: Provided by Celgene | Generic name: Bortezomib Brand name: Velcade Mayo abbreviation: VELCAD Availability: Commercial | Generic name: Dexamethasone Brand name: Decadron Mayo abbreviation: DXM Availability: Commercial |
|--|--|---|

1.0 Background

- 1.1 Multiple myeloma (MM) is a malignant plasma cell proliferative disorder characterized by bone destruction, anemia, hypercalcemia, and renal failure that causes about 11,000 deaths in the United States each year^{1,2}. Median survival with conventional dose melphalan and prednisone is 3-4 years, which has not been significantly improved by the addition of other chemotherapeutic agents³. Although improvement in survival occurs with high-dose therapy and stem cell transplantation, almost all patients eventually relapse and die of their disease.
- 1.2 Autologous stem cell transplantation (SCT) has been shown to be superior to conventional dose chemotherapy in the treatment of multiple myeloma in two randomized clinical trials^{4,5}. Despite the high response rates it is expected most patients will relapse and SCT is not considered curative. Given the limited therapeutic options available for patients with relapsed MM, there is an urgent need for novel therapeutic approaches.
- 1.3 Thalidomide was first reported as an active agent in relapsed MM in 1999⁶. Most patients had failed stem cell transplantation, and the overall response rate (greater than 50% reduction in M protein level) was 32% using doses of 200 to 800 mg orally per day. A subsequent study of 16 patients performed at the Mayo Clinic used 200 to 800 mg orally per day and found a 25% response to therapy with a > 50% reduction in the serum or urine m-protein level. Side effects included constipation, sedation, rash, and peripheral neuropathy⁷. Several trials including ones at Mayo Clinic have since confirmed the significant activity of thalidomide in myeloma.
- 1.4 Glucocorticoids have significant activity in myeloma. They are often used in relapsed and refractory disease. In a study of 112 patients with untreated myeloma, the response rate with dexamethasone alone was 43%⁸. Recent randomized trials comparing Thal/Dex to dexamethasone have confirmed this^{9,10}. Steroids also have anti-angiogenic properties and this may involve different mechanisms than thalidomide. There is evidence from pre-clinical models that anti-angiogenic therapy may be synergistic with conventional chemotherapy. Similarly, there may be an additive (or synergistic) anti-angiogenic effect when dexamethasone and thalidomide are combined. While there are no randomized trials comparing either thalidomide or lenalidomide alone to those agents with dexamethasone, available evidence from multiple phase 2 trials suggests the addition of dexamethasone greatly increases response rates from 25-30% to 50-60% among relapsed patients¹¹⁻¹⁷. However, the combination of either thalidomide or lenalidomide with dexamethasone greatly increases risk of thromboembolic events^{9,10,18-20}. Both aspirin and full dose anticoagulation appear to be effective prophylaxis against venous thromboembolism in this setting²¹⁻²³.
- 1.5 The utility of thalidomide in the relapsed setting led to its use upfront for newly diagnosed MM. Multiple phase 2 studies show response rates of 60-70% with Thal/Dex²⁴. In a randomized trial conducted by the Eastern Cooperative Oncology Group (ECOG)⁹, the response rate with Thal/Dex was significantly higher compared to dexamethasone alone, 58% versus 42%, respectively

($p=0.0164$). This was confirmed in an international randomized trial¹⁰ which showed response rate of 63% for Thal/Dex vs. 46% for dexamethasone alone ($p<0.0005$).

- 1.6 The astonishing success of thalidomide in this group of heavily treated patients led to interest in developing thalidomide analogues (IMiD®s) a proprietary class of Celgene compounds. Lenalidomide (CC-5013) belongs to this class of thalidomide analogues with immunomodulatory properties. It appears safer and more effective than thalidomide in preclinical and clinical studies^{14,16,25}. Data from phase II and phase III clinical trials in patients with relapsed myeloma suggests lenalidomide is less likely to cause peripheral neuropathy, constipation, and sedation than thalidomide, but the incidence of thromboembolism is similar^{15,17,19,26}. The combination of lenalidomide and dexamethasone has been used in newly diagnosed myeloma with a response rate of 91%²¹.
- 1.7 The myeloma cells are highly dependent on the bone marrow microenvironment, including the presence of certain cytokine macromolecules, eg, Interleukin (IL)-6, in the extracellular matrix, and supportive (stromal) cells for their growth and survival. Processes that change the bone marrow microenvironment either retard the growth of the tumor or cause the myeloma cells to undergo apoptosis. Corticosteroids, for example, which inhibit IL-6 expression, have efficacy in the treatment of multiple myeloma. Thalidomide's activity in multiple myeloma is postulated to derive from a number of pharmacologic properties, including inhibition of tumor necrosis factor (TNF)- α an angiogenic factor present in the tumor microenvironment. Thalidomide also stimulates IL-12 secretion that induces interferon gamma (IFN- γ). IFN- γ has numerous effects, including the induction of IFN inducible protein 10 (IP-10), which inhibits neovascularity by inhibiting vascular endothelial growth factor synthesis (VEGF) and stimulation of T cells. IFN- γ also alters the expression of intracellular adhesion molecules and other adhesion molecules. The resulting absence of appropriate adhesion molecule binding causes multiple myeloma cells to undergo apoptosis. Thalidomide also modifies extracellular matrix expression, directly inhibits both basic fibroblast growth factor (bFGF) and VEGF expression, and inhibits the induction of cyclooxygenase-2 (COX-2), an enzyme whose expression is essential for inhibiting neovascular apoptosis.
- 1.8 **Pomalidomide:** Pomalidomide (CC4047), α -(3-aminophthalimido) glutarimide, is a novel IMiD under development for potential use in the treatment of various conditions. Pomalidomide shares a number of the beneficial pharmacologic properties with thalidomide, but has a higher potency. For example, an in vitro model of anti-TNF activity has shown that pomalidomide has an IC₅₀ of approximately 13 nM (3.6 ng/mL) against TNF produced by lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells (PBMCs). Thalidomide, by comparison, has an IC₅₀ of ~194 μ M (50.1 μ g/mL)²⁷. In LPS-stimulated human whole blood, the 50% inhibitory concentration (IC₅₀) for pomalidomide is 25 nM (6.8 ng/mL)²⁸. Pomalidomide's antitumor activity has also been demonstrated in vitro with MM tumor cell lines. Concentrations of 2.73 to 27.3 ng/mL (0.01 to 0.1 μ M) achieved a 50% inhibition of MM.1S and Hs Sultan cell proliferation. In contrast, at concentrations of 25.8 μ g/mL (100 μ M) thalidomide was less potent and inhibited the proliferation of MM.1S and Hs Sultan cells by 15% and 20%, respectively.

- 1.9 **Preclinical animal studies:** A cardiovascular study in dogs was performed using an IV formulation in order to maximize systemic exposure. Pomalidomide (systolic, diastolic, and mean arterial blood pressure; heart rate; left ventricular pressure and its derivative, the maximum force of ventricular contraction (dP/dtmax); maximum and mean femoral blood flow and femoral resistance; RR, ST, QRS, PR, QT, and QTc-intervals; heights of the R, P, and T-waves of the electrocardiogram (ECG) complex; and peak inspiratory and expiratory flow, tidal volume, minute volume, and rate of respiration were recorded up to 30 minutes following completion of the infusion of each dose. Mean plasma concentrations 30 minutes postdose were 1010.4 ng/mL following the 2.5 mg/kg dose, and 2421.1 ng/mL following the 10 mg/kg dose. The mean plasma concentration for the high dose (25 mg/kg) was 6686.0 ng/mL. At doses of 2.5 and 10 mg/kg there were no significant adverse cardiovascular effects compared with the vehicle control group. At 25 mg/kg no significant differences between the vehicle group and the test article treated group were observed in 3 of 4 dogs. One female animal exhibited an adverse reaction; 7 to 8 minutes into the infusion of the 25 mg/kg dose, there was a marked increase in respiration rate and decreases in blood pressure, femoral artery blood flow, and dP/dtmax. Peak inspiratory flow (PIF) and tidal volume (TV) were more variable in pomalidomide treated animals than in control animals. PIF values showed a statistically significant increasing dose response in PIF. Administration was stopped and the animal was artificially ventilated in order to control the respiration. About 18 minutes later, on stopping the respiratory pump, it was noticed that although the animal was breathing spontaneously, the respiratory rate was still very high (up to 117 brpm). It was decided to artificially ventilate the animal. Approximately 40 minutes after the cessation of the high dose, values for cardiovascular parameters stabilized and the administration of the high dose was repeated. No further changes in any of the vascular parameters were observed for at least 30 minutes after the high dose administration. Between 45 and 120 minutes after the second administration of the high dose, similar cardiovascular changes were noted, as previously seen at the beginning of the prior infusion at the same dose level. These changes may have been related to the assisted ventilation given to the animal for the prolonged period of time. A thoracotomy was performed on the animal to determine the possible causes of the respiratory problems experienced by this animal. Examination of the lungs revealed a large red patch on the posterior lobe indicative of a possible pulmonary embolus. Several other smaller patches were also apparent on the lungs. Pink fluid was found in the endotracheal tube and in the ventilator tubing. Propofol and alfentanil have not been previously associated with any adverse effects on pulmonary function. It is expected that these changes may be due to prolonged artificial ventilation rather than the effects of the anesthetics or pomalidomide. Pomalidomide, therefore, had no significant effects on the cardiovascular and respiratory systems following intravenous administration to anesthetized beagles at dose levels of up to 25 mg/kg.
- 1.9a A single oral dose bioavailability study was conducted in the rat and monkey. Both species received single oral doses of 100 mg/kg. Pomalidomide was formulated in a 1% carboxymethylcellulose (CMC) suspension and administered in a volume of 5 mL/kg by oral gavage. Peak plasma concentrations (C_{max}), time of peak concentration (t_{max}), area under the plasma concentration curve (AUC),

and half-life ($t_{1/2}$) are summarized in the toxicity of pomalidomide after a single dose was studied after intravenous administration to rats (1398/51-1032) and mice. In rats, there were no deaths in the study animals dosed with 50 mg/kg and no treatment-related macroscopic changes in animals killed on Day 15. In mice administered pomalidomide by intravenous injection of 10, 25, and 50 mg/kg, the high dose produced piloerection, hunching, and tachypnea. Palpebral closure was observed at doses of 25 and 50 mg/kg, and hypernea at 50 mg/kg. The severity and persistence of clinical observations increased with increased dose. No macroscopic abnormalities in mice were found during necropsy. The acute toxicity of pomalidomide after oral administration was also studied in rats and mice. In rodents administered 2000 mg/kg pomalidomide, there were no deaths and no significant clinical observations. Pomalidomide at oral doses of 100, 500, or 1500 mg/kg was well tolerated when administered once daily to male and female rats for 90 consecutive days. Therefore the no-observable adverse-effects level (NOAEL) under the conditions of this study was considered to be the highest dose administered (1500 mg/kg).

- 1.9b Oral administration of pomalidomide to male and female cynomolgus monkeys resulted in lesions in the bone marrow, spleen, and thymus in animals dosed at 2 mg/kg and 10 mg/kg. Treatment was stopped at Week 6 for the 10 mg/kg monkeys. Bone marrow lesions included hypercellularity, myeloid series immaturity, and decreased megakaryocytes. Spleen lesions included primarily lymphoid depletion, but also occasionally lymphoid hyperplasia, and thymic lesions were of lymphoid depletion. Thymic lesions were resolved but spleen and bone marrow lesions persisted although they were reduced in incidence and/or severity in animals dosed with 10 mg/kg for 5 weeks followed by 8 weeks of recovery. Based on the results from this study, the NOAEL in this study was 0.2 mg/kg/day; the C_{max} and AUC values at this dosage were approximately 150 ng/mL and 600 ng•h/mL, respectively.
- 1.9c Pomalidomide was administered by oral gavage at dose levels of 100 or 250 mg/kg/day to pregnant New Zealand white female rabbits (4/group). Administration began on presumed Gestation Day 6 and continued daily through presumed Gestation Day 18 (inclusive). Control groups (4/group) received 1% w/v CMC (vehicle control) or thalidomide (10, 100, or 250 mg/kg/day). Fetal external malformations, characterized by the presence of inward/outward hindlimb/hindfoot rotation, shortened limbs, missing or abnormal digits, missing or abnormal dew claws, extra digits, or a clubbed foot were seen in fetuses from animals that received the positive control (thalidomide, all doses) and in animals that had received pomalidomide (100 and 250 mg/kg/day). A relationship was noted between increasing pomalidomide dose and the number of fetuses affected, as well as the frequency of occurrence of each type of malformation. In administered doses of pomalidomide at 100 mg/kg/day, inward/outward rotation of hindlimbs/hindfeet, the presence of shortened limbs, and a clubbed foot were observed in 31% of viable fetuses. In addition to these malformations, does administered pomalidomide 250 mg/day/kg had missing/abnormal dew claws, missing/abnormal digits, extra digits on forelegs, and the presence of an umbilical hernia; 93% of fetuses from does treated at this higher dose of pomalidomide were affected. Based on these data, it was concluded that pomalidomide causes significant fetal malformations. The genotoxic potential of pomalidomide in a bacterial mutagenesis assay was evaluated at pomalidomide

concentrations of up to 5000 µg/plate in 4 strains of *Salmonella typhimurium* (TA98, TA100, TA1535, and TA1537) and 2 strains of *Escherichia coli* (WP2 pKM101 and WP2 uvrA pKM101) in the absence and presence of metabolic activation. Pomalidomide was found not to be mutagenic.

- 1.9d **Human studies:** In 20 healthy male subjects in study pomalidomide-1398/132, nine (56%) of 16 subjects in the 5 mg or higher pomalidomide treatment groups reported a total of 13 adverse events and 3 (30%) of 10 subjects in the placebo group reported 6 adverse events. All events were mild or moderate in nature. While there were no clinically significant changes in any laboratory or other parameter tested, there was a dose-related decrease in the CD4+ cell count, reaching a maximum at the 50-mg dose. The results of this study showed that pomalidomide had an acceptable safety profile and was well tolerated at all doses in healthy male subjects.
- 1.9e **Phase 1 trial in multiple myeloma:** Schey and colleagues²⁹ conducted a phase 1 trial using pomalidomide in 24 patients with relapsed or refractory multiple myeloma. Dose levels were 1, 2, 5, and 10 mg/day by mouth. The maximum tolerated dose (MTD) was 2 mg/day. Dose-limiting grade 4 neutropenia occurred in a total of six patients at a median of 3 weeks after starting therapy. Two events occurred on 10 mg daily at 2 and 3 weeks, two occurred on 5 mg at 3 weeks, and two occurred on 2 mg at 3 weeks. Non-hematologic toxicity consisted of DVT in 4 patients. Other non-hematologic toxicity was mild and consisted of grade 1 or 2 gastrointestinal toxicity (36%), grade 1 skin rash (21%), grade 1 neuropathy (16%) and grade 1 or 2 edema (12%). Treatment resulted in a greater than 25% reduction in paraprotein in 67% of patients, 13 patients (54%) experienced a greater than 50% reduction in paraprotein, and four (17%) of 24 patients entered complete remission.
- 1.9f **Phase II trial in multiple myeloma:** A Phase II trial in relapsed multiple myeloma was conducted at Mayo Clinic³⁰. Sixty patients were enrolled. Treatment consisted of pomalidomide 2 mg by mouth daily with dexamethasone 40 mg by mouth once a week. (Pom/dex). The overall remission rate was 63% with a CR+VGPR rate of 33%. Importantly responses were seen in 40% of the patients who were refractory to lenalidomide, 60% of the patients who were refractory to bortezomib, and 37% of patients who were refractory to thalidomide suggesting a role for this drug in patients who have relapsed after other novel agents. Toxicity was manageable and consisted primarily of neutropenia (32% with at least one episode grade 3 or 4) and fatigue. One patient died of sepsis while neutropenic. Grade 1 or 2 neuropathy was seen in 28%, but neuropathy was present at baseline in 60 % of patients. No grade 3/4 neuropathy was seen. No patients had thromboembolic complications.

Based on these results, another cohort of patients with relapsed myeloma that was refractory to lenalidomide was accrued³¹. The same Pom/dex dose regimen was used. The cohort was heavily pre-treated with a median of 4 prior regimens. All were lenalidomide-refractory. Overall remission rate was 50% including VGPR+PR rate of 32% and MR 18%. The major toxicity was myelosuppression with grade 3 or 4 neutropenia seen in 26%.

- 1.9g **Bortezomib, lenalidomide and dexamethasone in myeloma:** The combination of bortezomib, lenalidomide and dexamethasone was shown to be safe and effective in myeloma patients. A phase I, dose-escalation study evaluated safety and determined the maximum-tolerated dose (MTD) of lenalidomide plus bortezomib in patients with relapsed or with relapsed and refractory MM³². Patients received lenalidomide 5, 10, or 15 mg/d on days 1 through 14 and received bortezomib 1.0 or 1.3 mg/m² on days 1, 4, 8, and 11 of 21-day cycles. Dexamethasone (20 mg or 40 mg on days 1, 2, 4, 5, 8, 9, 11, and 12) was added for progressive disease after two cycles. Primary end points were safety and MTD determination. Thirty-eight patients were enrolled across six dose cohorts. The MTD was lenalidomide 15 mg/d plus bortezomib 1.0 mg/m². Dose-limiting toxicities (n = 1 for each) were grade 3 hyponatremia and herpes zoster reactivation and grade 4 neutropenia. The most common treatment-related, grades 3 to 4 toxicities included reversible neutropenia, thrombocytopenia, anemia, and leukopenia. Among 36 response-evaluable patients, 61% (90% CI, 46% to 75%) achieved minimal response or better. Among 18 patients who had dexamethasone added, 83% (90% CI, 62% to 95%) achieved stable disease or better. Median overall survival was 37 months.
- 1.9h **CC-4047-MM-002 Phase 1b Safety and Efficacy Summary**
CC-4047-MM-002 is a 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 myeloma³³. 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 phase 1 segment is determining the starting dose of pomalidomide to be used in both treatment arms in the randomized phase 2 segment of the study. The primary endpoint of the phase 1 study is to determine the MTD, and subjects were enrolled sequentially to the 2 mg, 3 mg, 4 mg, and 5 mg dose levels. A 3 +3 design was used to define the MTD for single agent pomalidomide. Oral pomalidomide was administered according to a cyclic schedule (once daily on Days 1-21 of a 28-day cycle); however, patients who developed PD at any time or who had not achieved at least a 25% reduction of serum M-protein (if measurable) and a 50% reduction of urine M-protein (if measurable) compared to baseline after completion of 4 cycles, had the option to receive low-dose oral dexamethasone in addition to their current dose of pomalidomide. Patients with PD who choose to not add dexamethasone to pomalidomide therapy were discontinued from study treatment. The phase 2 study primary objective will be to determine the efficacy of pomalidomide alone and in combination with low-dose dexamethasone as treatment for patients with relapsed and refractory multiple myeloma. The primary study endpoint is PFS. The secondary endpoints are: objective response determined by European Group for Blood and Marrow Transplantation (EBMT) criteria, time to response, duration of response, overall survival, time to progression, safety, response by International Myeloma Working Group Uniform Response criteria, and exploration of the relationship between response and cytogenetic abnormalities. Patients will be randomized (1:1) to receive single agent pomalidomide or pomalidomide in combination with low-dose dexamethasone. Patients in the

single agent pomalidomide treatment arm who develop confirmed PD at any time will have the option to receive oral dexamethasone in addition to their current dose of pomalidomide. Preliminary data is available from the phase 1b segment of this study. To date, 32 patients have been enrolled and 18 patients have discontinued. Fourteen patients are still ongoing for both safety and efficacy analyses. The mean age was 66.5 years (range: 38-83 years), 62% were women, 66% had Stage III disease, and the median number of prior MM regimens was 6.8 (range, 2-18). Prior multiple myeloma therapies were as follows: lenalidomide (100%), bortezomib (100%), dexamethasone (100%), thalidomide (78%), and stem cell transplant (59%). The MTD was 4 mg (there were 4 drug-related DLTs [grade 4 neutropenia] at 5 mg). Overall, there were a total of 10 dose reductions (7 -neutropenia, 1-rash, 1-peripheral neuropathy, and 1-fatigue) and 9 DLTs (all grade 4 neutropenia) after 133 completed cycles; most of dose reduction occurred at 5 mg (see Table 1). Neutropenia and anemia were the most common grade 3/4 toxicities; there was a dose-dependent increase in grade 4 neutropenia. There were 22 serious adverse events (SAEs) involving 12 patients; the events that were attributed to pomalidomide were deep vein thrombosis, syncope, 2nd degree AV block, asthenia, and diarrhea. In addition, an event of lung infection with neutropenia was attributed to dexamethasone and an event of sepsis with a pharyngeal abscess was attributed to pomalidomide plus dexamethasone. Common adverse events were fatigue, neutropenia, anemia, dyspnea, back pain, nausea, thrombocytopenia, constipation, asthenia, and vomiting. There were 4 deaths which were not attributed to pomalidomide; three patients died of disease progression (PD) and one patient died of gastrointestinal perforation due to amyloidosis. There were responses seen at each dose level. In 25 evaluable patients, clinical activity (stable disease or better) was reported in 23 patients (92%). During the treatment period with pomalidomide alone (25 evaluable patients), the overall response rate (ORR; 1 complete response [CR], 3 partial response [PR], 6 minimal response [MR]) was 40% (10 of 25 patients), mean duration of response (DOR) was 13.5 weeks (range: 4-36 weeks), and mean time to progression (TTP) was 9.5 weeks (range: 2-32 weeks). Fifteen of 25 evaluable patients (60%) had dexamethasone added to their regimens at different cycles (median cycle: 3, range: 2-9) for PD or lack of response. During the treatment period with pomalidomide plus dexamethasone, the ORR (2 PR, 4 MR) was 40% (6 of 15 patients), mean DOR of 16.9 weeks (range: 4-36 weeks), and mean TTP of 16.6 weeks (range: 8-36 weeks). In addition, there were 8 stable disease (SD; 36%) with pomalidomide alone and 7 stable disease (47%) with pomalidomide plus dexamethasone. In 7 of 15 patients (47%), their responses improved after dexamethasone was added (2 PR, 3 MR, and 2 SD). Median number of completed cycles of pomalidomide was 4 (range: 0-12).

In conclusion, the MTD is 4 mg. The safety profile was similar across cohorts except for grade 4 neutropenia, which increased in the 5 mg cohort. There were responses seen at each dose levels; however, the best response and duration of response increased with the dose of pomalidomide and the addition of dexamethasone. Based on the preliminary safety and response data, 4 mg is the recommended dose for the phase 2 segment.

Table 1

| Dose level | Completed cycles (mean / median / range) | DLTs | Dose reductions |
|--------------------------|---|---|--|
| 2 mg (n=6 / 24Jun08) | 17 (2.8 / 0.5 / 0-12) | 0 | 0 |
| 3 mg (n=8 / 25Aug08) | 38 (4.8 / 4 / 1-11) | 2 (2-not drug related neutropenia) | 1 (1-neutropenia) |
| 4 mg (n=8 / 03Nov08) | 49 (6.1 / 7 / 0-11) | 1 (1-not drug related neutropenia) | 0 |
| 5 mg (n=10 / 03Apr09) | 29 (2.9 / 2.5 / 0-5) | 6 (4-drug related neutropenia; 2- not drug related neutropenia) | 9 (6-neutropenia, 1-rash, 1- peripheral neuropathy, 1- fatigue) |
| Total | 133 (4.1 / 4 / 0-12) | 9 | 10 |

2.0 Goals

2.1 Primary Objective.

2.11 Phase I: Determine the maximum tolerated dose (MTD) of bortezomib in combination with pomalidomide and dexamethasone

2.12 Phase II: To evaluate the confirmed response rate (PR, VGPR, or CR) of pomalidomide, bortezomib and dexamethasone in patients with relapsed or refractory myeloma

2.2 Secondary Objectives

2.21 Overall survival, progression-free survival, and duration of response

2.22 To assess the toxicity of pomalidomide, bortezomib and dexamethasone in this patient population.

3.0 Patient Eligibility

3.1 Inclusion Criteria

- 3.11 Age \geq 18 years.
- 3.12 The following laboratory values obtained \leq 14days prior to registration.
- Serum Creatinine \leq 3 mg/dL
 - Absolute neutrophil count \geq 1000/ μ L
 - Untransfused platelet count \geq 75,000/ μ L
- 3.13 Measurable disease of multiple myeloma as defined by at least ONE of the following:
- Serum monoclonal protein \geq 1.0 g/dL (see section 11.1 for definitions)
 - $>$ 200 mg of monoclonal protein in the urine on 24 hour electrophoresis
 - Serum immunoglobulin free light chain \geq 10 mg/dL AND abnormal serum immunoglobulin kappa to lambda free light chain ratio.
 - Monoclonal bone marrow plasmacytosis \geq 30% (evaluable disease).
 - Measurable plasmacytoma that has not been radiated.
- 3.14 ECOG Performance status (PS) 0, 1, or 2 (Appendix I).
- 3.15 Previously treated relapsed or refractory multiple myeloma.
- Patients must have received at least one prior therapy but no more than 4 therapies.
 - One or more of the prior regimens must have included lenalidomide and it has been determined the patient is refractory, resistant, or relapsed this therapy.
 - Prior bortezomib not required but if prior exposure, patients should not be refractory. Refractory means progression on therapy or within 60 days from the last dose of bortezomib.
- 3.17 Provide informed written consent.

- 3.18 Females of reproductive potential must be willing to adhere to the scheduled pregnancy testing as required in the POMALYST REMS™ program.
 - 3.19a Willing and able to take aspirin or alternate prophylactic anticoagulation.
 - 3.19b All previous cancer therapy, including chemotherapy, high dose corticosteroids, immune modulatory drugs or proteasome inhibitors must have been discontinued ≥ 2 weeks prior to study registration.
 - 3.19c Any prior treatment with investigational agents must be discontinued ≥ 28 days prior to study registration.
 - 3.19d Willing to abstain from donating blood during study participation and for 28 days after discontinuation of study drug.
 - 3.19e Men must agree to abstain from donating semen or sperm during study participation and for 28 days after discontinuation of study drug.
 - 3.19f Willingness to return to enrolling institution for follow-up.
 - 3.19g Willing to be registered into the mandatory POMALYST REMS™ program, and willing and able to comply with the requirements of the POMALYST REMS™ program.
- 3.2 Exclusion Criteria
- 3.21 Concomitant high dose corticosteroids (concurrent use of corticosteroids). EXCEPTION: Patients may be on chronic steroids (maximum dose 20 mg/day prednisone equivalent) if they are being given for disorders other than myeloma, i.e., adrenal insufficiency, rheumatoid arthritis, etc.
 - 3.22 Another malignancy undergoing active treatment with the exception of non melanoma skin cancer or in situ cervical or breast cancer.

- 3.23 Any of the following:
- Pregnant women or women of reproductive ability who are unwilling to use effective contraception
 - Nursing women
 - Men who are unwilling to use a condom (even if they have undergone a prior vasectomy) while having intercourse with any woman, while taking the drug and for 4 weeks after stopping treatment.
- 3.24 Other co-morbidity which would interfere with patient's ability to participate in trial, e.g. uncontrolled infection, uncompensated heart or lung disease.
- 3.25 Other concurrent chemotherapy, radiotherapy, or any ancillary therapy considered investigational. **NOTE:** Bisphosphonates are considered to be supportive care rather than therapy, and are thus allowed while on protocol treatment.
- 3.26 Active DVT or PE that has not been therapeutically anticoagulated.
- 3.27 Known positive for HIV or active hepatitis infection.
- 3.28a Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.
- 3.28b Known hypersensitivity to thalidomide or lenalidomide including development of erythema nodosum if characterized by a desquamating rash.
- 3.28c > grade 2 peripheral neuropathy.
- 3.29 Any prior use of pomalidomide.

4.0 Test Schedule As of Addendum 6, discontinue active monitoring and remove patient from study.

| | Active Monitoring | | | | |
|---|----------------------------|-------------------|----------------------------------|--|--|
| | Days Prior to Registration | | Weekly for 1 st cycle | Prior to each Cycle beginning with Cycle 2, pre-treatment ^{1, 16} | End of Cycle 3 and Q 3 cycles ^{1, 6,} |
| | ≤30 days | ≤14 days | | | |
| Complete medical history | X | | | | |
| Adverse Event monitoring | | X | | X | X |
| Physical exam, including height, weight and vital signs | | X | | X | X |
| Performance status (ECOG scale) | | X | | X | X |
| CBC with diff. | | X | X | X | X |
| Chemistry group to include sodium, potassium, glucose, alkaline phosphatase; Total bilirubin; SGOT (AST); serum creatinine, calcium | | X | X ¹³ | X | X |
| LDH, Beta ₂ -microglobulin | X | | | | |
| Electrophoresis of serum and urine | | X ¹² | | X ¹² | X ¹² |
| Affected Immunoglobulin | | X ⁸ | | X ⁸ | X ⁸ |
| Immunofixation serum and urine | X | | | X ² | X ² |
| Immunoglobulin free light chain | | X | | X | X |
| X-ray skeletal survey | X | | | X ⁴ | |
| ECG | X | | | | X |
| TSH | X | | | | X |
| Bone marrow aspirate and biopsy, myeloma FISH, metaphase cytogenetics, flow cytometry ¹⁴ | X | | | | X ⁵ |
| Research bone marrow and blood sample as per 521-93 (patients enrolled in Rochester only) | X ^R | | | | X ^{5, R} |
| Research blood sample (see Section 14.0) | X ^{15, R} | | | X ^{11, R} | |
| Research bone marrow aspirate (see Section 14.0) | X ^R | | | | X ^R |
| Chest x-ray | X | | | | |
| Serum or urine pregnancy test | | X ^{3, 9} | X ^{3, 9} | X ^{3, 9} | |
| Pomalidomide Counseling | | | | X ¹⁰ | |
| Patient Medication Diary (Appendix IV) | | | | X ⁷ | |

Footnotes on the following page.

- 1) All scheduled visits will have a window of ± 7 days unless otherwise stated.
 - 2) Immunofixation (IF) needed only in the absence of M-spike.
 - 3) Pregnancy tests for females of childbearing potential. Patient must follow pregnancy testing requirements as outlined in the POMALYST REMS™ program.
 - 4) Once a year while on active treatment.
 - 5) Required after cycle 3, required beyond that only to document CR or if used to assess response.
 - 6) Must return to registering institution every 3 months during pomalidomide maintenance.
 - 7) Must begin the day the patient starts taking and be completed on a daily basis. Compliance should be documented in the medical record.
 - 8) Affected immunoglobulin refers to the baseline M-protein type, that is, IgG, IgA, or IgD. Not applicable if patient “non-secretory” or if patient has no heavy chain, i.e. light chain myeloma.
 - 9) Pregnancy tests must occur 10 – 14 days and again within 24 hours prior to initiation of pomalidomide with a sensitivity of at least 25 mIU/mL. 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 pomalidomide and at Day 28 post the last dose of pomalidomide. 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 pomalidomide and at Day 14 and Day 28 post the last dose of pomalidomide (see Appendix VI: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).
 - 10) All patients must be counseled according to the POMALYST REMS™ program.
 - 11) Every cycle for the first 4 cycles. If patient had sample collected at on study, the Cycle 1 Day 1 sample is not needed.
 - 12) Urine electrophoresis only needed at baseline if not measurable.
 - 13) AST only.
 - 14) Non-Mayo sites: If flow cytometry cannot be ordered clinically, you may send sample to Mayo Clinic Rochester along with the other research samples (see Section 14.0 and Appendix VIII).
 - 15) Patient may have the first sample collected at on study or on Cycle 1 Day 1 but both are not needed.
 - 16) After the first 3 months of pomalidomide maintenance, if on a stable dose of CC-4047, CBC, chemistry, and tests necessary for disease response can be obtained per test schedule and mailed/faxed to Mayo Clinic and patient can return at least every 3 months for follow up to Mayo. All other procedures are per MD discretion. All unused study drug must be returned to Mayo Clinic and all study drug must be accounted for. Only one month supply of study drug may be provided at each cycle.
- R Research test. Will be charged to study and not to patient’s account.

5.0 Grouping Factor:

5.1 Phase: I (permanently closed 11/13/2012) vs. II.

6.0 Registration/Randomization Procedures

6.1 Registration Procedures for Phase I portion – **Mayo Institutions only**

6.11 Phase I Dose Escalation – Prior to discussing protocol entry with the patient, call the Registration Office [REDACTED] to insure that a place on the protocol is open to the patient.

6.111 To register a patient, fax [REDACTED] a completed eligibility checklist to the Registration Office between 8 a.m. and 4:30 p.m. central time Monday through Friday.

6.2 Registration Procedures for Phase II portion

6.21 Mayo Clinic Cancer Center

To register a patient, access the Mayo Clinic Cancer Center (MCCC) web page and enter the remote registration/randomization application. The remote registration/randomization application is available 24 hours a day, 7 days a week. Back up and/or system support contact information is available on the Web site. If unable to access the Web site, call the MCCC Registration Office at [REDACTED] between the hours of 8 a.m. and 5:00 p.m. Central Time (Monday through Friday).

The instructions for remote registration are available on the MCCC web page [REDACTED] and detail the process for completing and confirming patient registration. Prior to initiation of protocol treatment, this process must be completed in its entirety and a MCCC subject ID number must be available as noted in the instructions. It is the responsibility of the individual registering the patient to confirm the process has been successfully completed prior to release of the study agent. Patient registration via the remote system can be confirmed in any of the following ways:

- Contact the MCCC Registration Office [REDACTED]. If the patient was fully registered, the Registration Office staff can access the information from the centralized database and confirm the registration.
- Refer to “Instructions for Remote Registration” in section “Finding/Displaying Information about A Registered Subject.”

6.22 Dana Farber Cancer Institute and the University of Chicago

To register a patient, fax a completed eligibility checklist to the MCCC Registration Office at [REDACTED] between the hours of 8 a.m. and 4:30 p.m. Central Time (Monday through Friday).

6.3 Phase I and Phase II

6.31 Correlative Research

An optional correlative research component is part of this study, there will be an option to select if the patient is to be registered onto this component (see Section 14.0).

- Patient has/has not given permission to give his/her blood sample for research testing.
- Patient has/has not given permission to give his/her bone marrow sample for research testing.

6.32 Documentation of IRB approval must be on file in the Registration Office before an investigator may register any patients.

In addition to submitting initial IRB approval documents, ongoing IRB approval documentation must be on file (no less than annually) at the Registration Office [REDACTED] [REDACTED]. If the necessary documentation is not submitted in advance of attempting patient registration, the registration will not be accepted and the patient may not be enrolled in the protocol until the situation is resolved.

When the study has been permanently closed to patient enrollment, submission of annual IRB approvals to the Registration Office is no longer necessary.

6.33 Prior to accepting the registration, the following will be verified:

- IRB approval at the registering institution
- Patient eligibility
- Existence of a signed consent form
- Existence of a signed authorization for use and disclosure of protected health information

6.34 Treatment on this protocol must commence at a Mayo Clinic institution, Dana Farber Cancer Institute, or the University of Chicago under the supervision of a medical oncologist or hematologist.

6.35 Treatment cannot begin prior to registration and must begin ≤ 7 days after registration.

6.36 Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule.

6.37 All required baseline symptoms must be documented and graded.

6.38 Study drug availability checked.

6.39 The CRA must notify the Celgene study monitor of each confirmed patient registration.

7.0 Protocol Treatment

7.1 Treatment schedule

Cohort I (Dose Escalation phase)

| Agent | Dose | Route | Day | Cycle length |
|---------------|--|-------------------|-------------------|--------------|
| Pomalidomide* | 4 mg/day | PO | Days 1-21 | 28 days |
| Bortezomib | As assigned by MCCC Registration Office | IV | Days 1, 8, 15, 22 | |
| Dexamethasone | 40 mg/day | PO (with food) | Days 1, 8, 15, 22 | |
| Aspirin** | 325 mg/day | PO (with food) | Days 1-28 | |

Cohort II (Phase II studies at MTD)

| Agent | Dose | Route | Day | Cycle length |
|---------------|-----------------------|-------------------|-------------------|--------------|
| Pomalidomide* | 4 mg/day | PO | Days 1-21 | 28 days |
| Bortezomib | 1.3 mg/m ² | IV or SQ | Days 1, 8, 15, 22 | |
| Dexamethasone | 40 mg/day | PO (with food) | Days 1, 8, 15, 22 | |
| Aspirin** | 325 mg/day | PO (with food) | Days 1-28 | |

* Pomalidomide will be provided free of charge by Celgene.

** Full dose anticoagulation with either warfarin or low molecular weight heparin may be substituted at MD discretion. This is advised for patients with personal or strong family history of thromboembolism. If patient cannot tolerate 325 mg/day, they may take 81 mg/day.

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.

7.2 Cohort I

7.21 Dose Escalation:

| Dose Level | Pomalidomide (mg/day) | Bortezomib (mg/m ²) | Dexamethasone (mg/day) |
|------------|-----------------------|---------------------------------|------------------------|
| 0 | 4 (days 1-21) | 0.7 (days 1, 8, 15, 22) | 40 (days 1, 8, 15, 22) |
| 1* | 4 (days 1-21) | 1.0 (days 1, 8, 15, 22) | 40 (days 1, 8, 15, 22) |
| 2 | 4 (days 1-21) | 1.3 (days 1, 8, 15, 22) | 40 (days 1, 8, 15, 22) |

* Starting dose level

7.22 Three patients will be treated at each dose level and observed for a minimum of 28 days (i.e. one cycle) before new patients are treated. The study will temporarily close during this time.

7.23 For this protocol, dose-limiting toxicity (DLT) will be defined as an adverse event attributed (definitely, probably, or possibly) in the first cycle to the study treatment and meeting the following criteria:

| <i>Toxicity</i> | <i>DLT Definition*</i> |
|------------------------|--|
| Hematologic | Grade 4 ANC for ≥ 7 days or Grade 4 PLT for ≥ 7 days |
| Infection | Grade 4 |
| Febrile Neutropenia | Defined as fever $\geq 38.5^{\circ}\text{C}$ ($38 > 1$ hour) with \geq grade 3 Neutropenia |
| Other Non-hematologic | Any other \geq grade 3 event as per NCI Common Terminology Criteria for Adverse Events v4.0**. |

* Any toxicities that cause dose delay of > 2 weeks of the intended next dose will also be considered dose-limiting.

** Grade 3 nausea, vomiting, or diarrhea with maximal supportive treatment(s) will be considered dose-limiting. Fatigue and mouth sores that are considered Grade 3 with an attribution of definitely, probably, or possibly related to treatment will be reviewed by the study team to determine if they were due to other causes (i.e. disease progression or infection) or treatment. If it is determined that the fatigue or mouth sores were due to other causes they would not be considered a DLT.

7.24 MTD Determination:

7.241 MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of patients (at least 2 of a maximum of 6 new patients).

7.242 Three patients will be treated at a given dose level combination and observed for at least 4 weeks to assess toxicity.

- 7.243 If dose-limiting toxicity (DLT) is not seen in any of the 3 patients, up to 3 new patients will be accrued and treated at the next higher dose level. If DLT is seen in 2 patients treated at a given dose level, no more patients will be treated at that dose level and the next 3 patients will be treated at the next lower dose level.
- 7.244 If a DLT is seen in 1 of 3 patients treated at a given dose level, up to 3 additional patients will be enrolled and treated at the same dose level. If DLT is seen in at least one of these additional three patients (≥ 2 of 6), the MTD will have been exceeded, and further accrual will cease to this cohort (see 7.245 for further details). If dose-limiting toxicity (DLT) is not seen in any of the three additional patients, 3 new patients will be accrued and treated at the next higher dose level.
- 7.245 If DLT is observed in at least 2 of 6 patients after enrolling 6 patients on a specific dose level, then the MTD will have been exceeded and defined as the previous dose unless only 3 patients were treated at the lower dose level. In that case, 3 additional patients will be treated at this lower dose level such that a total of 6 patients are treated at the MTD to more fully assess the toxicities associated with the MTD.

7.25 Dose de-escalation:

If the starting dose exceeds the MTD, then patients will be accrued to level 0. If level 0 is tolerated, that will be the dose taken forward to the Phase II. If level 0 is not tolerated, the study team will consider an alternative dosing schedule to study.

7.26 Dose escalation:

All patients will receive their assigned dose for the first cycle. If no DLT criteria are encountered, patients may be dose escalated (per schedule in Section 7.21) in subsequent cycles per investigator and patient discretion as long as that dose level has been shown to be safe. Patients on the starting dose level will not be allowed to dose escalate until subsequent cohorts of patients have been treated at the higher dose levels.

- 7.27 If a patient fails to complete cycle 1 for reasons other than toxicity, the patient will be regarded as inevaluable and an additional patient will be treated at the current dose level; however, all toxicity information will be utilized in the analysis.

7.3 **Cohort II**

- 7.31 The phase II portion of the trial will be based on findings from cohort I. At that time, an amendment will be completed updating the treatment schedule table in section 7.1.

7.4 Pomalidomide maintenance (Cohort I and Cohort II)

- 7.41 After 8 cycles of treatment patients will discontinue bortezomib and dexamethasone and continue pomalidomide 4 mg by mouth daily (or the dose they were on at the end of 8 cycles if the pomalidomide was dose reduced) for 21 days of every 28 day cycle until progression, adverse event, or refusal of treatment. Patients returning to study site every 3 months during maintenance may have drug mailed monthly.

7.5 Treatment by Local Medical Doctor (LMD)

Cycle 1 and Day 1 of Cycles 2-8 must be administered at the registering site. When it has been determined that the patient is tolerating therapy without excessive toxicity at a stable dose level, the bortezomib may be administered by the patient's Local Medical Doctor's Office (LMD). The registering physician retains responsibility for the patient.

In this case, a written statement outlining drug dosage, method of administration, follow-up tests required, and telephone number to call to discuss any questions with the responsible investigator must be sent with the patient to provide necessary information to the LMD. The LMD will be required to supervise the administration of the study drugs as stipulated in the protocol and provide written documentation that the drug was administered.

8.0 Dosage Modification Based on Adverse Events

Strictly follow the modifications in this table for the first **two** cycles, until individual treatment tolerance can be ascertained. Thereafter, these modifications should be regarded as guidelines to produce mild-to-moderate, but not debilitating, side effects. If multiple adverse events are seen, administer dose based on greatest reduction required for any single adverse event observed. If adverse event could be related to more than 1 drug, attribution and dose modifications are at the discretion of the physician. Reductions or increases apply to treatment given in the preceding cycle and are based on adverse events observed since the prior dose. Treatment modifications are based on adverse events. All adverse events should be graded according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. Dose modification recommendations listed below are general guidelines, and appropriate dose adjustments for patient safety should be done if needed after approval by the principal investigator or his representative.

ALERT: ADR reporting may be required for some adverse events (See Section 10)

Subjects will be evaluated for AEs at each visit with the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 used as a guide for the grading of severity.

8.1 Pomalidomide

8.11 Pomalidomide Dose Reduction Levels

| Pomalidomide Dose Reduction Steps | |
|--|--|
| Starting Dose | 4 mg PO daily on days 1 through 21 every 28 days |
| Dose Level -1 | Decrease to 3 mg PO daily on days 1 through 21 every 28 days |
| Dose Level -2 | Decrease to 2 mg PO daily on days 1 through 21 every 28 days |
| Dose Level -3 | Decrease to 1.5 mg PO daily on days 1 through 21 every 28 days |
| Dose Level -4 | Decrease to 1.0 mg PO daily on days 1 through 21 every 28 days |
| Dose Level -5 | Decrease to 0.5 mg PO daily on days 1 through 21 every 28 days |
| Dose Level -6 | Discontinue |

8.12 Pomalidomide Dose Modifications

Pomalidomide is to be dose modified as described in the table below using the following dose modifications:

| Dose Modification for Pomalidomide (Based on Pomalidomide-Related Adverse Event Observed on Days 2-28) | | |
|---|---|---|
| ADVERSE EVENT/SYMPTOMS | Day 2-14 of Cycle | ≥Day 14 of Cycle |
| ≥ Grade 3 Febrile neutropenia or Grade 4 Neutrophil Count Decreased | <ul style="list-style-type: none"> Omit pomalidomide. Follow CBC weekly. If neutropenia has resolved to ≤ grade 2 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit pomalidomide for remainder of cycle. Begin next cycle at next lower dose. |
| ≥ Grade 4 Platelet Count Decreased | <ul style="list-style-type: none"> Omit pomalidomide. Follow CBC weekly. If thrombocytopenia resolves to ≤ grade 2 restart at next lower dose level and continue the cycle Hold anticoagulation for platelet count < 50,000 | <ul style="list-style-type: none"> Omit pomalidomide for remainder of cycle. Begin next cycle at next lower dose. Hold anticoagulation for platelet count < 50,000 |
| Erythroderma Grade 3 | <ul style="list-style-type: none"> If Grade 3 Omit pomalidomide. Follow weekly. If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit pomalidomide for remainder of cycle. If the adverse event resolves to ≤ grade 2 restart next cycle at next lower dose. |
| Grade 4 | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |
| Grade 1-3 Rash maculo-papular | <ul style="list-style-type: none"> Omit pomalidomide and bortezomib for remainder of cycle. If the adverse event resolves to ≤ grade 2 restart at next lower dose level on next cycle. | <ul style="list-style-type: none"> Omit pomalidomide and bortezomib for remainder of cycle. If the adverse event resolves to ≤ grade 2 restart at next lower dose level on next cycle. |
| Grade 3-4 Stevens-Johnson syndrome | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |
| ≥ Grade 3 Erythema multiforme | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |

| Dose Modification for Pomalidomide (Based on Pomalidomide-Related Adverse Event Observed on Days 2-28) | | |
|---|--|---|
| ADVERSE EVENT/SYMPTOMS | Day 2-14 of Cycle | ≥Day 14 of Cycle |
| Peripheral motor neuropathy Or Peripheral sensory neuropathy Grade 3 | <ul style="list-style-type: none"> If Grade 3 Omit pomalidomide. Follow weekly. If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit pomalidomide for remainder of cycle. Begin next cycle at next lower dose. |
| Grade 4 | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |
| Sinus bradycardia/other cardiac arrhythmia Grade 2 | <ul style="list-style-type: none"> Omit pomalidomide. Follow at least weekly. If the adverse event resolves to ≤ grade 1 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit pomalidomide for the remainder of the cycle. Begin next cycle at next lower dose. |
| Grade 3 | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |
| Allergic reaction Grade 2-3 | <ul style="list-style-type: none"> Omit pomalidomide. Follow at least weekly. If the adverse event resolves to ≤ grade 1 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit pomalidomide for the remainder of the cycle. Begin next cycle at next lower dose. |
| Anaphylaxis Grade 4 | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |
| Constipation Grade 1-2 | <ul style="list-style-type: none"> Initiate bowel regimen and maintain dose level. | <ul style="list-style-type: none"> Initiate bowel regimen and maintain dose level. |
| ≥ Grade 3 | <ul style="list-style-type: none"> If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit pomalidomide for the remainder of the cycle. Begin next cycle at next lower dose. |
| Thromboembolic event ≥ Grade 3 | <ul style="list-style-type: none"> Omit pomalidomide and start anticoagulation; restart at investigator's discretion (maintain dose level). | <ul style="list-style-type: none"> Omit pomalidomide for remainder of cycle and start anticoagulation. Begin next cycle at physician discretion (maintain dose level). |

| Dose Modification for Pomalidomide (Based on Pomalidomide-Related Adverse Event Observed on Days 2-28) | | |
|---|---|---|
| ADVERSE EVENT/SYMPTOMS | Day 2-14 of Cycle | ≥Day 14 of Cycle |
| Other Non-hematologic adverse events Assessed as POMALIDOMIDE-Related ≥ Grade 3 | <ul style="list-style-type: none"> Omit pomalidomide. Follow at least weekly. If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit pomalidomide for remainder of cycle. Begin next cycle at next lower dose. |
| ≥ Grade 2 Hyperthyroidism or Hypothyroidism | <ul style="list-style-type: none"> Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart pomalidomide next cycle (decrease dose by one dose level). | <ul style="list-style-type: none"> Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart pomalidomide next cycle (decrease dose by one dose level). |

8.2 Bortezomib

8.21 Bortezomib Dose Reduction Levels

| Bortezomib Dose Reduction Steps | | | |
|--|---|--|--|
| Starting Dose | 1.3 mg/m² | 1.0 mg/m² | 0.7 mg/m² |
| Dose Level -1 | Decrease to 1.0 mg/m ² IV daily on days 1,8,15,22 every 28 days | Decrease to 0.7 mg/m ² IV daily on days 1,8,15,22 every 28 days | Decrease to 0.3 mg/m ² IV daily on days 1,8,15,22 every 28 days |
| Dose Level -2 | Decrease to 0.7 mg/m ² IV daily on days 1,8,15,22 every 28 days | Decrease to 0.3 mg/m ² IV daily on days 1,8,15,22 every 28 days | Discontinue |
| Dose Level -3 | Decrease to 0.3 mg/m ² IV daily on days 1,8,15,22 every 28 days | Discontinue | |
| Dose Level -4 | Discontinue | | |

8.22 Bortezomib Dose Modifications

Bortezomib is to be dose modified as described in the table below using the following dose modifications:

| Dose Modification for Bortezomib (Based on Bortezomib-Related Adverse Event Observed on Days 2-21) | | |
|---|--|---|
| ADVERSE EVENT/SYMPTOMS | Day 2-14 of Cycle | ≥Day 14 of Cycle |
| ≥ Grade 3 Febrile neutropenia or Grade 4 Neutrophil Count Decreased | <ul style="list-style-type: none"> Omit bortezomib. Follow CBC weekly. If neutropenia has resolved to ≤ grade 2 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit bortezomib for remainder of cycle. Begin next cycle at next lower dose. |
| ≥ Grade 4 Platelet Count Decreased | <ul style="list-style-type: none"> Omit bortezomib. Follow CBC weekly. If thrombocytopenia resolves to ≤ grade 2 restart at next lower dose level and continue the cycle until Day 11 Hold anticoagulation for platelet count < 50,000 | <ul style="list-style-type: none"> Omit bortezomib for remainder of cycle. Begin next cycle at next lower dose. Hold anticoagulation for platelet count < 50,000 |
| Erythroderma Grade 3 | <ul style="list-style-type: none"> If Grade 3 Omit bortezomib. Follow weekly. If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit bortezomib for remainder of cycle. Begin next cycle at next lower dose. |
| Grade 4 | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |
| Grade 1-3 Rash maculo-papular | <ul style="list-style-type: none"> Omit pomalidomide and bortezomib for remainder of cycle. Restart at next lower dose level on next cycle. | <ul style="list-style-type: none"> Omit pomalidomide and bortezomib for remainder of cycle. Restart at next lower dose level on next cycle. |
| Grade 3-4 Stevens-Johnson syndrome | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |
| ≥ Grade 3 Erythema multiforme | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |

| Dose Modification for Bortezomib (Based on Bortezomib-Related Adverse Event Observed on Days 2-11) | | |
|---|--|--|
| ADVERSE EVENT/SYMPTOMS | Day 2-14 of Cycle | ≥Day 14 of Cycle |
| Peripheral motor neuropathy Or Peripheral sensory neuropathy Grade 3 | <ul style="list-style-type: none"> If Grade 3 Omit bortezomib. Follow weekly. If the adverse event resolves to ≤ grade 1 or baseline grade and restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit bortezomib for remainder of cycle. Begin next cycle at next lower dose. |
| Grade 4 | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |
| Sinus bradycardia/ other cardiac arrhythmia Grade 2 | <ul style="list-style-type: none"> Omit bortezomib. Follow at least weekly. If the adverse event resolves to ≤ grade 1 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit bortezomib for the remainder of the cycle. Begin next cycle at next lower dose. |
| Grade 3 | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |
| Allergic reaction Grade 2-3 | <ul style="list-style-type: none"> Omit bortezomib. Follow at least weekly. If the adverse event resolves to ≤ grade 1 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit bortezomib for the remainder of the cycle. Begin next cycle at next lower dose. |
| Anaphylaxis Grade 4 | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. | <ul style="list-style-type: none"> Discontinue all study drugs and go to event monitoring. |
| Constipation Grade 1-2 | <ul style="list-style-type: none"> Initiate bowel regimen and maintain dose level. | <ul style="list-style-type: none"> Initiate bowel regimen and maintain dose level. |
| ≥ Grade 3 | <ul style="list-style-type: none"> If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> Omit bortezomib for the remainder of the cycle. Begin next cycle at next lower dose. |
| Thromboembolic event ≥ Grade 3 | <ul style="list-style-type: none"> Omit bortezomib and start anticoagulation; restart at investigator's discretion (maintain dose level). | <ul style="list-style-type: none"> Omit bortezomib for remainder of cycle and start anticoagulation. Begin next cycle at next lower dose. |

| Dose Modification for Bortezomib (Based on Bortezomib -Related Adverse Event Observed on Days 2-28) | | |
|--|--|--|
| ADVERSE EVENT/SYMPTOMS | Day 2-7 of Cycle | ≥Day 8 of Cycle |
| Other Non-hematologic adverse events Assessed as bortezomib - Related ≥ Grade 3 | <ul style="list-style-type: none"> • Omit bortezomib. Follow at least weekly. • If the adverse event resolves to ≤ grade 2 restart at next lower dose level and continue the cycle | <ul style="list-style-type: none"> • Omit bortezomib for remainder of cycle. Begin next cycle at next lower dose. |

8.3 Dexamethasone

8.31 Dexamethasone Dose Reduction Levels

| Dexamethasone Dose Reduction Steps | |
|---|---|
| Starting Dose | 40 mg/day PO on days 1, 8, 15, 22. Cycles repeat every 28 days |
| Dose Level -1 | Decrease to 20 mg/day PO on Days 1, 8, 15, 22 |
| Dose Level -2 | Decrease to 12 mg/day PO on Days 1, 8, 15, 22 |
| Dose Level -3 | Decrease to 8 mg/day PO on Days 1, 8, 15, 22 |
| Dose Level -4 | Decrease to 4 mg/day PO on Days 1, 8, 15, 22 |
| Dose Level -5 | Discontinue |

8.32 Dexamethasone Dose Modifications

Dexamethasone is to be dose modified as described in the table below using the following dose modifications:

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) CTEP Active Version unless otherwise specified ← ←

| SYSTEM ORGAN CLASS (SOC) | ADVERSE EVENT/SYMPTOMS | AGENT | DOSAGE CHANGE |
|--|--|---------------|--|
| BASED ON INTERVAL Adverse Events | | | |
| Gastrointestinal Disorders | Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management) | DEXAMETHASONE | Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level. |
| | ≥Grade 3 (requiring hospitalization or surgery) | | Omit dexamethasone until symptoms adequately controlled. Restart by decreasing dose by 1 dose level along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. |
| Investigations | Grade 3 or 4 Serum amylase increased | | Discontinue dexamethasone and do not resume. Hold pomalidomide and bortezomib at physician discretion and restart once resolved to ≤grade 2. |
| General disorders and administration site conditions | Edema limbs or Edema trunk ≥Grade 3 (limiting function and unresponsive to therapy or anasarca). | | Diuretics as needed, and decrease dexamethasone dose by 1 dose level. |
| Psychiatric disorders | Confusion or Anxiety or Depression ≥ Grade 2 (interfering with function +/- interfering with activities of daily living). | | Omit dexamethasone until symptoms adequately controlled. Restart by decreasing dose by 1 dose level. |
| Musculoskeletal and connective tissue disorders | Muscle weakness ≥ Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living). | | Decrease dexamethasone dose by 1 dose level. If weakness persists decrease dose by 1 dose level as needed. |

→ → Use Common Terminology Criteria for Adverse Events (CTCAE) CTEP Active Version unless otherwise specified ← ←

| SYSTEM ORGAN CLASS (SOC) | ADVERSE EVENT/SYMPTOMS | AGENT | DOSAGE CHANGE |
|---|--------------------------------------|---------------|--|
| BASED ON INTERVAL Adverse Events | | | |
| Metabolism and nutrition disorders | Hyperglycemia ≥ Grade 3 or higher | DEXAMETHASONE | Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by 1 dose level. |
| Any Other non-hematologic | ≥ Grade 3 or higher | | Omit dexamethasone until symptoms adequately controlled. Restart by decreasing dose by 1 dose level. |

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

- The ANC is ≥ 1,000/μL;
- The platelet count is ≥ 50,000/μL;
- Any pomalidomide-related allergic reaction/hypersensitivity or sinus bradycardia/ other cardiac arrhythmia adverse event that may have occurred has resolved to ≤ Grade 1 severity;
- Any other pomalidomide-related adverse event that may have occurred has resolved to ≤ Grade 1 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 pomalidomide will not be initiated until the adverse event has resolved as described above. When therapy is resumed it will be considered Day 1 of the new cycle. If pomalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. **If pomalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to adverse event newly encountered on the scheduled Day 1**, then the new cycle will be started with a one-level dose reduction. If the study drug cannot be restarted within 35 days of the scheduled Day 1 of a given cycle, the principal investigator must be contacted.

NOTE: If the patient experiences a significant adverse event requiring a dose reduction at the start of the next cycle, then the dose will remain lowered for that entire subsequent cycle. If that cycle is completed with no further adverse events greater than Grade 2, then the dose may be increased, at the investigator’s discretion, one level at a time, in the following cycles.

NOTE: Adverse events requiring a dose-reduction step for any or all drugs beyond the two dose-reduction steps (levels –1 and –2) will be at the discretion of the treating physician, if the decision is made for the patient to be kept on study. These dose reductions must be clearly recorded in reported clinical data.

9.0 Ancillary Treatment/Supportive Care

- 9.1 Patients should receive prophylaxis for varicella zoster with acyclovir or an equivalent antiviral. Prophylaxis for other opportunistic infections such as *Pneumocystis* pneumonia is also encouraged.
- 9.2 Patients may receive concurrent treatment with a bisphosphonate.
- 9.3 Patients may be on chronic steroids (maximum dose 20 mg/day prednisone equivalent) if they are being given for disorders other than myeloma, i.e., adrenal insufficiency, rheumatoid arthritis, etc.
- 9.4 The following medications are not permitted during the trial:
- Any other investigational treatment
 - Any cytotoxic chemotherapy
 - Any other systemic anti-neoplastic therapy including, but not limited to, immunotherapy, hormonal therapy or monoclonal antibody therapy.
- 9.5 Antiemetics may be used at the discretion of the attending physician.
- 9.6 Blood products and growth factors should be utilized as clinically warranted and following institutional policies and recommendations. The use of growth factors should follow published guidelines of the American Society of Clinical Oncology 2006 Update of Recommendations for the Use of White Blood Cell Growth Factors: An Evidence-Based Clinical Practice Guideline. *Journal of Clinical Oncology* 2006;24(19):3187-3205.
- 9.7 Patients should receive full supportive care while on this study. This includes blood product support, antibiotic treatment, and treatment of other newly diagnosed or concurrent medical conditions. All blood products and concomitant medications such as antidiarrheals, analgesics, and/or antiemetics received from the first day of study treatment administration until 30 days after the final dose will be recorded in the medical records.
- 9.8 Diarrhea: This could be managed conservatively with loperamide. The recommended dose of loperamide is 4 mg at first onset, followed by 2 mg every 2-4 hours until diarrhea free (maximum 16 mg/day).
- In the event of grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals.
- If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting **should be hospitalized** for intravenous hydration and correction of electrolyte imbalances.
- 9.9 White cell growth factors [G-CSF (Neupogen or Neulasta) or GM-CSF]: Use of growth factors during Phase I to maintain doses is not allowed. The use of white cell growth factors is not allowed *prophylactically* during Cycle 1 but can be used to treat neutropenia during Cycle 1. In Cycles 2 and beyond, the drug can be used prophylactically or to treat neutropenia per physician discretion. Platelet growth factors such as Neumega may be used at physician discretion for

thrombocytopenia. Recombinant erythropoietin to maintain adequate hemoglobin levels and avoid packed red blood cell transfusions is allowed and should be in concordance with current guidelines. Patients can be placed on prophylactic antibiotics as per Infectious Diseases Society of America guidelines (Clinical Infectious Diseases 2002; 34:730–751). During the Phase II growth factors may be used in any cycle at physician discretion.

10.0 Adverse Event (AE) Reporting and Monitoring

10.1 Adverse Event Characteristics

CTCAE term (AE description) and grade: The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm)

10.11 Adverse event monitoring and reporting is a routine part of every clinical trial. First, identify and grade the severity of the event using the CTCAE version 4.0. Next, determine whether the event is expected or unexpected (see Section 10.2) and if the adverse event is related to the medical treatment or procedure (see Section 10.3). With this information, determine whether the event must be reported as an expedited report (see Section 10.4). Expedited reports are to be completed within the timeframes and via the mechanisms specified in Sections 10.4. All AEs reported via expedited mechanisms must also be reported via the routine data reporting mechanisms defined by the protocol (see Sections 10.52 and 18.0).

10.12 Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term (LLT).

- **NOTE:** A severe AE, as defined by the above grading scale, is **NOT** the same as serious AE which is defined in the table in Section 10.4.

10.2 Expected vs. Unexpected Events

- The determination of whether an AE is expected is based on agent-specific information provided in Section 15.0 of the protocol.
- Unexpected AEs are those not listed in the agent-specific information provided in Section 15.0 of the protocol.

NOTE: “Unexpected adverse experiences” means any adverse experience that is neither identified in nature, severity, or frequency of risk in the information provided for IRB review nor mentioned in the consent form.

10.3 Assessment of Attribution

When assessing whether an adverse event is related to a medical treatment or procedure, the following attribution categories are utilized:

Definite - The adverse event *is clearly related* to the agent(s).

Probable - The adverse event *is likely related* to the agent(s).

Possible - The adverse event *may be related* to the agent(s).

Unlikely - The adverse event *is doubtfully related* to the agent(s).

Unrelated - The adverse event *is clearly NOT related* to the agent(s).

10.31 **AEs Experienced Utilizing Investigational Agents and Commercial Agent(s) on the SAME Arm**

NOTE: The combination of an investigational agent with a commercial agent is considered investigational.

Routine Reporting

- Routine AE reporting for Phase 1 and Phase 2 clinical studies using an investigational agent /intervention in combination with a commercial agent is stated in the protocol. See Section 10.52.

NOTE: When a commercial agent(s) is (are) used on the same treatment arm as the investigational agent/intervention (also, investigational drug, biologic, cellular product, or other investigational therapy under an IND), the entire combination (arm) is then considered an investigational intervention for reporting-

Expedited Reporting

- An AE that occurs on a combination study must be assessed in accordance with the guidelines for CTEP investigational agents/interventions in Section 10.4, and where indicated, an expedited report must be submitted.
- An AE that occurs prior to administration of the investigational agent/intervention must be assessed as specified in the protocol. In general, only Grade 4 and 5 AEs that are unexpected with at least possible attribution to the commercial agent require an expedited report. Refer to Section 10.4 for specific AE reporting requirements or exceptions.
- Commercial agent expedited reports must be submitted by the Cooperative Group to the FDA via MedWatch.
- An investigational agent/intervention might exacerbate the expected AEs associated with a commercial agent. Therefore, if an expected AE (for the commercial agent) occurs with a higher degree of severity, expedited reporting is required. The clinical investigator must determine severity.

10.32 Special Situations for Expedited Reporting¹

Exceptions to Expedited Reporting: EXPECTED Serious Adverse Events

An expedited report may not be required for specific Grade 1, 2 and 3 Serious Adverse Events where the AE is listed in Section 15.0 of the protocol or the consent form* as **EXPECTED**. Any protocol specific reporting procedures **MUST BE SPECIFIED BELOW** and will supercede the standard Expedited Adverse Event Reporting Requirements:

| System Organ Class (SOC) | Adverse event/ Symptoms | CTCAE Grade at which the event will not be expeditedly reported. | Expected Frequency per Section 15.0 or IB | Expected Frequency per PI experience |
|--------------------------------------|----------------------------|--|---|--------------------------------------|
| Blood and lymphatic system disorders | Anemia | Grade 3 or 4 | % | 30% |
| Investigations | White blood cell decreased | Grade 3 or 4 | % | 30% |
| | Lymphocyte count decreased | Grade 3 or 4 | % | 30% |
| | Neutrophil count decreased | Grade 3 or 4 | % | 30% |
| | Platelet count decreased | Grade 3 or 4 | % | 30% |

¹ This exception only applies if the adverse event does not result in hospitalization ≥ 24 hours. If this adverse event results in hospitalization ≥ 24 hours, then the standard expedited adverse events reporting requirements must be followed.

Specific protocol exceptions to expedited reporting should be reported expeditiously by investigators **ONLY** if they exceed the expected grade of the event.

*The consent form may contain study specific information at the discretion of the Principal Investigator; it is possible that this information may NOT be included in the protocol or the investigator brochure.

10.331 Persistent or Significant Disabilities/Incapacities

Any AE that results in persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions (formerly referred to as disabilities), congenital abnormalities or birth defects, must be reported immediately if they occur at any time following treatment with an agent under an IND/IDE since they are considered to be a serious AE and must be reported to the sponsor as specified in 21 CFR 312.64(b).

10.332 Death

- Any death occurring within 30 days of the last dose, regardless of attribution to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- Any death occurring greater than 30 days with an attribution of possible, probable, or definite to an agent/intervention under an IND/IDE requires expedited reporting within 24-hours.
- **Reportable categories of Death**
 - Death attributable to a CTCAE term.
 - Death Neonatal: A disorder characterized by cessation of life during the first 28 days of life.
 - Death NOS: A cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
 - Sudden death NOS: A sudden (defined as instant or within one hour of the onset of symptoms) or an unobserved cessation of life that cannot be attributed to a CTCAE term associated with Grade 5.
 - Death due to progressive disease should be reported as **Grade 5 “Neoplasms benign, malignant and unspecified (incl cysts and polyps) – Other (Progressive Disease)”** under the system organ class (SOC) of the same name. Evidence that the death was a manifestation of underlying disease (e.g., radiological changes suggesting tumor growth or progression: clinical deterioration associated with a disease process) should be submitted.
- Any death occurring **within 30 days of the last dose, regardless of attribution to the investigational agent/intervention requires expedited reporting within 24 hours.**
- **Any death occurring greater than 30 days after the last dose of the investigational agent/intervention requires expedited reporting within 24 hours only if it is possibly, probably, or definitely related to the investigational agent/intervention.**

10.333 Secondary Malignancy

- A **secondary malignancy** is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

- All secondary malignancies that occur following treatment with an agent under an IND/IDE be reported. Three options are available to describe the event:
 - Leukemia secondary to oncology chemotherapy (e.g., Acute Myelocytic Leukemia [AML])
 - Myelodysplastic syndrome (MDS)
 - Treatment-related secondary malignancy
- Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

10.334 **Second Malignancy**

- A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting-

10.335 **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 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 (see Forms Packet).

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 (see Forms Packet).

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 Celgene SAE Report Form (see Forms Packet).

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 Celgene SAE Report Form (see Forms Packet).

Male Subjects

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

Celgene Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management

[Redacted]

Fax: [Redacted]
E-mail: [Redacted]

10.336 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 or MEDWATCH 3500A form (see Forms Packet) 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-0019) 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

[Redacted]

[Redacted]

10.4 Expedited Reporting Requirements for IND/IDE Agents

10.41 Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention^{1,2}

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)
NOTE: Investigators **MUST** immediately report to the sponsor **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)
 An adverse event is considered serious if it results in **ANY** of the following outcomes:

- 1) Death
- 2) A life-threatening adverse event
- 3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- 4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- 5) A congenital anomaly/birth defect.
- 6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to the sponsor within the timeframes detailed in the table below.

| Hospitalization | Grade 1 Timeframes | Grade 2 Timeframes | Grade 3 Timeframes | Grade 4 & 5 Timeframes |
|---|--------------------|--------------------|--------------------|-------------------------|
| Resulting in Hospitalization ≥ 24 hrs | 7 Calendar Days | | | 24-Hour 3 Calendar Days |
| Not resulting in Hospitalization ≥ 24 hrs | Not required | 7 Calendar Days | | |

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in section 10.33 of the protocol.

Expedited AE reporting timelines are defined as:

- “24-Hour; 3 Calendar Days” - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 3 calendar days of the initial 24-hour report.
- “7 Calendar Days” - A complete expedited report on the AE must be submitted within 7 calendar days of learning of the AE.

¹Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:
Expedited 24-hour notification followed by complete report within 3 calendar days for:

- All Grade 4, and Grade 5 AEs

Expedited 7 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

² For studies using PET or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote “1” above applies after this reporting period.

Effective Date: May 5, 2011

See additional instructions included on the next page.

Additional instructions:

1. Contact Celgene Drug Safety via fax at [REDACTED] or via mail at Celgene Corporation, Worldwide Drug Safety Surveillance (WWDSS), [REDACTED], Summit, NJ 07901..
2. Use the Celgene Serious Adverse Event Report Form (see Forms Packet). Submit to Celgene Drug Safety via fax at [REDACTED] or via mail at Celgene Corporation, Worldwide Drug Safety Surveillance (WWDSS), [REDACTED], Summit, NJ 07901.

Mayo Clinic Cancer Center (MCCC) Institutions: Provide copies, along with the UPIRTSO cover sheet, by fax [REDACTED] to the MCCC Regulatory Affairs Unit (RAU) Risk Information Specialist who will determine and complete IRB reporting. The RAU will submit to the MCCC SAE Coordinator and the MCCC IND Coordinator to determine if FDA submission is needed.

Non-MCCC Institutions: Provide copies by fax [REDACTED] to the MCCC SAE Coordinator who will forward to the MCCC IND Coordinator to determine if FDA submission is needed.

10.5 Other Required Reporting

- 10.51 Adverse events to be graded at each evaluation and pretreatment symptoms/conditions to be evaluated at baseline per the CTCAE v4.0 grading unless otherwise stated in the table below:

| SYSTEM ORGAN CLASS (SOC) | Adverse event/Symptoms | Baseline | Each evaluation |
|--|--|----------|-----------------|
| Investigations | Neutrophil count decreased | X | X |
| | White blood cell decreased | X | X |
| | Platelet count decreased | X | X |
| Blood and lymphatic system disorders | Anemia | X | X |
| Vascular disorders | Thromboembolic event | X | X |
| General disorders and administration site conditions | Fatigue | X | X |
| Nervous system disorders | Peripheral sensory neuropathy | X | X |
| Gastrointestinal disorders | Number of stools | X | |
| | Diarrhea | | X |
| | Nausea | X | X |
| | Vomiting | X | X |
| Infections and infestations | Lung infection | X | X |
| | Infections and infestations – Other, specify (Herpes Zoster) | X | X |

- 10.52 Submit via appropriate MCCC Case Report Forms (i.e., paper or electronic, as applicable) the following AEs experienced by a patient and not specified in Section 10.5:
- 10.521 Grade 2 AEs deemed *possibly, probably, or definitely* related to the study treatment or procedure.
- 10.522 Grade 3 and 4 AEs regardless of attribution to the study treatment or procedure.
- 10.523 Grade 5 AEs (Deaths)
- 10.5231 Any death within 30 days of the patient's last study treatment or procedure regardless of attribution to the study treatment or procedure.
- 10.5232 Any death more than 30 days after the patient's last study treatment or procedure that is felt to be at least possibly treatment related must also be submitted as a Grade 5 AE, with a CTCAE type and attribution assigned.
- 10.53 Refer to the instructions in the Forms Packet (or electronic data entry screens, as applicable) regarding the submission of late occurring AEs following completion of the Active Monitoring Phase (i.e., compliance with Test Schedule in Section 4.0).

11.0 Treatment Evaluation – The International Myeloma Working Group (IMWG) uniform response criteria³⁷ will be used to assess response to therapy.

11.1 Terms and definitions

- **M-protein:** synonyms include M-spike, monoclonal protein and myeloma protein, paraprotein, M-component.

Serum M-protein level is quantitated using densitometry on SPEP except in cases where the SPEP is felt to be unreliable.

- M-proteins migrating in the β -region (usually IgA M-proteins)
- Cases in which the M-protein is so large and narrow on agarose (some specimens >4 g/dL) that they underestimate the actual immunoglobulin level (by greater than 1500 mg/dL) due to technical staining properties of the agarose gel.
- Cases in which there are multiple peaks of same M-protein (aggregates or dimers)

If SPEP is not available or felt to be unreliable (above examples) for routine M-protein quantitation, then quantitative immunoglobulin levels derived from nephelometry or turbidometry can be accepted. However, this must be explicitly reported at baseline, and only nephelometry can be used for that patient to assess response. SPEP derived M-protein values and quantitative nephelometric immunoglobulin values cannot be used interchangeably.

Urine M-protein measurement is estimated using 24-h UPEP only. Random or 24 h urine tests measuring kappa and lambda light chain levels are not reliable and are not recommended.

FLC estimation is currently carried out using the serum FLC assay (Freelite, The Binding Site Limited, UK). Patients with kappa/lambda FLC ratio <0.26 are defined as having monoclonal lambda FLC and those with ratios >1.65 as having a monoclonal kappa FLC. The monoclonal light chain isotype is considered the involved FLC isotype, and the opposite light chain type as the uninvolved FLC type.

- **Response terms:** The following response terms will be used: stringent Complete Response (sCR), complete response (CR), very good partial response (VGPR), partial response (PR), Minimal Response (MR), stable disease (SD), and progressive disease (PD).

In addition, for each response category, there will be an “unconfirmed” response category, which will be for internal use, for the purpose of guiding decision making and test ordering. These designations will be applied at the time of the first measurement at which the quantitative aspect of the response category has been satisfied without the confirmation step having been satisfied. The designation “u” will precede the standard abbreviations, and will include usCR, uCR, uVGPR, uPR, uMR, uPD.

- **Measurable disease:** Patients who have a measurable serum or urine M-protein.
 - Serum M-protein ≥ 1 g/dl
 - Urine M-protein ≥ 200 mg/24 h
 - Serum FLC assay: Involved FLC level ≥ 10 mg/dl provided serum FLC ratio is abnormal
 - Bone marrow plasma cells $\geq 30\%$

The serum free light chain (FLC) assay is of particular use in monitoring response to therapy in patients who have oligo-secretory or non-secretory disease and **should be used in assessing response only if the baseline serum and/or urine M proteins are not “measurable” as above, and the baseline level of the involved FLC is “measurable.”** When using this assay, it is important to note that the FLC levels vary considerably with changes in renal function and in patients with renal insufficiency, the levels of both the kappa and lambda may remain elevated, but the ratio normalizes with achievement of CR. Thus, both the level of the involved and the uninvolved FLC isotype (i.e., the involved/uninvolved ratio or involved-uninvolved difference) should be considered in assessing response. *Patients included on the study on the basis of FLC alone (i.e., no measurable serum/urine M-protein) should be the only ones who are evaluated using FLC response criteria. The others should follow usual criteria and ignore FLC results with the exception of defining stringent complete response.*

- **Evaluable disease:** Patients who do not have a “measurable” serum M-protein, serum free light chain, or urine M-protein.
- **Oligosecretory myeloma:** Patient with multiple myeloma who has NEVER had “measurable” serum M-protein or urine M-protein, but has had a detectable M-protein in his/her serum and/or urine and/or measurable serum free light chain.
- **Non-secretory myeloma:** Patient with multiple myeloma who has NEVER had a detectable M-protein in his/her serum and/or urine.

11.2 Clarification of test indications

Listed below are the minimal required tests required to assess response based on the characteristics of their disease at on study.

| Table 11.2 | | | | |
|--|-------------------------|-------------------------------|---------------|----------------|
| Tests Required To Assess Response (Must Be Done At Each Disease Measurement Visit except as indicated^{1,2}) | | | | |
| On Study Baseline Value | SPEP⁴ | 24 hr UPEP² | Ig FLC | BM Bx |
| Serum M-protein \geq 1 g/dl, and urine M-protein \geq 200 mg/24 hrs | X | X | | |
| Serum M-protein \geq 1 g/dl, but urine M-protein < 200 mg/24 hrs | X | | | |
| Serum M-protein <1 g/dl, and urine M-protein \geq 200 mg/24 hrs | | X | | |
| Serum M-protein < 1 g/dl, urine M-protein < 200 mg/24 hrs, but involved Ig FLC is \geq 10 mg/dL | | | X | |
| Serum M-protein < 1 g/dl, urine M-protein < 200 mg/24 hrs, involved Ig FLC is <10 mg/dL, bone marrow \geq 30% plasma cells | | | | X ³ |

¹ **SPEP, UPEP, Immunofixation studies of both serum and urine, and Bone marrow biopsy** are required to document CR regardless of registration values, and in addition **FLC** measurement and **bone marrow immunophenotyping** is required to document sCR. SPEP and UPEP are required to document VGPR regardless of registration values.

² For serum measurable patients, 24 hour urine does not need to be confirmed (i.e. repeated after documented response) for any response category

³ At a minimum, a bone marrow biopsy should be repeated every 3 months until documented response. Bone marrow biopsy results do not need to be repeated after documented response.

⁴ If serum M-protein is being followed by quantitative immunoglobulin levels derived from nephelometry or turbidometry, quantitative immunoglobulins are required. SPEP is only required to document CR or VGPR.

11.3 Confirmed response

In order to be classified as a hematologic response, confirmation of serum M- protein, serum immunoglobulin free light chain (when primary determinant of response) and urine M- protein (when primary determinant of response) results must be made by verification on two consecutive determinations.

- Bone marrow aspirate and biopsy are **only** required to document CR or sCR, except for

patients with evaluable disease **only**, where a bone marrow is required to document all response categories including progression. However, a second confirmatory bone marrow is **not** required to confirm response in any case.

- Radiographic studies are not required to satisfy these response requirements; however, if radiographic studies were performed there should be no evidence of progressive or new bone lesions.

Appropriate tests required to document and confirm response are listed in Table 11.2

11.4 Bone progression

Caution must be exercised to avoid rating progression on the basis of variation of radiologic technique alone. Compression fracture does not exclude continued response and may not indicate progression. When progression is based on skeletal disease alone, it should be discussed with the Study Chair before removing the patient from the study.

11.5 Response and Progression

Criteria for response and progression are listed in Table 11.5. Progressive disease for all patients as defined in Table 11.5.

| CATEGORY | RESPONSE CATEGORY ^a |
|--|--|
| Stringent Complete Response (sCR) ^b | <ul style="list-style-type: none"> • CR as defined <i>plus</i> • Normal FLC ratio <i>and</i> • Absence of clonal PCs by immunohistochemistry or 2- to 4- color flow cytometry ⁱ |
| Complete Response (CR) ^b | <ul style="list-style-type: none"> • Negative immunofixation of serum and urine ^c <i>and</i> • Disappearance of any soft tissue plasmacytoma <i>and</i> • <5% PCs in Bone Marrow <i>and</i> • If the only measurable disease is FLC, a normal FLC ratio ^d |
| Very Good Partial Response (VGPR) | <ul style="list-style-type: none"> • Serum and urine M-protein detectable by immunofixation but not on electrophoresis ^c <i>or</i> • $\geq 90\%$ reduction in serum M-protein and urine M-protein <100 mg/24 h ^c • If the only measurable disease is FLC, a $>90\%$ reduction in the difference between involved and uninvolved FLC levels |
| Partial Response (PR) | <ul style="list-style-type: none"> • If present at baseline, $\geq 50\%$ reduction of serum M-protein and reduction in 24-hour urinary M-protein by $\geq 90\%$ or to <200 mg/24hrs ^c • If the only measurable disease is FLC, a $\geq 50\%$ reduction in the difference between involved and uninvolved FLC levels • If the only measurable disease is BM, a $\geq 50\%$ reduction in BM PCs (provided the baseline PCs was $\geq 30\%$) • If present at baseline, $\geq 50\%$ reduction in the size of soft tissue plasmacytomas |
| Minor Response (MR) | <ul style="list-style-type: none"> • If present at baseline, $\geq 25\%$ but $\leq 49\%$ reduction of serum M protein <i>and</i> reduction in 24-hour urine M-protein by 50-89% |

| | |
|--|--|
| | <p>which still exceeds 200mg/24 hours^c <i>and</i></p> <ul style="list-style-type: none"> • If present at baseline, 25-49% reduction in the size of soft tissue plasmacytoma <i>and</i> • No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response) |
| Progressive Disease (PD) ^{b, h} | <p>Increase of 25% from lowest value in any of the following^{f, g}:</p> <ul style="list-style-type: none"> • Serum M-protein (absolute increase must be ≥ 0.5 g/dL) <i>and/or</i> • Urine M-protein (absolute increase must be ≥ 200 mg/24 hrs) <i>and/or</i> • If the only measurable disease is FLC, the difference between involved and uninvolved FLC levels (absolute increase must be >10 mg/dL) <i>and/or</i> • If the only measurable disease is BM, bone marrow PC percentage (absolute increase must be $\geq 10\%$)^e <p>Or any one or more of the following:</p> <ul style="list-style-type: none"> • Development of new bone lesion or soft tissue plasmacytoma or definite increase in the size of existing bone lesions or soft tissue plasmacytoma • Development of hypercalcemia (corrected serum calcium > 11.5mg/dL) that can be attributed solely to the PC proliferative disorder |
| Stable Disease (SD) | Not meeting criteria for sCR, CR, VGPR, PR, MR or PD |

^a All response categories require two consecutive assessments (sCR, CR, VGPR, PR, MR, PD) made at any time before the institution of any new therapy; sCR, CR, VGPR, PR, MR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. Each category, except for stable disease, will have a working subcategory of "unconfirmed" [prefix 'u'] to designate first time point at which response category MAY have been achieved if confirmed.

^b CR patient will need to progress at the same level as VGPR and PR patients to be considered a PD. A positive immunofixation alone is not sufficient.

^c If more than one M protein spike meets the criteria for measurable disease at baseline, then both need to be followed for response. Otherwise, only follow the measurable M protein spike for response.

^d In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26-1.65 in addition to the CR criteria listed above.

^e Bone marrow criteria for PD are only to be used in patients without measurable disease by M protein and by FLC;

^f A "25% increase" refers to M protein, FLC and bone marrow results and does not refer to bone lesions, soft tissue plasmacytoma or hypercalcemia. The lowest value does not need to be a confirmed value. If the lowest serum M-protein is ≥ 5 g/dL, an increase in serum M-protein of ≥ 1 g/dL is sufficient to define disease progression.

^g In the case where a value is felt to be a spurious result per physician discretion (for example, a possible lab error), that value will not be considered when determining the lowest value.

^h Progressive disease should be confirmed. However, treatment may be discontinued for progressive disease that is unconfirmed per physician discretion. In this case, an objective status of PD should be entered on the measurement form and progressive disease should be reported on the event monitoring form.

ⁱ Presence/absence of clonal cells is based upon the k/l ratio. An abnormal k/l ratio by immunohistochemistry requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is k/l of 4:1 or 1:2.

12.0 Descriptive Factors

- 12.1 Prior stem cell transplant: Yes vs. no
- 12.2 High risk cytogenetics or FISH hypodiploidy or karyotypic deletion of chromosome 13), FISH (presence of translocations t(4;14) or t(14;16) or deletion 17p: yes vs no
- 12.3 Bone Marrow Labeling index: High (>3.0%) vs. low (≤3.0%).
- 12.4 Previous Thalidomide: Yes vs. no.
- 12.5 Thalidomide refractory: yes vs no
- 12.6 Previous Bortezomib: yes vs. no.
- 12.7 Bortezomib refractory: yes vs no
- 12.8 Parameters of hematologic response (pick all that apply): serum M-spike ≥ 1 g/dL (distinguish between SPEP measurement versus quantitative IgA measurement), serum immunoglobulin free light chain ≥10 mg/dL, urine M-spike ≥200 mg/24 hours, bone marrow plasma cells >30%, measurable plasmacytoma.
- 12.9 Dose Level: 0 vs. 1 vs. 2.

13.0 Treatment/Follow-up Decision at Evaluation of Patient

- 13.1 Patients will have disease response measured as per the test schedule in Section 4.0. Stable or responding patients will stay on treatment until they have progressive disease, an unacceptable toxicity or refuse further treatment at which time they will proceed to Event Monitoring. NOTE: As of Addendum 6, patient follow-up is no longer required.
- 13.2 Patients on Event Monitoring will be followed at progression or initiation of new treatment and 6 months after progression or initiation of new treatment NOTE: As of Addendum 6, patient follow-up is no longer required.

- 13.3 A patient is deemed *ineligible* if at the time of registration, the patient did not satisfy each and every eligibility criteria for study entry. The patient may continue treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. If the patient continues to receive treatment they should be followed according to the protocol.
- If the patient received treatment but does not continue with study treatment after deemed ineligible, all data up until the point of confirmation of ineligibility must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
 - If the patient never received treatment, on-study material must be submitted. Event monitoring will be required per Section 18.0 of the protocol.
- 13.4 A patient is deemed a *major violation*, if protocol requirements regarding treatment in cycle 1 of the initial therapy are severely violated that evaluability for primary end point is questionable. All data up until the point of confirmation of a major violation must be submitted. The patient will go directly to the event-monitoring phase of the study. Event monitoring will be required per Section 18.0 of the protocol. The patient may continue treatment at the discretion of the physician as long as there are no safety concerns, and the patient was properly registered. If the patient continues to receive treatment they should be followed according to the protocol. If the patient does not continue with study treatment, the patient will go to event monitoring and be followed.
- 13.5 A patient is deemed a *cancel* if he/she is removed from the study for any reason before any study treatment is given. On-study material and the End of Active Treatment/Cancel Notification Form must be submitted. No further data submission is necessary.

14.0 Body Fluid Biospecimens

14.1 Summary Table of Research Blood and Body Fluid Specimens to be Collected for this Protocol

| Correlative Study (Section for more information) | Mandatory or Optional | Blood or Body Fluid being Collected | Type of Collection Tube (color of tube top) | Volume to collect per tube (# of tubes to be collected) | On Study | Day 1 of first 4 cycles, pre- treatment ² | End of Cycle 3 & every 3rd cycle ² | Process at site? (Yes or No) | Temperature Conditions for Storage /Shipping |
|---|--------------------------|---|---|---|----------------|--|--|---------------------------------------|---|
| Parameters of immune activation (14.42); Circulating tumor cells (14.45) | Optional | Peripheral blood | ACD (yellow) | 7 ml (4) | X ³ | X ³ | | No | Cold Pack |
| Gene expression profiles (14.43); Cell Proliferation and Apoptosis (14.44); Tumor cells (14.45); Quantitative T, B, NK Cells (14.42) | Optional | Bone marrow aspirate | ACD (yellow) | 4 ml (2) | X | | X ¹ | No | Cold Pack |
| PCLI (non-Mayo sites only) | Mandatory | Bone marrow aspirate | Plasma Cell Labeling Index tube | 2-3 ml (1) | X | | X ¹ | No | Cold Pack |

1. Required after Cycle 3, required beyond that only to document CR or if used to assess response.

2. +/- 7 days.

3. If patient agrees to optional blood sample collection, they may have the first sample collected at on study or on Cycle 1 Day 1 but both are not needed.

NOTE: The correlative studies samples should not be submitted prior to the patient signing the informed consent.

NOTE: Baseline samples for research are collected, if possible, at the same time as the diagnostic blood and bone marrow studies that are required to establish the diagnosis of myeloma and determine eligibility.

14.2 Collection and Processing

14.21 See Appendix VIII for Specimen Checklist and Shipping Instructions.

14.3 Shipping and Handling

14.31 **Kits will be used for this study.**

Myeloma Tumor Biology Kits are available to order, and will include materials necessary for the preparation and shipment of samples. Kits should be ordered at least 24 hours in advance of each sample time point. To order kits call [REDACTED] - Mayo Reference Laboratories at [REDACTED].

Any questions concerning sample collection and shipments can be directed to [REDACTED] - Mayo Reference Laboratory, at [REDACTED].

14.32 Shipping Specimens

14.321 Mayo Clinic Florida, Mayo Clinic Arizona, University of Chicago, and Dana Farber

See Appendix VIII for Specimen Checklist and Shipping Instructions.

14.322 Mayo Clinic Rochester

The Clinical Research Associate will coordinate the sample acquisition with the area performing the biopsy and notify the Hematology Research Lab on [REDACTED] of the sample (For patients accrued at Mayo Clinic Rochester). Pre-printed, protocol specific cards accompany the patient to the biopsy suite and follow the sample to the lab.

14.4 Background and Methodology

14.41 Specific Aims:

1. Examine the effect of treatment on parameters of immune function and correlate changes in parameters of immune response and measures of disease response.
2. Examine the gene expression profiling before and after treatment to understand changes in tumor cells and potential markers of response.
3. Examine the effect of pomalidomide alone on tumor cell survival and proliferation.

14.42 ***Parameters of immune activation:***

One of the expected immunomodulatory changes resulting from therapy will be a change in the relative ratio of Th1 to Th2 cells in peripheral blood. This will be performed by flow cytometric methods.

The “global” impact of therapy on immune cell subsets will be ascertained by immunophenotypic analysis of PBMCs for subsets of T, B, NK cells, monocytes and dendritic cells (DC) and their activation status using commercially available monoclonal antibodies directed at the following antigens: CD3, CD4, CD8, CD11c, CD14, C16, CD19, CD20, CD25, CD45RA/RO, CD56, CD69, CD63L, CD80, CD83, CD86, CD123, DR. The flow cytometric analysis will also be performed on the bone marrow samples.

Activation of DC and subsequent modulation of the immune response caused by treatment with lenalidomide may directly or indirectly alter the cytokines present in plasma. The BioRad human 27-plex cytokine panel will be used for the measurements of plasma concentrations of IL-1 β , IL-1 α , IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70), IL-13, IL-15, IL-17, basic FGF, eotaxin, G-CSF, GM-CSF, IFN- γ , IP-10, MCP-1, MIP-1 α , MIP-1 β , $\square\square$ PDGF, RANTES, TNF α , and VEGF.

14.43 *Gene expression profiles of myeloma cells before and after treatment.*

CD138-sorted MM tumors cells, obtained from clinical bone marrow sampling, will be banked before and after 3 cycles of therapy; high-resolution array-based gene expression studies of paired (before/after) samples from matched responding and non-responding patients will be undertaken to look more broadly for additional transcriptional markers of response, including those existing prior to therapy (for example, to identify markers that are upregulated or suppressed in a subgroup of tumors that respond or fail to respond). The dynamic change in the transcriptional profile of responding versus non-responding samples, from before to after treatment, will also be examined to assess if suppression of specific transcripts correlates with response. Samples will be analyzed using high-density oligonucleotide microarrays containing probes for 50,000 transcripts and variants including 14,500 known genes (U133 Plus 2.0 array; Affymetrix, Santa Clara, CA) using standard methods.

Sample Preparation, Fragmentation, Array Hybridization, and Scanning: The purified cDNA is used as the template for in vitro transcription reaction for synthesizing biotinylated complementary RNA (cRNA) using an RNA transcript labeling reagent (Affymetrix). The quality of the fragmented biotin-labeled cRNA in each experiment is evaluated before hybridizing by both gel electrophoresis and hybridizing (fraction of the sample) onto test-3 microarray and analyzing as a measure of quality control. Appropriate amounts of labeled cRNA and control oligonucleotide B2 are added along with control cRNA (BioB, BioC, BioD), herring sperm DNA, and bovine serum albumin to the hybridization buffer. The hybridization mixture is heated at 99°C for 5 minutes followed by incubation at 45°C for 5 minutes before applying the sample onto the GeneChip. Hybridization is performed at 45°C for 16 hours with mixing, following which the solutions are removed, and arrays washed and stained with streptavidin-phycoerythrin (Molecular Probes, Portland, OR). After washes, probe arrays are scanned using the gene chip system confocal scanner. All samples will run individually with no pooling.

Data Analysis and Interpretation: The arrays will be scanned using a Genechip 300 scanner and GeneChip 5.0 software (Affymetrix) will be used to quantitatively analyze the scanned image. Algorithms in the software use probe cell fluorescence intensities to

calculate an average intensity for each set of probe pairs representing a gene, which directly correlates with the amount of mRNA. The plasma cell gene expression from different patient groups as described before will be compared using Genespring. The selection criteria for all genes reported as differentially expressed will be as follows: (1) in absolute analysis, a detection call of present; (2) a change either increased or decreased; (3) signal of greater than 1,000; and (4) greater than 2-fold differences in expression in all pair wise comparisons. Only genes with transcript levels that satisfied all 4 criteria will be considered as significantly differentially expressed. Average differences in mean expression (as measured by fluorescence intensity) of transcripts that met all of these criteria are compared across groups using the 2-sided Student's t test. P values for differences between means of P less than .05 are considered statistically significant.

- 14.44 ***Cell Proliferation and Apoptosis:*** These studies will be performed on marrow aspirates. The multiple myeloma cells are separated by positive selection using CD138 coated magnetic beads in a Robosep system. The tumor cells are suspended in RPMI-1640 media containing 20% fetal bovine serum, 2 mmol/L L-glutamine, 100 U/mL penicillin, and 100 µg/mL streptomycin, placed in 24 well plates and drug added at different concentrations. Patient cells are cultured for 48 hours, harvested and washed twice with PBS, and stained with FITC conjugated CD45 monoclonal antibody and PE conjugated Apo 2.7 antibody or 7-AAD for identification of apoptotic cells. The cells are then analyzed using software on an FACS CANTOS FC.
- 14.45 ***Circulating tumor cells:*** Plasma cells are identified by their characteristic CD45/CD38 staining pattern. Using BD Biosciences TruCount bead technology, an absolute count is calculated in the lysed but not washed sample. 100 microliter of whole blood or BM is added to a TruCount tube containing CD45 FITC, CD31 PE and CD38 APC. The tube is incubated for 15 minutes at room temperature, in the dark. One ml of ACK (ammonium chloride potassium) lyse is added to each tube, mixed, and incubated for 15 minutes at room temperature, in the dark. Using FL2 (CD31 PE) as the threshold, up to 2 million events are collected for each tube on the Cantos flow cytometer (BD Biosciences, San Jose, CA). The number of events in the plasma cell (PC) gate and the number of events in the bead gate are used to calculate the absolute number of PC per milliliter.

15.0 Drug Information

15.1 15.1 Pomalidomide (CC-4047)

15.11 **Background:** Pomalidomide (CC-4047) is a novel drug in the class of immunomodulatory agents known as IMiD compounds. Pomalidomide binds to its molecular target cereblon (CRBN), a protein that is part of an E3 ubiquitin ligase complex, which is responsible for the polyubiquitination of substrate proteins, targeting them for subcellular redistribution and destruction by the proteasome. The pharmacologic properties of pomalidomide are of potential therapeutic benefit in the treatment of various hematologic neoplasms (such as multiple myeloma and myeloproliferative neoplasm-associated myelofibrosis), non-neoplastic hematologic disorders (such as β -thalassemia and sickle cell disease) and non-hematologic disorders such as systemic sclerosis, as well as solid tumor neoplasms.

15.12 **Formulation:** Pomalidomide capsules can be 0.5-mg gelatin capsules (size 4 reddish brown), 1-mg hard gelatin capsules (size 4 reddish brown), 2-mg (size 2 reddish-brown), 3-mg and 4-mg hard gelatin capsules (size 2 reddish-brown), and 5-mg gelatin capsules (size 1 reddish-brown), containing pomalidomide, mannitol, pregelatinized starch, and sodium stearyl fumarate.

Placebo capsules for pomalidomide are available to use in blinded studies. The placebo capsules contain microcrystalline cellulose.

Pomalidomide capsules and pomalidomide placebo capsules are supplied in high density polyethylene (HDPE) containers fitted with induction seals and child-resistant plastic closures or PVC/PCTFE blister with push-through foil.

15.13 **Preparation and storage:** Store drug at controlled room temperature, between 68-77 °F (20-25°C) or as indicated on the manufacturer's label. The expiration date is indicated on the label.

Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

15.14 **Administration:** Pomalidomide is administered by mouth at approximately the same time each day. Pomalidomide should be taken without food (at least 2 hours before or 2 hours after a meal). 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 should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment. 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.

15.15 Pharmacokinetic information:

- a) Absorption – oral absorption has been moderately rapid with first dose C_{max} occurring in 1.5 to 4 hrs. More than 70% of the pomalidomide dose is absorbed in humans. A high fat meal decreased the rate of absorption but had minimal effect on overall extent of absorption; therefore drug may be administered without regard to food intake.
- b) Distribution – Apparent volume of distribution in healthy subjects ranged from 74-138 L across a dose range of 1 to 10 mg daily. Pomalidomide protein binding in human plasma is low to moderate (15.8% for R-enantiomer, 42.2% for S-enantiomer) and the binding is concentration independent in the concentration range of 30 and 1000 ng/mL. Drug distributes into semen.
- c) Metabolism – Eight metabolites were detected in plasma, each at exposures <10% of the plasma pomalidomide. CYP-dependent metabolites accounted for approximately 43% of the excreted radioactivity, while non-CYP dependent hydrolytic metabolites accounted for 25%, and excretion of unchanged pomalidomide accounted for 10%.
- d) Excretion – In healthy patients, 72.8% of the dose was recovered in urine and 15.5% was recovered in feces. Less than 3% of the dose is excreted as unchanged pomalidomide in the urine. The geometric mean terminal elimination half-life ($t_{1/2}$) of pomalidomide was approximately 7.5 hours.

- 15.16 Potential Drug Interactions:** No formal drug interaction studies have been conducted with pomalidomide. Pomalidomide is primarily metabolized by CYP1A2 and CYP3A. Pomalidomide is also a substrate for P-glycoprotein (P-gp).

1) Drugs That May Increase Pomalidomide Plasma Concentrations

CYP3A, CYP1A2 or P-gp inhibitors: Co-administration of pomalidomide with drugs that are strong inhibitors of CYP1A2, CYP3A, or P-gp could increase exposure and should be avoided.

Strong inhibitors of CYP1A2 include ciprofloxacin, enoxacin, and fluvoxamine. Strong inhibitors of CYP3A include boceprevir, clarithromycin, conivaptan, grapefruit juice, indinavir, itraconazole, ketoconazole, lopinavir/ritonavir, mibefradil, nefazodone, nelfinavir, posaconazole, ritonavir, saquinavir, telaprevir, telithromycin, and voriconazole.

Inhibitors of P-gp include amiodarone, azithromycin, captopril, carvedilol, clarithromycin, conivaptan, cyclosporine, diltiazem, dronedarone, erythromycin, felodipine, itraconazole, ketoconazole, lopinavir and ritonavir, quercetin, quinidine, ranolazine, and verapamil.

2) Drugs That May Decrease Pomalidomide Plasma Concentrations

CYP3A, CYP1A2 or P-gp inducers: Co-administration of pomalidomide with drugs that are strong inducers of CYP1A2, CYP3A (or P-gp) could decrease exposure and should be avoided.

CYP3A inducers include rifampin and carbamazepine.

P-gp inducers include Avasimibe, carbamazepine, phenytoin, rifampin, St John's wort, tipranavir/ritonavir

Smoking: Cigarette smoking may reduce pomalidomide exposure due to CYP1A2 induction. Patients should be advised that smoking may reduce the efficacy of pomalidomide.

Dexamethasone: Co-administration of multiple doses of 4 mg pomalidomide with 20 mg to 40 mg dexamethasone (a weak inducer of CYP3A) to patients with multiple myeloma had no effect on the pharmacokinetics of pomalidomide compared with pomalidomide administered alone.

15.17 **Known potential toxicities:**

Common known potential toxicities, > 10%:

Cardiovascular: Peripheral edema (23%)

Central nervous system: Fatigue (55%), dizziness (18% to 20%), fever (19%), neuropathy (18%), headache (13%), confusion (10% to 12%), anxiety (11%)

Dermatologic: Skin rash (22%), pruritus (15%)

Endocrine & metabolic: Hypercalcemia (21%), hyperglycemia (12%)

Gastrointestinal: Constipation (36%), nausea (36%), diarrhea (34%), decreased appetite (22%), vomiting (14%), weight loss (14%)

Hematologic & oncologic: Neutropenia (50% to 52%; Grades 3/4: 43% to 47%), anemia (38%; grades 3/4: 22%), thrombocytopenia (25%; grades 3/4: 22%), leukopenia (11%; grades 3/4: 6%)

Neuromuscular & skeletal: Back pain (32%), musculoskeletal chest pain (22%), muscle spasm (19%), arthralgia (16%), ostealgia (12%), myasthenia (12%), and musculoskeletal pain (11%)

Renal: Increased serum creatinine (15%), renal failure (15%)

Respiratory: Dyspnea (34%), upper respiratory tract infection (32%), pneumonia (23%), epistaxis (15%), cough (14%)

Less common known potential toxicities, 1% - 10%:

Cardiovascular: Thrombosis (venous thrombosis, pulmonary embolism, 3%), atrial fibrillation (2%)

Central nervous system: Peripheral neuropathy (10%), chills (9%), insomnia (7%), pain (6%)

Dermatologic: Xeroderma (9%), hyperhidrosis (6%)

Endocrine & metabolic: Hypokalemia (10%), hyponatremia (10%), hypocalcemia (6%), and dehydration (5%)

Gastrointestinal: Weight gain (1%)

Genitourinary: Urinary tract infection (8%)

Hematologic & oncologic: Lymphocytopenia (4%; grades 3/4: 2%), febrile neutropenia (3% to 5%)

Infection: Sepsis (6%)

Neuromuscular & skeletal: Tremor (9%), limb pain (5%)

Miscellaneous: Night sweats (5%)

Frequency not defined: Acute myelocytic leukemia, hyperbilirubinemia, hyperkalemia, increased serum ALT, hepatotoxicity, interstitial pulmonary disease (including pneumonitis), neutropenic sepsis, pelvic pain, Pneumocystis jiroveci pneumonia, respiratory syncytial virus infection, urinary retention, vertigo, pancytopenia, tumor lysis syndrome, angioedema, severe dermatologic reactions (including urticaria)

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. Females of reproductive potential must adhere to the scheduled pregnancy testing. Females of childbearing potential should not handle or administer pomalidomide unless they are wearing gloves.

15.18 Drug procurement:

Pomalidomide 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 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.

Drug will be shipped on a per patient basis by the contract pharmacy to the clinic site for IND studies. Only enough pomalidomide for one cycle of therapy will be supplied to the patient each cycle.

15.19 Nursing Guidelines:

15.191 Agent is known to be teratogenic in rabbits. Therefore all women who are pregnant or who could become pregnant, should not handle the agent outside of the original packaging. Chemotherapy gloves should be worn if contact is necessary.

15.192 Because of the similarity of this agent to thalidomide certain precautions MUST be employed by all subjects on protocol and for 4 weeks after discontinuation of agent. Instruct patients the following must be adhered to: No donation of tissue/blood/semen/sperm; sexually active males/females must use protocol-specific contraception (regardless of fertility status-i.e. history of vasectomy).

15.193 Cytopenias are common (neutropenia most common). Monitor CBC closely and instruct patient to report any signs/symptoms of infection or unusual bruising or bleeding to the study team.

- 15.194 Thrombotic events have been reported. Anticoagulation prophylaxis may be recommended. Instruct patients to report any problems with bleeding, extremity pain or swelling, or shortness of breath to the study team immediately.
- 15.195 Patients may experience cough, URI, pneumonia, or sinusitis. Instruct patients to report respiratory symptoms to the study team.
- 15.196 Gastrointestinal side effects consisting of diarrhea, constipation, stomatitis, nausea, decreased appetite, and abdominal pain have been seen. Treat symptomatically and monitor for effectiveness.
- 15.197 Drug should be taken without food (at least 2 hours before or 2 hours after a meal). Do not open or crush capsules.
- 15.198 Patients may experience myalgias and muscle spasms. Treat symptomatically and monitor for effectiveness.
- 15.199a Fatigue is common. Instruct patient in energy conserving lifestyle.
- 15.199b Warn patients about the possibility of peripheral neuropathy, headache, confusion, and dizziness.

15.2 **Bortezomib (Velcade®, PS341)**

- 15.21 **Background:** Bortezomib inhibits proteasomes, enzyme complexes which regulate protein homeostasis within the cell. Specifically, it reversibly inhibits chymotrypsin-like activity at the 26S proteasome, leading to activation of signaling cascades, cell-cycle arrest, and apoptosis.
- 15.22 **Formulation:** Bortezomib for Injection is supplied as individual cartons with 10 mL vials containing 3.5 mg of bortezomib as a white to off-white cake or powder.
- 15.23 **Preparation, storage, and stability:** Unopened vials may be stored at controlled room temperature 25°C (77°F); excursions permitted from 15°C to 30°C (59°F-86°F). Retain in original package to protect from light.
- IV administration: Dilute each 3.5 mg vial with 3.5 mL 0.9% Sodium Chloride, resulting in a final concentration of 1 mg/mL bortezomib.
- Subcutaneous administration: To minimize volume of injected solution, dilute each 3.5 mg vial with 1.4 mL 0.9% Sodium Chloride, resulting in a final concentration of 2.5 mg/mL bortezomib. Attach a subcutaneous needle to syringe.

Bortezomib contains no antimicrobial preservative. Reconstituted product should be administered within 8 hours of preparation. When reconstituted

as directed, bortezomib may be stored at 25°C (77 °F), in the original vial and/or syringe. Protect from light. See investigator brochure or package insert for more complete information. .

- 15.24 **Administration:** Bortezomib is administered intravenously as a 3 to 5 second bolus IV injection at a concentration of 1 mg/mL; or subcutaneously at a concentration of 2.5 mg/mL. Rotate injection sites for subcutaneous administration between the abdomen (right or left) and thighs (right or left).

Bortezomib is contraindicated for intrathecal administration.

- 15.25 **Pharmacokinetic information:**

Distribution: 498-1884 L/m². The rapid distribution period has a half-life ($t_{1/2}$) of less than 10 minutes. Data from studies conducted in nonhuman primates have shown that the tissue distribution for bortezomib is extensive with the exception of penetration into the central nervous system and various regions of the eye and testes, where bortezomib levels were below the limit of quantification of the assays.

Pharmacokinetic parameters from SC administration were comparable with those from the established IV route, with no differences in overall systemic availability between SC and IV administration on Days 1 and 11 in Cycle 1. Following SC administration, mean C_{max} values were significantly lower and T_{max} was longer as was expected since drugs administered SC require more time to be absorbed. Mean volume of distribution (V_d) was similar and high for both routes, confirming extensive distribution of bortezomib into peripheral tissues.

Protein binding, plasma: ~83%

Metabolism: Hepatic primarily via CYP2C19 and 3A4 and to a lesser extent CYP1A2; forms metabolites (inactive) via deboronization followed by hydroxylation. Total exposure to bortezomib is increased in patients with moderate to severe hepatic impairment; consider reduction of starting dose in these patients (0.7 mg/m² per injection during the first cycle, with a subsequent dose escalation to 1.0 mg/m² or further dose reduction to 0.5 mg/m² considered based on patient tolerance).

Half-life elimination: Single dose: 9-15 hours; multiple dosing, twice weekly schedule: 1 mg/m²: 40-193 hours; 1.3 mg/m²: 76-108 hours

- 15.26 **Potential Drug Interactions:**

Co-administration of ketoconazole, a potent CYP3A4 inhibitor, increased the exposure to bortezomib. Therefore, subjects should be closely monitored when given bortezomib in combination with potent CYP3A4 inhibitors such as ketoconazole or ritonavir. Co-administration of omeprazole, a potent inhibitor of CYP2C19, had no effect on the exposure of bortezomib. Co-administration of rifampicin, a strong CYP3A4 inducer, decreased the systemic exposure of bortezomib by 45%. Efficacy may be reduced when bortezomib is used in combination with strong CYP3A4 inducers; therefore, concomitant use of strong CYP3A4 inducers is not recommended in patients receiving bortezomib. Co-administration of

dexamethasone, a relatively weak CYP3A4 inducer, had no effect on systemic exposure of bortezomib.

- 15.27 **Known potential adverse events:** Consult the package insert for the most current and complete information.

Common known potential toxicities, $\geq 10\%$:

Blood and Lymphatic System Disorders: Thrombocytopenia, anemia, neutropenia

Gastrointestinal Disorders: Constipation, diarrhea, nausea, vomiting, abdominal pain (excluding oral and throat)

General Disorders and Administration Site Conditions: Fatigue, pyrexia, chills, edema peripheral, asthenia

Infections and Infestations: Upper respiratory tract infection, nasopharyngitis, pneumonia, Herpes zoster

Metabolism and Nutritional Disorders: Decreased appetite, anorexia, dehydration

Musculoskeletal and Connective Tissue Disorders: Bone pain, myalgia, arthralgia, back pain

Nervous System Disorders: Peripheral neuropathy, paresthesia, dizziness excluding vertigo, headache

Psychiatric Disorders: Anxiety, insomnia

Respiratory, Thoracic, and Mediastinal Disorders: Cough, dyspnea

Skin and Subcutaneous Tissue Disorders: Rash

Less common known potential toxicities, 1% to $< 10\%$:

Blood and Lymphatic System Disorders: Lymphopenia, pancytopenia, leukopenia, febrile neutropenia

Cardiac Disorders: Tachycardia, atrial fibrillation, palpitations, cardiac failure congestive

Eye Disorders: Blurred vision, conjunctivitis, conjunctival hemorrhage

Gastrointestinal Disorders: Dyspepsia, pharyngolaryngeal pain, gastroesophageal reflux, abdominal distension, gastritis, stomatitis, mouth ulceration, dysphagia, gastrointestinal hemorrhage, lower gastrointestinal hemorrhage, rectal hemorrhage

General Disorders and Administration Site Conditions: Neuralgia, lethargy, malaise, chest pain, mucosal inflammation

Infections and Infestations: Lower respiratory tract infection, sinusitis, pharyngitis, oral candidiasis, urinary tract infection, sepsis, bacteremia, cellulitis, Herpes simplex, bronchitis, gastroenteritis, infection

Injury, Poisoning, and Procedural Complications: Fall

Investigations: Weight decreased, alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, blood alkaline phosphatase increased, liver function test abnormal, blood creatinine increased

Metabolism and Nutritional Disorders: Hyperglycemia, hypoglycemia, hyponatremia, hypokalemia, hypercalcemia

Musculoskeletal and Connective Tissue Disorders: Muscular weakness

Nervous System Disorders: Polyneuropathy, syncope, dysesthesia, dysgeusia, postherpetic neuralgia

Psychiatric Disorders: Confusional state
Renal and Urinary Disorders: Renal impairment, renal failure, hematuria
Respiratory, Thoracic, and Mediastinal Disorders: Epistaxis, dyspnea exertional, pleural effusion, rhinorrhea, hypoxia, pulmonary edema
Skin and Subcutaneous Tissue Disorders: Rash pruritic, rash erythematous, urticaria, petechiae
Vascular Disorders: Hypotension, orthostatic hypotension
Uncommon (<1%):
Cardiac Disorders: Cardiogenic shock, atrial flutter, cardiac tamponade, bradycardia, atrioventricular block complete, arrhythmia, cardiac arrest, cardiac failure, arrhythmia, pericardial effusion, pericarditis, pericardial disease, cardiopulmonary failure
Ear and Labyrinth Disorders: Deafness, hearing impaired
Gastrointestinal Disorders: Eructation, gastrointestinal pain, tongue ulceration, retching, upper gastrointestinal hemorrhage, hematemesis, oral mucosal petechiae, ileus paralytic, ileus, odynophagia, enteritis, colitis, esophagitis, enterocolitis, diarrhea hemorrhagic, acute pancreatitis, intestinal obstruction
General Disorders and Administration Site Conditions: Injection site pain, injection site irritation, injection site phlebitis, general physical health deterioration, catheter-related complication
Hepatobiliary Disorders: Hyperbilirubinaemia, hepatitis
Immune System Disorders: Drug hypersensitivity, angioedema
Infections and Infestations: Septic shock, catheter-related infection, skin infection, Herpes zoster disseminated, lung infection, infusion site cellulitis, catheter site cellulitis, infusion site infection, urosepsis, Aspergillosis, tinea infection, Herpes zoster ophthalmic, Herpes simplex ophthalmic, meningoencephalitis herpetic, varicella, empyema, fungal esophagitis
Injury, Poisoning, and Procedural Complications: Subdural hematoma
Investigations: Gamma-glutamyltransferase (GGT) increased, oxygen saturation decreased, blood albumin decreased, ejection fraction decreased
Musculoskeletal and Connective Tissue Disorders: Limb discomfort
Neoplasms, Benign, Malignant, and Unspecified (including cysts and polyps): Tumor lysis syndrome
Nervous System Disorders: Convulsion, loss of consciousness, ageusia, encephalopathy, paralysis, autonomic neuropathy, posterior reversible encephalopathy syndrome
Psychiatric Disorders: Delirium
Renal and Urinary Disorders: Micturition disorder
Respiratory, Thoracic, and Mediastinal Disorders: Hemoptysis, acute respiratory distress syndrome, respiratory failure, pneumonitis, lung infiltration, pulmonary alveolar hemorrhage, interstitial lung disease, pulmonary hypertension, pleurisy, pleuritic pain
Skin and Subcutaneous Tissue Disorders: Cutaneous vasculitis, leukocytoclastic vasculitis
Vascular Disorders: Cerebral hemorrhage

- 15.28 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.
- 15.29 **Nursing Guidelines:**
- 15.191 Monitor CBC. Instruct patient to report any signs or symptoms of infection, unusual bruising, or bleeding to the health care team.
- 15.192 Gastrointestinal side effects were common (i.e diarrhea, etc). Instruct patient to report symptoms and treat symptomatically. Evaluate for effectiveness
- 15.193 Instruct patient to report any cardiac palpitations, increased pulse, lightheadedness, visual changes, feelings of weakness or dizziness. Periodically assess vital signs.
- 15.194 Peripheral neuropathy can be seen. Instruct patient to report any numbness, tingling, or pain in the hands and/or feet to the health care team.
- 15.195 Instruct patient to report any rash.
- 15.196 Thrombus and embolisms are a rare but serious and potentially life threatening side effect of bortezomib. Instruct patient to report any signs or symptoms of DVT or PE (calf pain, extremity swelling, SOB, chest pain) immediately or seek immediate medical attention.
- 15.197 Review all of patient's medications. There are drug-to drug interactions with other drugs that are metabolized through the CYP3A4 pathway. Instruct patient to contact the study team prior to starting any new medications.
- 15.198 Progressive Multifocal Leukoencephalopathy (PML) is a rare, but serious condition. Instruct patients to report any mental status changes, or other neurological symptoms to the study team immediately.

15.3 **Dexamethasone for Oral Administration (DXM)**

- 15.31 **Background:** Dexamethasone is an adrenal corticosteroid compound. Dexamethasone decreases inflammation by suppression of neutrophil migration, decreased production of inflammatory mediators, and reversal of increased capillary permeability; suppresses normal immune response. Dexamethasone's mechanism of antiemetic activity is unknown.
- 15.32 **Formulation:** Commercially available for oral administration as:
Tablets [scored]: 0.5 mg, 0.75 mg, 1 mg, 1.5 mg, 2 mg, 4 mg, and 6 mg
Solution, oral: 0.5 mg/mL (500 mL)
Solution, oral concentrate: Dexamethasone Intensol: 1 mg/mL (30 mL)

- 15.33 **Preparation, storage, and stability:** Refer to package insert for complete preparation and dispensing instructions. Store oral tablets at room temperature between 20°C to 25°C (60°F to 77°F). Protect from moisture. Dispense in a well-closed, light-resistant container as defined in the USP/NF. Store oral liquid at room temperature, do not freeze. Do not use if solution contains a precipitate. Refer to commercial package for drug expiration date.
- 15.34 **Administration:** Refer to the treatment section for specific administration instructions. May be taken with meals to decrease GI upset.
- 15.35 **Pharmacokinetic information:**
Onset of action: Prompt
Duration of metabolic effect: 72 hours
Metabolism: Hepatic
Half-life elimination: Normal renal function: 1.8-3.5 hours; **Biological half-life:** 36-54 hours
Time to peak, serum: Oral: 1-2 hours
Excretion: Urine and feces
- 15.36 **Potential Drug Interactions:**
Cytochrome P450 Effect: Substrate of CYP3A4 (major); **Induces** CYP2A6 (weak), 2B6 (weak), 2C8 (weak), 2C9 (weak), 3A4 (strong)
Increased Effect/Toxicity: Aprepitant, azole antifungals, calcium channel blockers, cyclosporine, estrogens, and macrolides may increase the serum levels of corticosteroids. Corticosteroids may increase the hypokalemic effects of amphotericin B or potassium-wasting diuretics (loop or thiazide); monitor. Refer to the package insert for a listing of other drugs.
Decreased Effect: Antacids and bile acid sequestrants may reduce the absorption of corticosteroids; may reduce the absorption of corticosteroids; separate administration by 2 hours. Aminoglutethimide, barbiturates, and CYP3A4 inducers may reduce the serum levels/effects of dexamethasone and dexamethasone may decrease the levels/effects of other CYP3A4 substrates. Serum concentrations of isoniazid may be decreased by corticosteroids. Corticosteroids may lead to a reduction in warfarin effect. Corticosteroids may suppress the response to vaccinations.
Ethanol/Nutrition/Herb Interactions:
Ethanol: Avoid ethanol (may enhance gastric mucosal irritation).
Food: Dexamethasone interferes with calcium absorption. Limit caffeine.
Herb/Nutraceutical: Avoid cat's claw, Echinacea (have immunostimulant properties)
- 15.37 **Known potential adverse events:** Consult the package insert for the most current and complete information.
- Common known potential toxicities,** frequency not defined:
Fluid and electrolyte disturbances, congestive heart failure in susceptible persons, hypertension, euphoria, personality changes, insomnia, exacerbation of infection, exacerbation or symptoms of diabetes,

psychosis, muscle weakness, osteoporosis, vertebral compression fractures, pancreatitis, esophagitis, peptic ulcer, dermatologic disturbances, convulsions, vertigo and headache, endocrine abnormalities, ophthalmic changes, and metabolic changes. Some patients have experienced itching and other allergic, anaphylactic or hypersensitivity reactions. Withdrawal from prolonged therapy may result in symptoms including fever, myalgia and arthralgia.

15.38 **Drug procurement:** Commercial supplies. Pharmacies or clinics shall obtain supplies from normal commercial supply chain or wholesaler.

15.39 **Nursing Guidelines:**

15.391 Monitor regularly for hypertension, CHF and other evidence of fluid retention.

15.392 Advise patient of possible mood or behavioral changes, i.e., depression, euphoria, insomnia, even psychosis. Instruct patient to report any suspected changes to healthcare team.

15.393 Assess for symptoms of gastric ulcer, heartburn, or gastritis. Suggest antacids. Instruct patient to report symptoms to healthcare team if unable to control.

15.394 Evaluate signs of infection, particularly local candidal infections and treat appropriately.

15.395 Monitor blood glucose frequently.

15.396 Instruct patient to report frequent, unrelenting headaches or visual changes to healthcare team.

15.397 Advise patient that easy bruising is a side effect.

16.0 Statistical Considerations and Methodology

16.1 Overview: This is a phase I/II study in multiple myeloma treated with a combination of pomalidomide, bortezomib, and dexamethasone. The phase I portion of the study is designed to determine the MTD of this treatment combination. The phase II portion will accrue patients at the MTD. The goal of the phase II portion is to assess the efficacy of the treatment regimen. A two-stage design will be utilized to assess this endpoint. Included will be a threshold at which we can report findings early based on extremely successful response rates.

16.11 Primary Endpoint: The primary endpoint of the phase I portion is toxicity, and more specifically, MTD determination. For the phase II portion of the trial, the primary endpoint is confirmed response rate.

16.12 Sample Size: The phase I portion of the trial will require at least 9 patients and as many as 12 patients to determine the MTD. The 6 phase I patients treated at

the MTD will also be included in the phase II portion. The phase II portion will require an additional 10 or 36 evaluable patients for a minimum of 16 evaluable patients and a maximum of 42 evaluable patients. We will plan to accrue an additional 6 patients (2 Phase I, 4 Phase II) to account for ineligibles, major protocol violations, etc. Considering all possibilities, this phase I/II will require a minimum of 9 patients (if a MTD is not found) and a maximum of 54 patients (12 in phase I plus 36 evaluable in phase II plus 6 to account for replaced patients).

- 16.13 **Accrual Rate and Study Duration:** Based on accrual on a recent pomalidomide trial, we can expect to accrue approximately 7-8 patients per month. At this rate, it will likely take about 2 months to enroll, treat, and evaluate each set of 3 patients in the phase I portion of this study. The phase I portion is expected to take between 6 and 12 months. Once the phase II portion of the trial begins, we can expect to accrue the required patients in about 10 months, assuming a month 4 month suspension to evaluate the first stage. Allowing for data maturity, we can expect to begin final analysis approximately 16 months after beginning the phase II portion, i.e. as soon as the last patient accrued has been observed for at least 6 months. The overall study duration is expected to be a maximum of 2.5 years.

Phase I Portion (Cohort I):

This portion of the study is designed to determine the MTD and toxicity of this 3-drug combination in patients with multiple myeloma.

- 16.2 **Study Design:** This portion of the study will consist of a standard 3+3 phase I design to determine the MTD of the 3-drug combination.
- 16.21 **MTD Determination:** MTD is defined as the dose level below the lowest dose that induces dose-limiting toxicity in at least one-third of patients (at least 2 of a maximum of 6 new patients). See section 7.24 for the MTD determination algorithm and section 7.23 for DLT definitions.
- 16.22 **Primary Outcome Analyses:**
- 16.221 **Adverse Events Profile:** The number and severity of all adverse events will be tabulated and summarized in this patient population. The grade 3+ adverse events will also be described and summarized in a similar fashion. This will provide an indication of the level of tolerance for this treatment combination in this patient group.
- 16.222 **Toxicity Profile:** The term toxicity is defined as adverse events that are classified as either possibly, probably, or definitely related to study treatment. Non-hematologic toxicities will be evaluated via the ordinal CTC standard toxicity grading. Hematologic toxicity measures of thrombocytopenia, neutropenia, and leukopenia will be assessed using continuous variables as the outcome measures (primarily nadir) as well as categorization via CTC standard toxicity grading. Overall toxicity incidence as well as toxicity profiles by dose level and patient will be

explored and summarized. Frequency distributions, graphical techniques and other descriptive measures will form the basis of these analyses.

Phase II Portion (Cohort II)

16.3 Statistical Design:

16.31 Decision Rule: In a previous study of Pomalidomide and Dexamethasone (MC0789), 52 patients had at least 2 prior regimens (one of which was lenalidomide). Of these 52 patients, 35% achieved a confirmed response. The addition of Bortezomib to this combination is expected to increase the confirmed response rate. A confirmed response rate of 45% for the combination of Pomalidomide, Bortezomib, and Dexamethasone in this patient population is of interest.

The largest success proportion where the proposed treatment regimen would be considered ineffective in this population is 25%, and the smallest success proportion that would warrant subsequent studies with the proposed regimen in this patient population is 45%. The following two-stage Fleming design requires a minimum of 16 evaluable patients or a maximum of 42 evaluable patients to test the null hypothesis that the true success proportion in a given patient population is at most 25%.³⁴ A patient is considered a success if they have an objective status of PR, VGPR, or CR on two consecutive evaluations.

16.311 Stage 1: Enter 16 patients into the study. If 3 or fewer successes are observed in the first 16 evaluable patients, we will consider this regimen ineffective in this patient population and terminate this study. If at least 4 successes are observed, we will continue accrual.

16.312 Early Reporting: If there are at least 9 successes, out of the first 16 evaluable patients, we will consider this enough evidence that the 3-drug combination is promising and will allow early reporting of efficacy results. This cutoff is based on the positive Stage 1 stopping rule from a two-stage Fleming design.

16.313 Stage 2: Enter an additional 26 patients into the study. If 14 or fewer successes are observed in the first 42 evaluable patients, we will consider this regimen ineffective in this patient population. If 15 or more successes are observed in the first 42 evaluable patients, we may recommend further testing of this regimen in subsequent studies in this patient population.

16.314 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making process.

16.32 Power and Significance Level: Assuming that the number of successes is binomially distributed, the significance level is .10 (i.e. there is a 10% chance of finding the drug to be effective when it truly is not). The probability of declaring that this regimen warrants further study (i.e. statistical power) under various

success proportions and the probability of stopping after the first stage can be tabulated as a function of the true success proportion as shown in the following table.

| | | | | | |
|---|-------|------|------|------|------|
| If the true success proportion is... | 0.25 | 0.30 | 0.35 | 0.40 | 0.45 |
| Then the probability of declaring that the regimen warrants further study is... | 0.08 | 0.25 | 0.51 | 0.75 | 0.90 |
| And the probability of stopping after the first stage is... | 0.41 | 0.25 | 0.13 | 0.07 | 0.03 |
| And the probability of early reporting of the first stage results is... | <0.01 | 0.03 | 0.07 | 0.14 | 0.26 |

16.33 Other considerations: Adverse events, quality/duration of response, and patterns of treatment failure observed in this study, as well as scientific discoveries or changes in standard care will be taken into account in any decision to terminate the study

16.4 Analysis Plan

16.41 Primary Outcome Analyses:

16.411 Definition: The primary endpoint for the phase II portion of this trial is confirmed response rate. As stated above, a success is defined as a patient that has achieved a response (PR, VGPR, or CR) on two consecutive evaluations.

16.412 Estimation: The proportion of successes will be estimated by the number of successes divided by the total number of evaluable patients. Confidence intervals for the true success proportion will be calculated according to the approach of Duffy and Santner.³⁵

16.42 Secondary Outcome Analyses

16.421 Overall survival: Survival time is defined as the time from registration to death due to any cause. The distribution of survival time will be estimated using the method of Kaplan-Meier.³⁶

16.422 Progression-free survival: The progression-free survival (PFS) time is defined as the time from registration to progression or death due to any cause. The distribution of progression-free survival will be estimated using the method of Kaplan-Meier.³⁶

16.423 Duration of response is defined for all evaluable patients who have achieved a confirmed response as the date at which the patient's objective status is first noted to be either a CR, VGPR, or PR to the earliest date progression is documented. The distribution of duration of response will be estimated using the method of Kaplan-Meier.³⁶

16.43 Adverse Events: All eligible patients that have initiated treatment will be considered evaluable for assessing adverse event rates. The maximum grade for each type of adverse event will be recorded for each patient, and frequency tables will be reviewed to determine patterns. Additionally, the relationship of the adverse events to the study treatment will be taken into consideration.

16.44 Over Accrual: If more than the target number of patients are accrued, the additional patients will not be used to evaluate the stopping rule or used in any decision making processes; however, they will be included in final point estimates and confidence intervals.

16.45 Data & Safety Monitoring:

16.451 The principal investigator(s) and the study statistician will review the study at least twice a year to identify accrual, adverse event, and any endpoint problems that might be developing. The Mayo Clinic Cancer Center (MCCC) Data Safety Monitoring Board (DSMB) is responsible for reviewing accrual and safety data for this trial at least twice a year, based on reports provided by the MCCC Statistical Office.

16.452 Adverse Event Stopping Rules (These rules apply to all patients in this study treated at the MTD): The stopping rules specified below are based on the knowledge available at study development. We note that the Adverse Event Stopping Rule may be adjusted in the event of either (1) the study re-opening to accrual or (2) at any time during the conduct of the trial and in consideration of newly acquired information regarding the adverse event profile of the treatment(s) under investigation. The study team may choose to suspend accrual because of unexpected adverse event profiles that have not crossed the specified rule below.

Accrual will be temporarily suspended to this study if at any time we observe events considered at least possibly related to study treatment (i.e. an adverse event with attribute specified as “possible”, “probable”, or “definite”) that satisfy either of the following:

- if 2 or more patients in the first 10 treated patients experience a grade 4 cardiac, lung, liver or neurological toxicity that is felt to be drug related
- if after the first 10 patients have been treated, 20% of all patients experience a grade 4 cardiac, lung, liver or neurological toxicity that is felt to be drug related

We note that we will review grade 4 and 5 adverse events deemed “unrelated” or “unlikely to be related”, to verify their attribution and to monitor the emergence of a previously unrecognized treatment-related adverse event.

The probability of meeting the stopping rule criteria under various scenarios is estimated to be the following (based on simulations with 10,000 iterations):

| | | | | | |
|---|-----|-----|-----|-----|-----|
| If the true proportion of patients that meet the stopping rule criteria is ... | .10 | .15 | .20 | .25 | .30 |
| Then the probability of meeting the stopping rule criteria in the 1 st 10 patients is.... | .26 | .44 | .61 | .75 | .84 |
| And the probability of meeting the stopping rule criteria after the 1 st 10 patients is... | .07 | .15 | .20 | .19 | .14 |
| And the probability of meeting the | | | | | |

| | | | | | |
|--|-----|-----|-----|-----|-----|
| stopping rule criteria at any time is... | .33 | .60 | .82 | .94 | .98 |
|--|-----|-----|-----|-----|-----|

- 16.5 Results Reporting on ClinicalTrials.gov: At study activation, this study will have been registered within the “ClinicalTrials.gov” website. The Primary and Secondary Endpoints (ie, “Outcome Measures”) along with other required information for this study will be reported on ClinicalTrials.gov. For purposes of timing of the Results Reporting, the initial estimated completion date for the Primary Endpoint of this study is 2 years after the study opens to accrual. The definition of “Primary Endpoint Completion Date” (PECD) for this study is the time the last patient registered has been followed for at least 6 months.
- 16.6 Inclusion of Women and Minorities
- 16.61 This study will be available to all eligible patients, regardless of race, gender, or ethnic origin.
- 16.62 There is no information currently available regarding differential effects of this regimen in subsets defined by race, gender, or ethnicity, and there is no reason to expect such differences to exist. Therefore, although the planned analysis will, as always, look for differences in treatment effect based on racial and gender groupings, the sample size is not increased in order to provide additional power for subset analyses.
- 16.63 The geographical region served by Mayo, has a population which includes approximately 3% minorities. Based on prior Mayo studies involving similar disease sites, we expect about 3-5% of patients will be classified as minorities by race and about 33% of patients will be women. Expected sizes of racial by gender subsets are shown in the following table:

| Ethnic Category | Sex/Gender | | | |
|---|------------|-------|---------|-----------|
| | Females | Males | Unknown | Total |
| Hispanic or Latino | 0 | 1 | 0 | 1 |
| Not Hispanic or Latino | 18 | 35 | 0 | 53 |
| Unknown | 0 | 0 | 0 | 0 |
| Ethnic Category: Total of all subjects | 18 | 36 | 0 | 54 |
| Racial Category | | | | |
| American Indian or Alaskan Native | 0 | 0 | 0 | 0 |
| Asian | 0 | 0 | 0 | 0 |
| Black or African American | 1 | 1 | 0 | 2 |
| Native Hawaiian or other Pacific Islander | 0 | 0 | 0 | 0 |
| White | 17 | 35 | 0 | 52 |
| More than one race | 0 | 0 | 0 | 0 |
| Unknown | 0 | 0 | 0 | 0 |
| Racial Category: Total of all subjects | 18 | 36 | 0 | 54 |

Ethnic Categories: **Hispanic or Latino** – a person of Cuban, Mexican, Puerto Rico, South or Central American, or other Spanish culture or origin, regardless of race. The term “Spanish origin” can also be used in addition to “Hispanic or Latino.”

Not Hispanic or Latino

Racial Categories: **American Indian or Alaskan Native** – a person having origins in any of the original peoples of North, Central, or South America, and who maintains tribal affiliations or community attachment.

Asian – a person having origins in any of the original peoples of the Far East, Southeast Asia, or the Indian subcontinent including, for example, Cambodia, China, India, Japan, Korea, Malaysia, Pakistan, the Philippine Islands, Thailand, and Vietnam. (Note: Individuals from the Philippine Islands have been recorded as Pacific Islanders in previous data collection strategies.)

Black or African American – a person having origins in any of the black racial groups of Africa. Terms such as “Haitian” or “Negro” can be used in addition to “Black or African American.”

Native Hawaiian or other Pacific Islander – a person having origins in any of the original peoples of Hawaii, Guam, Samoa, or other Pacific Islands.

White – a person having origins in any of the original peoples of Europe, the Middle East, or North Africa.

17.0 Pathology Considerations:

17.1 Bone marrow reports will be obtained from the laboratory reports. No special review will be required prior to patient entry on the study.

18.0 Records and Data Collection Procedures (As of Addendum 6, patients in active monitoring and in event monitoring will be removed from study. No further follow-up is required)

18.1 Submission Timetable

Initial Material(s)

| CRF | Active-Monitoring Phase (Compliance with Test Schedule Section 4.0) |
|---|---|
| On-Study Form | ≤ 2 weeks after registration |
| Baseline Adverse Event Form | |
| Pretreatment Measurement Form | |
| Baseline Research Blood Submission Form | |
| Research Bone Marrow Aspirate Submission Form | |
| Bone marrow biopsy report | |
| SPEP, UPEP, FLC, Immunofixation, FISH, Cytogenetics, PCLI reports | |
| Skeletal Survey | Submit ≤ 2 weeks after registration if withdrawal/refusal occurs prior to beginning protocol therapy |
| End of Active Treatment/Cancel Notification Form | |

Test Schedule Material(s)

| CRF | Active-Monitoring Phase (Compliance with Test Schedule Section 4.0) | |
|--|---|---------------------|
| | At each evaluation during treatment | At end of treatment |
| Evaluation/Treatment Form | X ¹ | X |
| Nadir/Adverse Event Form | X | X |
| Measurement Form | X | X |
| Research Blood Submission Form | X ² | |
| Research Bone Marrow Aspirate Submission Form | X ² | |
| End of Active Treatment/Cancel Notification Form | | X |
| Notification Form – Grade 4 or 5 Non-AER Reportable Events/Hospitalization Form (see Section 10.2) | At each occurrence | |
| ADR/AER (see Section 10.0) | At each occurrence | |
| Bone marrow biopsy report | X ² | X |
| SPEP, UPEP, FLC, Immunofixation reports | X ³ | X ³ |
| Skeletal Survey | X ² | X |

1. Complete at each evaluation during Active Treatment (see Section 4.0).
2. Only when required by the Test Schedule (see Section 4.0).
3. Submission of these reports is only required for documentation of CR (including sCR) or progression. For documentation of CR, submit all of these reports at the first confirmation of CR. For documentation at first signs of progression, submit reports to the [REDACTED].

Follow-up Material(s)

| CRF | Event Monitoring Phase | | | |
|-----------------------|---|--|-------|--------------------|
| | At PD or initiation of new treatment ¹ | 6 months After PD or initiation of new treatment | Death | New Primary |
| Event Monitoring Form | X | X | X | At each occurrence |

1. Submit documentation of progression to the MCCC Operations Office, Attention: [REDACTED].

18.2 Dana Farber Cancer Institute and the University of Chicago

18.21 Submit forms for computer entry to:

Data CRA for MC1082
Mayo Clinic Cancer Center

[REDACTED]
Rochester, MN 55905

Fax: [REDACTED]

18.22 Patient identification labels will be produced for each patient entry. The labels are produced for use on the data forms and will be mailed to the co-sponsors twice weekly. Additional labels may be obtained by directly calling the Mayo Clinic Cancer Center (MCCC) Registration Office [REDACTED].

18.23 Each co-sponsor will be responsible for insuring that all materials contain the patient's initials, MCCC registration number, and MCCC protocol number. Patient's name must be removed.

18.24 Any materials deemed incomplete by the MCCC Operations Office will be considered "not received" and will not be edited or otherwise processed until the missing information is received. A list of the missing documents will be made available to the appropriate co-sponsor.

18.25 Overdue lists: A list of overdue materials and forms for study patients will be generated monthly. The listings will be sorted by location and will include the patient study registration number. The appropriate co-sponsor will be responsible to obtain the overdue material.

18.26 Corrections forms: If a correction is necessary the QAS will query the co-sponsor. The query will be sent to the appropriate co-sponsor who will make the correction and return the query and documentation of correction back to the QAS.

19.0 Budget Considerations

19.1 Costs charged to patient: routine office visits and pharmacy charges. Patients and their insurance carriers will also be billed for non-research lab tests deemed necessary to safely administer the drugs. Since bortezomib and dexamethasone are standard therapy of myeloma, commercial supplies will be used and it is reasonable to charge for its distribution. Pomalidomide will be supplied free by Celgene.

19.2 Other budget concerns: Protocol administration, data management, research testing on samples and statistical analysis efforts will be by funded by Celgene, according to the terms of the contract.

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Model Consent Form

- *NOTES FOR LOCAL INVESTIGATORS:** The goal of the informed consent process is to provide people with sufficient information for making informed choices. The informed consent form provides a summary of the clinical study and the individual's rights as a research participant. It serves as a starting point for the necessary exchange of information between the investigator and potential research participant. This template for the informed consent form is only one part of the larger process of informed consent. For more information about informed consent, review the "Recommendations for the Development of Informed Consent Documents for Cancer Clinical Trials" prepared by the Comprehensive Working Group on Informed Consent in Cancer Clinical Trials for the National Cancer Institute. The Web site address for this document is <http://cancer.gov/clinicaltrials/understanding/simplification-of-informed-consent-docs/>
- A blank line, _____, indicates that the local investigator should provide the appropriate information before the document is reviewed with the prospective research participant.
 - Suggestion for Local Investigators: An NCI pamphlet explaining clinical trials is available for your patients. The pamphlet is entitled: "If You Have Cancer... What You Should Know about Clinical Trials". This pamphlet may be ordered on the NCI Web site at <https://cissecure.nci.nih.gov/ncipubs/> or call 1-800-4-CANCER (1-800-422-6237) to request a free copy.
 - Optional feature for Local Investigators: Reference and attach drug sheets, pharmaceutical information for the public, or other material on risks. Check with your local IRB regarding review of additional materials.

*These notes for {authors and} investigators are instructional and should not be included in the informed consent form given to the prospective research participant.

1. General Information About This Research Study

Study Title: MC1082, “A Phase I/II Trial of Pomalidomide (CC-4047), Bortezomib, and Dexamethasone in Patients with Relapsed or Refractory Multiple Myeloma”

Name of Principal Investigator on this Study: *[investigator’s name(s)]* and Colleagues

A. Study Eligibility and Purpose

You are being asked to take part in this research study because you have multiple myeloma that has recurred or not responded to treatment.

This study is divided into 2 phases. The Phase I part will find the best dose of bortezomib that can be used in combination with pomalidomide and dexamethasone in patients with multiple myeloma. The Phase II part will further study the dose that is determined to be the best in Phase I and will study how effective the treatment is against multiple myeloma.

As you read this form describing the study, ask any questions you have. Take your time to decide. Feel free to discuss the study with your family, friends, and healthcare provider before you decide. If you decide to participate, you may stop participating at any time during the study. You may decide not to participate. If so, none of your current benefits or normal health care will be affected in any way. When you feel comfortable that all your questions have been answered, and you wish to take part in this study, sign this form in order to begin your participation. If you are agreeing for someone else, you need to sign this form. Your signature means you have been told about the study and what the risks are. Your signature on this form also means that you want yourself to take part in this study.

B. Number of Participants

The plan is to have 54 people take part in this study at Mayo Clinic, Dana Farber, and the University of Chicago.

C. Additional Information You Should Know

Celgene is funding the study. Celgene will pay your study doctor or the institution to cover costs related to running the study.

2. What Will Happen To You While You Are In This Research Study?

If you agree to be in the study, you will be asked to participate in the following:

On your first visit you will have tests done to evaluate your myeloma. These include routine blood and urine tests, routine bone marrow aspirate and biopsy (a large needle will be inserted into your hip to remove some bone marrow and small sample of bone tissue), a complete set of bone x-rays, and a chest x-ray. Your doctor will ask you questions about your medical history and examine you. If you are a woman who can have children, you will be required to have a negative pregnancy test 10 – 14 days prior to and again 24 hours before starting therapy. The pregnancy tests must be negative for you to start treatment.

If you are eligible and agree to participate, you will begin treatment. Twenty-eight days will be considered one cycle of treatment. During each cycle you will take pomalidomide in capsules at about the same time on days 1-21. You will also take dexamethasone, a steroid pill, once a week on days 1, 8, 15 and 22 of each cycle. You will also get bortezomib by intravenous infusion (through a vein in your arm) on days 1, 8, 15 and 22. You will also take aspirin daily, unless you can not tolerate aspirin, and then an alternative medication may be given. You will be asked to keep a diary to record when you take your oral medication.

Swallow pomalidomide capsules whole. Do not break, chew or open the capsules. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal. If you miss a dose of pomalidomide, it should be taken as soon as possible on the same day. If you miss taking your dose of pomalidomide for the entire day, it should not be made up. If you take more than your prescribed dose of pomalidomide, you should seek emergency medical care if needed and contact study staff immediately.

For the first cycle of treatment, you will need to receive all doses of bortezomib at [Insert local institution name]. You will need to return to [Insert local institution name] every month for a re-evaluation before receiving your next cycle of treatment. If your doctor feels you are tolerating treatment well you may be able to receive days 8, 15, and 22 of bortezomib from your local physician. You will be asked to return your diary, empty pill bottle or any remaining capsules at the end of each cycle.

In order to obtain pomalidomide free of charge from Celgene, your name, address, phone, date of birth and the fact that you are participating in this trial will be Celgene and its agents or vendors that supply pomalidomide and administer the POMALYST REMS™ program. By signing this consent form you agree to this disclosure.

Below is a table that shows the procedures and study visits:

| | |
|---|--|
| Before study enrollment | <ul style="list-style-type: none"> • Routine blood and urine tests and exams • Bone marrow biopsy and aspirate (removal of bone marrow with a needle and syringe). OPTIONAL: A portion of the bone marrow aspirate will be collected for research tests if you agree. • Bone x-rays • Chest x-ray • Pregnancy test 10 – 14 days and again 24 hours before starting treatment (only for females who may still become pregnant) • OPTIONAL: Research blood collection (about 2 tablespoons) • ECG (Electrocardiogram-a measurement of your heart's electrical activity) |
| Weekly for the first two months (may be done at home and sent to your doctor at Mayo) | <ul style="list-style-type: none"> • Pregnancy test (only for females who may still become pregnant) will be done weekly for the first month and then monthly for women with regular menstruation and every two weeks for women with irregular menstruation • Routine blood work including complete blood count |
| Every month during study | <ul style="list-style-type: none"> • Routine blood and urine tests and exams • Pregnancy test (only for females who may still become pregnant) • Check for side effects • OPTIONAL: Research blood collection (about 2 tablespoons) for the first 4 cycles. If you had a sample collected at the time you enrolled you will not have to have the Cycle 1 sample collected. |
| Every 3 months | <ul style="list-style-type: none"> • Disease assessment (includes blood tests, may include 24 hour urine collection) • Physical Exam • ECG • Bone x-ray (every 12 months while on treatment) • Bone marrow biopsy and aspirate after 3 cycles. This may be repeated if your doctor determines this is needed to see if your disease has responded to treatment or gotten worse. OPTIONAL: A portion of the bone marrow aspirate will be collected for research tests if you agree. |

| | |
|-------------------------------------|--|
| One month after discontinuing study | <ul style="list-style-type: none"> • Pregnancy test (only for females who may still become pregnant) – women with irregular menstruation will have a pregnancy tests 14 day and 28 days after discontinuing study |
|-------------------------------------|--|

I agree to have a portion of my bone marrow aspirate sample used for research testing at the timepoints described in the table above:

Yes No Please initial here: _____ Date: _____

I agree to the have my blood collected and used for research testing at the timepoints described in the table above:

Yes No Please initial here: _____ Date: _____

The drug used in this study is considered investigational, which means it has either not been approved by the Food and Drug Administration (FDA) for routine clinical use or for the use described in this study. However the FDA has allowed the use of this drug/device in this research study.

3. How Long Will You Be in This Research Study?

You will receive up to 8 cycles of treatment with pomalidomide, bortezomib and dexamethasone. After 8 cycles of treatment you will continue to take pomalidomide maintenance treatment until your disease gets worse, you experience a bad side effect, or you decide not to continue treatment. After you have completed treatment will followed every 6 months until your disease progresses or you begin another treatment.

4. Why You Might Want To Take Part In This Research Study

This study may not make your health better. However, this is the newest in a class of medicines that have been used successfully for myeloma. There is a chance this medicine combination may improve or stabilize your myeloma and information learned from this study may help other patients with myeloma in the future.

5. What Are the Risks Of This Research Study?

Pomalidomide

Likely risks of pomalidomide (*events occurring greater than 20% of the time*)

- A low number of white blood cells, which are the infection fighting cells, which could put you are risk for infection (Neutropenia or Leukopenia)

- A low number of a particular white blood cell, which is important to the immune system (Lymphopenia)
- Feeling tired (Fatigue)
- Difficulty passing stool (Constipation)
- Feeling sick to your stomach (Nausea)
- Decreased number of blood cells (platelets) that help to clot the blood (which could put you at increased risk of bleeding (Thrombocytopenia)
- Decrease in red blood cells, which are the oxygen carrying cells, which could make you feel tired (Anemia)
- Back pain
- Shortness of breath
- Loose stools (Diarrhea)

Less likely risks of pomalidomide (*events occurring less than or equal to 20% of the time*)

- When CC-4047 or related drugs (i.e. thalidomide and lenalidomide) have been used along with cortico steroids and certain other chemotherapy drugs, there has been an increased risk of individuals developing blood clots. Your doctor may request or require that you take aspirin or another blood thinner in this situation.
- Abdominal pain
- Sore mouth or throat
- Numbness, tingling, or inflammation of the nerves (usually in the hands and feet), which may be painful.(peripheral neuropathy)
- Drop in blood pressure or dizziness
- Headache
- Chest pain
- Swelling of the hands and feet
- Tremors
- Fever (Pyrexia)
- Infections including potentially life threatening infections
- Muscle aches or cramps
- Muscle weakness
- Joint swelling or achiness
- Dry or itchy skin
- Blushing or redness to face (Flushing)
- Decreased function of the thyroid gland, which can result in feeling tired and weight gain, that may first show up as an increased levels of thyroid stimulating hormone (hypothyroidism) If your thyroid function becomes abnormal, your doctor may have you take a thyroid replacement pill daily.
- Dizziness (Vertigo)
- Difficulty emptying the bladder (Urinary retention)
- Pelvic pain
- Rash
- Cough
- Vomiting
- Reduced appetite
- Decreased sodium levels in the blood (Hyponatremia)
- Abnormally high calcium in the blood stream, that can result in fatigue, confusion, feeling sick to your stomach, throwing up, difficulty passing stool, abnormal heartbeat, coma, and death (Hypercalcemia)
- Abnormally low calcium in the blood stream, that can result in muscle cramps,

- abdominal cramps, spasms (Hypocalcemia)
- Abnormal levels of potassium in the blood (Hyper or Hypokalemia)
- Weakness or lack of energy (Asthenia)
- Death
- Kidney failure (Renal failure)
- Excessive sweating (Hyperhidrosis)
- High blood sugar (Hyperglycemia)

Rare but serious risks of pomalidomide (*events occurring less than 2-3% of the time*)

- Chest wall pain
- Blood clot in a vein (deep venous thrombosis)
- Blood clots in the lungs which could be life threatening or cause death (pulmonary embolism)
- Inability of the heart to properly pump blood to the lungs (Right ventricular failure)
- Bleeding from the stomach large intestine and/or small intestine (Gastrointestinal bleeding)
- Narrowing of the stomach or intestines (Gastrointestinal stenosis)
- Chest pain that occurs when your heart doesn't get enough oxygen. It can be a warning sign of a heart attack (Angina unstable)
- An irregular heartbeat that results from the top/upper chambers of the heart “quivering” instead of beating normally. (Atrial Fibrillation)
- Fast heart rate (Tachycardia) or slow heart rate (Bradycardia)
- Decrease in the ability of the heart to pump blood, because of weakening of the heart muscle (congestive heart failure)
- Lack of oxygen to the heart muscle which can cause damage to the heart (Heart attack))
- Feeling like your heart is “fluttering or skipping” (Heart palpitations)
- Bleeding in the brain (Cerebral Hemorrhage)
- Lack of oxygen to the brain caused by either bleeding in the brain or blood clot. Also called a stroke.(Cerebral vascular accident)
- Memory impairment
- Blood creatinine increased
- Excessive or abnormal loss of body fluids (Dehydration)
- Failure to thrive
- Anxiety
- Confusion
- Feeling sad or blue (Depression)
- Difficulty falling or staying asleep (Insomnia)
- Changes in mood
- Kidney stones (Nephrolithiasis)
- Collection of fluid in the space around the lung (Pleural Effusion)
- Inability of the lungs to function properly (Respiratory failure)
- High blood pressure (Hypertension) or low blood pressure (Hypotension)
- Acute inflammation of the liver including hepatitis and possible jaundice
- Inflammation of the lungs (Interstitial lung disease)
- Possible second cancer with prolonged use
- Blurred vision
- Decreased level of phosphorus in the blood (Hypophosphatemia)
- Decreased albumin in the blood (Hypoalbuminemia)
- Low levels of magnesium in the blood (Hypomagnesemia)
- Night sweats
- Changes in the voice or hoarseness (Dysphonia)

- Nose bleed (Epistaxis)
- Very Sleepy, difficulty arousing (Lethargy)
- Fainting (Syncope)
- Excessive sleepiness (Somnolence/Depressed level of consciousness)
- Change in taste sensation (Dysgeusia)
- Dry mouth
- Chills
- Recurrent areas of skin or mucosal swelling of sudden onset, usually disappearing within 24 hours; an allergic reaction to the medication (Angioedema) an exaggerated or inappropriate immune response (hypersensitivity) to Pomalidomide.

ANIMAL STUDIES

In an animal study, one monkey developed acute myelogenous leukemia (AML) after receiving high doses of pomalidomide for several months. The cause of the leukemia is still being investigated and the risk of this animal finding to human subjects is unknown.

Bortezomib

Likely risks of Bortezomib (*events occurring greater than 20% of the time*)

- Decreased number of blood cells (platelets) that help to clot the blood (which could put you at increased risk of bleeding)(Thrombocytopenia)
- Decrease in red blood cells, which are the oxygen carrying cells, which could make you feel tired (Anemia)
- Fever (Pyrexia)
- Severe shaking chills (Rigors)
- Difficulty passing stool (Constipation)
- Loose stools (Diarrhea)
- Feeling sick to your stomach (Nausea)
- Throwing up (Vomiting)
- Loss of appetite not feeling hungry (Anorexia)
- Excessive or abnormal loss of body fluids (Dehydration)
- Weight loss
- Generalized weakness and loss of strength (Asthenia)
- Headache
- Difficulty falling or staying asleep (Insomnia)
- Cough
- Shortness of breath or difficulty breathing (Dyspnea)
- Numbness, tingling, or inflammation of the nerves, which may be painful or increase your tendency to trip or fall. (Neuropathy), which may not get better after discontinuation of this drug. Uncommonly the nerves that control things like your heart rate, gut movement, and urinary bladder may be affected.
- Back pain
- Swelling in the arms and legs (Edema)
- Infections, including bladder and/or kidney (urinary tract infection), lungs (for example, bronchitis or pneumonia), and blood stream (bacteremia), etc.
- Rash with itching and redness.

Less likely risks of Bortezomib (occurring greater than 3% and less than 20% of the time):

- Decreased white blood cells, which are the infection fighting cells, which could put you at risk for infection (Leukopenia)

- Muscle pain (Myalgia)
- Joint pain (Arthralgia)
- Low blood pressure (Hypotension)
- A painful blistery red rash that is confined to one side of the body, similar to chicken pox (herpes zoster) or blisters in the nose, mouth, genitals or elsewhere on the skin, caused by the herpes virus (herpes simplex virus)
- Decrease in kidney function
- Decrease in the ability of the heart to pump blood, because of weakening of the heart muscle (Congestive heart failure)
- A cluster of signs and symptoms (including but not limited to) chest pain, shortness of breath, sweating, feeling sick to your stomach, and/or throwing up, seen when there is a reduced amount of blood being supplied to the heart muscle (Acute coronary syndrome)
- Fever, aching joints (Flu-like-syndrome)
- Sore throat (Pharyngitis)
- Cold symptoms, such as runny or stuffy nose (Rhinitis)
- Abnormal Liver function tests which may indicate that your liver is not functioning properly
- Certain kind of infection of the liver which causes inflammation and can cause liver damage (Hepatitis)
- Changes in blood sugar have been reported in a few diabetic patients receiving oral anti-diabetic medication. If you are taking oral antidiabetic agents you may require close monitoring of your blood sugar levels
- Decreased sodium levels in the blood (Hyponatremia)
- Low potassium levels in the blood (Hypokalemia)
- Abnormally high calcium in the blood stream, that can result in fatigue, confusion, feeling sick to your stomach, throwing up, difficulty passing stool, abnormal heartbeat, coma, and death (Hypercalcemia)
- Infection around the eye, also called pink eye (Conjunctivitis)
- Inflammation and/or sores in the mouth that may make swallowing difficult and are painful (Mucositis)
- Heartburn (Dyspepsia)
- Abdominal pain
- Nose bleeds (Epistaxis)
- Infection that has spread to the bloodstream and can cause low blood pressure, fever, and/or death (Sepsis)
- Confusion and feeling anxious
- Blurred vision
- An uncommon risk, severe rash which causes blistering and peeling of the skin (Steven Johnson Syndrome)
- Inflammation/infection of the lungs (Pneumonitis/Pneumonia)
- Yeast (fungal) infection of the mouth and throat (Thrush/oral candidiasis)
- Fungal infection of the skin (Tinea corporis)
- Fungal infection of the nails (Onychomycosis)
- Change in taste sensation (Dysgeusia)
- Blood in the urine (Hematuria)
- Painful swallowing (Odynophagia)
- Decreased protein in blood
- Muscle weakness
- Increased blood pressure (hypertension)

Rare but serious events of Bortezomib (occurring less than 3% of the time):

- Severe bleeding, including bleeding from the stomach, large intestine and/or small intestine (gastrointestinal bleeding). Your doctor may recommend preventative platelet transfusions to reduce the risk of bleeding
- Inability of the intestines to pass food and drink normally (Ileus)
- Blockage in the intestines (Bowel obstruction)
- Inflammation of the intestines (Colitis)
- Inflammation of the pancreas (Pancreatitis)
- Inflammation of the stomach (Gastritis)
- Irritation and infection at site of injection
- Bleeding in the brain (Intracranial hemorrhage)
- Bleeding in the brain between the skull and the brain (Subarachnoid hemorrhage)
- Fluid buildup in the lungs (Pulmonary edema)
- A medical condition related to leakiness of the blood vessels in the brain (RPLS can cause confusion, blindness, or vision changes, seizures and other symptoms, as well as changes in brain scans). RPLS may go away after bortezomib is stopped. In rare cases, it may be potentially life-threatening and may have long-term effects on brain function. (Reversible posterior leukoencephalopathy or RPLS)
- A complication that may occur if the cancer cells die too quickly that includes inappropriate increase or decrease of various natural chemicals in the blood stream, called uric acid, phosphorus, potassium, creatinine, and calcium). Severe tumor lysis can result in kidney failure and may harm muscle or nerve function. (Tumor lysis syndrome)
- Loss of hearing
- Severe, life-threatening, or deadly lung diseases of unknown cause which may include inflammation of and accumulation of fluid in the lungs which can cause breathing problems and decrease in oxygen content of the blood. This problem has been seen most commonly in Japan. Other risk factors for this complication include co-administration of a drug called cytarabine and a drug called daunorubicin.
- Coughing up of blood or blood tinged sputum (Hemoptysis)
- Infections of the throat, stomach and intestines (gut), skin and at the area of skin where your catheter is placed
- Serious allergic reaction to the medication which can cause hives, itching, shortness of breath, swelling of the lips or throat, difficulty breathing, and could be life threatening (Anaphylactic reaction)
- Loss of control or weakness in the muscles under voluntary control- such as the arms, legs, or mouth (i.e talking), which can make movement of these areas difficult or not possible (Motor neuropathy).
- Inflammation and/or infection of the lining surrounding the lung which can be painful (Pleurisy/pleuritis)
- Collection of pus around the lungs (Empyema)
- Changes to the brain that may cause convulsions and confusion or loss of consciousness
- Abnormal heartbeat (Arrhythmia). These could be life threatening
- A collection of fluid or blood in the space around the heart (Pericardial effusion)
- Rash associated with fever (Acute febrile neutrophilic dermatosis)
- Herpes infection of the eye, damage to optic nerve and blindness
- Deterioration in brain function (Progressive multifocal leukoencephalopathy)

Dexamethasone

Likely risks of dexamethasone:

- Stomach and throat ulcers or worsening of any ulcers you had before treatment
- Swelling and pain of the pancreas
- Weight gain around the stomach
- Puffiness (especially in the face)
- Buildup of fluids and a rise in blood pressure
- Possible rise in your blood sugar
- Changes in the blood levels of potassium.
- Infection

Less Likely risks of dexamethasone:

- Muscle weakness
- Brittle bones
- Menstrual changes
- Itching, and other allergic reactions, some severe.

Rare but serious risks of dexamethasone:

- Mood swings
- Depression
- Trouble sleeping
- Changes in personality
- Seizures
- Dizziness
- Patients who are more likely to get heart disease may have heart failure

As with any medication, allergic reactions are a possibility.

The risks of drawing blood include pain, bruising, or rarely, infection at the site of the needle stick.

Pregnancy and Birth Control:

- 1) Will women of child-bearing-potential (able to become pregnant) be allowed to participate in this study?

Yes: Women of child-bearing-potential will be able to participate in this study if they have a negative pregnancy test and agree to use **TWO** reliable methods of birth control (see #5) or practice complete abstinence from heterosexual intercourse 28 days before starting pomalidomide, during treatment with pomalidomide, and for at least 28 days after you stop taking pomalidomide, since the risks to an unborn child are either unknown or potentially serious.

You will be considered a woman of child bearing potential unless you have had natural absence of menstrual periods for the past 24 consecutive months or have had a hysterectomy (the surgical removal of the uterus) or have had both ovaries surgically removed. If there is ANY chance that you can become pregnant, you will be considered a woman of child bearing potential.

You agree to inform the investigator immediately if: 1) you have any reason to suspect you are pregnant; 2) you find that circumstances have changed and that there is a risk of becoming pregnant; or 3) you have stopped using the approved forms of **TWO** reliable birth control methods.

- 2) Will pregnant, and/or nursing women be allowed to participate in this study?

No: There is not enough medical information to know what the risks might be to a breast-fed infant or to an unborn child carried by a woman who takes part in this study. Breast-feeding mothers must stop breast-feeding to take part in this study.

- 3) Do you need to have a pregnancy test done to be part of the study?

Yes: As part of this study a pregnancy test is required for all women who are able to become pregnant.

A blood/urine pregnancy test will be done within 10-14 days of starting CC-4047 and again within 24 hours of starting pomalidomide. For the blood pregnancy test, blood will be taken from your arm.

You will be told the results of the pregnancy test. If the pregnancy test is positive, you will not be able to take part in the study.

You will have pregnancy tests before and during treatment, even if you agree not to have reproductive heterosexual intercourse. You will have a pregnancy test done by the doctor every week during the first 28 days of this study. You will then have a pregnancy test every 28 days during your participation in this study if your menstrual cycles are regular or every 14 days if your cycles are irregular. You will also have a pregnancy test if you miss your period or have unusual menstrual bleeding. In addition, you will have pregnancy tests when you are discontinued from the study and at day 28 after discontinuation from the study if your menstrual cycles are regular. If your menstrual cycles are irregular, you will have pregnancy tests when you are discontinued from the study and at days 14 and 28 after discontinuation from the study.

If you have any reason to suspect you are pregnant, you must IMMEDIATELY stop taking pomalidomide and tell your doctor. If you have a positive pregnancy test while participating in this study, you must IMMEDIATELY stop taking pomalidomide and tell your doctor. If you have a positive pregnancy test within 28 days after you have stopped participating in the study, you must IMMEDIATELY tell your doctor.

Study subjects who become pregnant will be monitored throughout the pregnancy and will continue to be monitored for 30 days after delivery (premature delivery, aborted fetus, full-term pregnancy, or no longer pregnant).

You must **NEVER** share pomalidomide (or other study drugs) with someone else. You must **NEVER** donate blood while you are participating in this study and for at least 28 days after you have been discontinued from the study. You will be counseled at least every 28 days and at discontinuation from the trial about not sharing pomalidomide (and other study drugs), the potential risks of fetal exposure, and abstaining from blood and donations.

4) Will men who are able to father a child be allowed to participate in this study?

Yes: Men who are able to father a child are allowed to take part in this study and must agree to use a latex condom every time you have sex with a female of child bearing potential during treatment with pomalidomide and for at least 28 days after you stop taking pomalidomide even if you have had a vasectomy.

You must **NEVER** share pomalidomide (or other study drugs) with someone else. You must **NEVER** donate blood, sperm, or semen while you are participating in this study and for at least 28 days after you have been discontinued from the study. You will be counseled at least every 28 days regarding abstaining from donating blood, sperm, or semen; birth control requirements; not sharing pomalidomide (and other study drugs); and the potential risks of fetal exposure.

5) What types of birth control are acceptable?

Highly Effective Methods

Intrauterine device (IUD)

Hormonal (birth control pills, injections, implants)

Tubal ligation

Partner's vasectomy

Additional Effective Methods

Latex condom

Diaphragm

Cervical cap

Certain drugs interfere with hormonal contraception and may reduce the effectiveness of the contraception for up to 30 days after stopping these medications. These medications include HIV protease inhibitors, penicillins, modafinil (Provigil®), griseofulvin (Fulvicin®), phenytoin (Dilantin®), carbamazepine (Carbatrol®, Tegretol®), rifampin (Rifamycin®, Rifamate®, Rifater®), rifbutin (Mycobutin®), or certain herbal supplements such as St. John's Wort. If you are taking any of these medications, please notify your doctor. If you are a female of childbearing potential taking these medications you must use two other effective or highly effective methods of contraception.

PREGNANCY

Pomalidomide was found to cause birth defects in an experimental study in animals. Pomalidomide is related to thalidomide. Thalidomide is known to cause severe life-threatening human birth defects. Pomalidomide is therefore considered to have the potential to cause birth defects in humans. If pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby. Females must not become pregnant while taking pomalidomide.

In order to participate in this study you must register into and follow the requirements of the POMALYST REMS™ program of Celgene Corporation. This program provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. You will be required to receive counseling, follow the pregnancy testing and birth control requirements of the program that are appropriate for you and take surveys regarding your compliance with the POMALYST REMS™ program.

By signing this consent form you understand and agree to receive counseling and to comply with the pregnancy precaution requirements of the POMALYST REMS™ program.

Risk summary

Many side effects go away shortly after the pomalidomide, dexamethasone, and bortezomib are stopped, but in some cases side effects can be serious, long lasting, or may never go away. There may be a risk of death.

Some side effects may not be known. Side effects may range from mild to life-threatening. Other drugs may be given to make side effects less serious and less uncomfortable. Talk to the researcher and/or your healthcare provider about side effects and ask any other questions.

6. What Other Choices Do You Have If You Don't Take Part In This Research Study?

You do not have to be in this study to receive treatment for your condition. Your other choices may include chemotherapy, thalidomide, lenalidomide, corticosteroids, other research studies or supportive care. You should talk to the researcher and your regular physician about each of your choices before you decide if you will take part in this study.

7. Are There Reasons You Might Leave This Research Study Early?

Taking part in this research study is voluntary. You may decide to stop at any time. You should tell the researcher if you decide to stop and you will be advised whether any additional tests may need to be done for your safety.

In addition, the researchers, Celgene, or Mayo may stop you from taking part in this study at any time:

- if it is in your best clinical interest,
- if you do not follow the study procedures,
- if the study is stopped.

8. Will You Need To Pay For Any Of The Tests And Procedures?

You will not need to pay for tests and procedures which are done just for this research study. These tests and procedures are:

- Study drug (pomalidomide)
- Research tests done on your blood and bone marrow aspirate sample

However, you and/or your health plan will need to pay for all other tests and procedures that you would normally have as part of your regular medical care. These tests and procedures are:

- Bortezomib and dexamethasone as well as preparation charges and other drugs or treatment given to help control side effects
- Routine physical exams and blood and urine tests
- Bone marrow aspirate and biopsy
- X-ray skeletal survey
- Chest x-ray
- Pregnancy tests for women of childbearing potential

If you have study related questions regarding billing, insurance or reimbursement, stop by or call:
Rochester: Admission and Business Services office, or call Patient Account Services at (507) 287-1819

Florida: The receptionist at the Registration Desk at the first floor, main lobby of the Davis Building or call (904) 953-7058

Arizona: The concourse level Patient Financial Services office or call this office at 800-603-0558

9. Will You Be Paid For Participating In This Research Study?

You will not be paid for taking part in this study.

10. What Happens If You Are Injured Or Ill Because You Were In This Research Study?

If you have side effects from the study treatment, you need to report them to the researcher and your regular physician, and you will be treated as needed. Mayo will bill you or your insurer for these services at the usual charge. Mayo will not offer free medical care or payment for any bad side effects from taking part in this study.

11. What Are Your Rights If You Are In This Research Study?

Taking part in this research study will not change your rights and benefits. Taking part in this research study does not give you any special privileges. If you decide to not participate in this study, or stop in the middle of the study, no benefits are taken away from you. Specifically, you do not have to be in this research study to receive or continue to receive medical care from Mayo Clinic.

You will be told of important new findings or any changes in the study or procedures that may affect you or your willingness to continue in the study.

12. What About Your Privacy?

Your privacy is important to us, and we want to protect it as much as possible. By signing this form, you authorize (name of institution) and the investigators to use and disclose any information created or collected in the course of your participation in this research protocol. This information might be in different places, including your original medical record, but we will only disclose information that is related to this research protocol for the purposes listed below.

This information will be given out for the proper monitoring of the study, checking the accuracy of study data, analyzing the study data, and other purposes necessary for the proper conduct and reporting of this study. If some of the information is reported in published medical journals or scientific discussions, it will be done in a way that does not directly identify you.

Information Disclosed to Study Supporter

The study data sent by the study doctor to the study supporter does not include your name, address, social security number, or other information that directly identifies you. Instead, the study doctor assigns a code number to the study data and may use your initials. Some study data sent to the sponsor may contain information that could be used (perhaps in combination with other information) to identify you (eg, date of birth). If you have questions about the specific health information that will be sent to the sponsor, you should ask the study doctor.

This information may be given to other researchers in this study, including those at other institutions, representatives of the company supplying drug and funding for the study, including representatives in the USA or other countries, or private, state or federal government parties or regulatory authorities in the USA and other countries responsible for overseeing this research. These may include the Food and Drug Administration, the Office for Human Research Protections, or other offices within the Department of Health and Human Services.

[Note to Local Investigators: The NCI has recommended that HIPAA regulations be addressed by the local institution. The regulations may or may not be included in the informed consent form depending on local institutional policy.]

13. What Will Happen to Your Samples?

Your sample of blood and bone marrow will be kept at Mayo for use in this study. Researchers at Mayo who are not involved with this study may ask to use your sample for more research. You have a say in how your stored sample is used in future research. You can still take part in the treatment study without giving your sample for future use.

Identification information:

If you agree to allow your sample to be used for further research, the sample may be stored forever. The sample will be stored at Mayo and would be given a code (instead of your name) while it is stored and when it is used in research. This code allows your sample to be used without anyone knowing that it is your sample just by looking at the label.

There is a very small chance that some commercial value may result from the use of your donated sample. If that happens, you will not be offered a share in any profits.

Risks:

Some future studies may be for testing the genes you inherited from your parents (also known as genetic testing). If a researcher finds that future test results may be useful for your health care, you will be contacted and given the choice to learn the test results. At that time, you will be given general information on the potential risks, benefits, and costs of choosing to learn the test results. The risks of learning genetic test results may include emotional upset, insurance or job discrimination, and/or family conflicts from learning unknown information about your parents or blood relatives. Test results will only be put into your medical record if you chose to learn the results. Sometimes results should be released only through a genetic counselor, who can help explain the possible risks and benefits of learning the results.

Exceptions when your samples may be used without your permission:

- 1) When government rules allow your sample to be used without identifying you, even with a code.
- 2) When use of the sample is not considered human subject research.

At all other times:

- You can let Mayo use your sample.
- You can say NO to have your sample used by Mayo.

Please read the following statements and mark your choice:

1. I permit my sample to be stored and used in future research of multiple myeloma at Mayo:

Yes No Please initial here: _____ Date: _____

2. I permit my sample to be stored and used in future research at Mayo to learn about, prevent, or treat any other health problems:

Yes No Please initial here: _____ Date: _____

Who will use your sample?

If you agree to give your sample, it will be the property of Mayo and may be used for research by Dr. Lacy and other staff at Mayo Clinic. Researchers at other institutions may also ask for a part of your sample for future studies.

How do researchers from other institutions get the sample?

Researchers from universities, hospitals, and other health organizations conduct research using tissue. They may contact Mayo and request samples for their studies. If you approve release of your sample by checking 'yes' below, Mayo may send the tissue sample(s) and some information about you to researchers who request them, but Mayo will not send your name, address, phone number, social security number, or any other identifying information with the sample. If you allow your sample to be given to researchers at other institutions, it will be given to them with a code number rather than your name. If these researchers use the sample for future research and decide that a test result may be useful for your health care, they may contact the *[Insert local institution name]* and *[Insert local institution name]* would then contact you to offer you the choice to learn the test results. *[Insert local institution name]* has the right to end storage of the sample without telling you.

I permit Mayo to give my sample to researchers at other institutions:

Please mark one box:

Yes No Please initial here: _____ Date: _____

If you want your sample destroyed at any time, write to:

Secretary of the _____ Institutional Review Board _____.

14. Who Can Answer Your Questions?

| You can call ... | At ... | If you have questions or concerns about ... |
|--|--|---|
| <p>Insert site Principal Investigator(s) if applicable</p> <p>Insert study coordinator's name (optional)</p> | <p>Phone:</p> <p>insert SC's phone #</p> | <p>Questions about the study tests and procedures</p> <p>Research-related injuries or emergencies</p> <p>Any research-related concerns or complaints</p> |

15. Summary and Enrollment Signatures

You have been asked to take part in a research study, at Mayo Clinic. The information about this study has been provided to you to inform you about this study.

- I have read the whole consent form, and all of my questions have been answered to my satisfaction.
- I am satisfied that I have been given enough information about the purpose, methods, risks, and possible benefits of the study to decide if I want to join.
- I know that joining the study is voluntary and I agree to join the study.
- I know that I can call the investigator and research staff at any time with any questions or to tell them about side effects.
- I know that I may withdraw from the study at any time.

A copy of this form will be put in my medical records and I will be given a copy of this completed form.

Please sign and date to show that you have read all of the above guidelines. Please do not sign unless you have read this entire consent form. If you do not want to sign, you don't have to, but if you don't you cannot participate in this research study.

(Date / Time)

(Printed Name of Participant)

(Clinic Number)

(Signature of Participant)

(Date / Time)

(Printed Name of Individual Obtaining Consent)

(Signature of Individual Obtaining Consent)

This model informed consent form has been reviewed by the Mayo Clinic Cancer Center and is the official consent document for this study. Local IRB changes to this document are allowed. Sections “What are the risks of the research study” or “What other choices do I have if I don’t take part in this research study?” should always be used in their entirety if possible. Editorial changes to these sections may be made as long as they do not change information or intent. If the institutional IRB insists on making deletions or more substantive modifications to these sections, they must be justified in writing by the investigator and approved by the IRB. Under these circumstances, the revised language and justification must be forwarded to the Mayo Clinic Cancer Research Protocol Specialist for approval before a patient may be registered to this study.

Consent forms will have to be modified for each institution as it relates to where information may be obtained on the conduct of the study or research subject. This information should be specific for each institution.

**Appendix I:
ECOG Performance Status Scale**

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

Appendix II
Mayo Risk Stratification

High Risk

FISH deletion 17p

FISH t(4:14)

FISH t(14:16)

Metaphase cytogenetic del 13

Hypodiploidy

PCLI >3%

**Appendix III
NYHA Classification**

Class I: NO Symptoms with ordinary activity

Class II: Symptoms with ordinary activity

Class III: Symptoms with minimal activity

Class IV: Symptoms at rest

Patient Initials _____

Study No. MC1082

Patient ID number _____

**Appendix IV:
MEDICATION DIARY**

Please complete this diary on a daily basis. Write in the amount of the dose of pomalidomide, bortezomib, and dexamethasone that you took in the appropriate "Day" box.

On the days that you do not take any study drug, please write in "0". Swallow pomalidomide capsules whole. Do not break, chew or open the capsules. Pomalidomide should be taken without food, at least 2 hours before or 2 hours after a meal. If you miss a dose of pomalidomide, it should be taken as soon as possible on the same day. If you miss taking your dose of pomalidomide for the entire day, it should not be made up, please write in "0", and remember to take your prescribed dose at the next regularly scheduled time.

If you experience any health/medical complaints or take any medication other than pomalidomide, bortezomib, or dexamethasone, please record this information.

Week of: _____

| Study Drug | Day 1 | Day 2 | Day 3 | Day 4 | Day 5 | Day 6 | Day 7 |
|---------------|-------|-------|-------|-------|-------|-------|-------|
| Dexamethasone | | | | | | | |
| Bortezomib | | | | | | | |
| Pomalidomide | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 8 | Day 9 | Day 10 | Day 11 | Day 12 | Day 13 | Day 14 |
|---------------|-------|-------|--------|--------|--------|--------|--------|
| Dexamethasone | | | | | | | |
| Bortezomib | | | | | | | |
| Pomalidomide | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 15 | Day 16 | Day 17 | Day 18 | Day 19 | Day 20 | Day 21 |
|---------------|--------|--------|--------|--------|--------|--------|--------|
| Dexamethasone | | | | | | | |
| Bortezomib | | | | | | | |
| Pomalidomide | | | | | | | |
| Aspirin* | | | | | | | |

Week of: _____

| Study Drug | Day 22 | Day 23 | Day 24 | Day 25 | Day 26 | Day 27 | Day 28 |
|---------------|--------|--------|--------|--------|--------|--------|--------|
| Dexamethasone | | | | | | | |
| Bortezomib | | | | | | | |
| Pomalidomide | | | | | | | |
| Aspirin* | | | | | | | |

*Warfarin or low molecular weight heparin can be substituted in place of Aspirin at MD discretion. Discuss with your doctor.

| |
|---|
| My next scheduled visit is: _____ If you have any questions, please call: _____ Patient Signature: _____ Date: _____ |
|---|

Appendix V: Myeloma Tumor Biology Kit
Specimen Checklist and Shipping Instructions

**** PLEASE AVOID DRAWING OR SENDING SPECIMENS ON FRIDAYS AND HOLIDAYS****

Kit Contents:

- 5 lb Styrofoam box and cardboard mailing sleeve
- Patient Information Form
- 7ml ACD (yellow top) collection tubes
- Plasma Cell Labeling Index (PCLI) Kit
- (2) zip lock specimen bags labeled for bone marrow and peripheral blood
- (1) ice pack. Place the ice pack in the freezer for at least 24 hours prior to specimen shipment. Allow the frozen ice pack to thaw at room temperature for 2-3 hours before preparing the specimen for shipment.

Packing and Shipping Instructions:

1. Collect the following specimens:
 - Peripheral blood - Draw 28 mL of peripheral blood in four ACD tubes
 - Bone marrow aspirate - Draw 8 mL of a 'redirect' bone marrow aspirate in two ACD tubes
 - Bone marrow aspirate - Draw 2-3 mL of a 'redirect' bone marrow aspirate and place in the Plasma Cell Labeling Index tube; process according to kit instructions
2. Label specimens with the protocol number MC1082, the patient's initials (last name, first name), date of collection, and type of sample (PB, BM).
3. Place the slightly thawed Kool-PAK in bottom of Styrofoam container.
4. Place absorbent toweling on top of Kool-PAK.
5. Place specimens in their individual plastic bags provided, wrap in paper toweling and place them in the Styrofoam container and close the lid. Do not place the specimen(s) directly on the ice pack.
6. Place the Styrofoam container and the completed Patient Information Form within the cardboard mailing sleeve.
7. Prepare the package for shipping, applying packing tape as needed. Ship specimens Fed Ex priority overnight delivery the same day collected.
8. Notify Federal Express for pick-up and/or leave package at the designated FedEx drop-off location. **Please call [REDACTED] or e-mail [REDACTED] to notify the Mayo Clinic Myeloma Reference Laboratory when specimen(s) are being shipped.** The samples in prepared kits should be shipped to the following:

[REDACTED]
Mayo Clinic Myeloma Reference Laboratory
[REDACTED]
200 First Street Southwest
Rochester, MN 55905

