Protocol Title: A Phase I/II Trial of Pomalidomide and Dexamethasone in Subjects with Previously-Treated AL Amyloidosis

STUDY DRUG	**Pomalidomide (CC-4047)**
CELGENE REFERENCE NUMBER:	**PO-AMYL-PI-0024**
VERSION:	***5/11/15***
IND:	**112758**
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PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Principal Investigator:

Signature of Investigator	Date
Printed Name of Investigator	Date

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

STUDY PERSONNEL

Supporter:	**Celgene Corporation** **86 Morris Ave,** **Summit, NJ 07901** **1-800-742-3107**
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1 Protocol Synopsis

PROTOCOL TITLE: A Phase I/II Trial of Pomalidomide and Dexamethasone for the treatment of subjects with previously treated AL Amyloidosis	
PROTOCOL NUMBER:	PO-AMYL-PI-0024
DATE PROTOCOL FINAL:	
STUDY DRUG:	Pomalidomide (CC-4047)
INDICATION:	AL Amyloidosis
STUDY PHASE:	I/II

BACKGROUND AND RATIONALE:

AL amyloidosis is a variant plasma cell disorder in which clonal bone marrow plasma cells produce immunoglobulin light chains that misfold into fibrils that are deposited in visceral organs, leading to organ dysfunction and failure. Untreated, the disease has a median survival of only about one year. Oral treatment with melphalan and dexamethasone produces improvement in survival, with hematologic remissions and improvement in organ function. Aggressive treatment with high dose intravenous melphalan with autologous stem cell transplantation (HDM/SCT) produces complete hematologic responses (CR) in about 40% of subjects and partial responses in a similar proportion; these are frequently accompanied by stabilization or improvement in organ function. Unfortunately only about half of referred subjects are eligible for HDM/SCT. Furthermore, it has been observed by us as well as other groups that achievement of a hematologic complete response after treatment with oral melphalan and dexamethasone as well as HDM/SCT is associated with improved survival, QOL, and clinical/organ response. Thus, we continue to seek more effective regimens for subjects ineligible for aggressive treatment with HDM/SCT or not achieving a complete hematologic response to HDM/SCT or other modalities.

The advent of novel agents in the treatment of multiple myeloma has changed the therapeutic landscape of plasma cell dyscrasias. Thalidomide has been studied as a single agent and in combination with dexamethasone for the treatment of AL amyloidosis. Unfortunately, thalidomide is poorly tolerated with 50-65% of subjects experiencing grade 3 and 4 toxicities, leading to drug withdrawal in approximately half of the subjects.

We are concluding a phase II study of lenalidomide alone and in combination with dexamethasone for subjects with AL amyloidosis. This study included untreated as well as relapsed subjects after HDM/SCT. Interim analysis of the first 34 subjects suggests achievement of a complete hematologic response CR in ~30% subjects and of partial

hematologic response in ~40% subjects, with most responses occurring with the lenalidomide/dexamethasone combination. A variety of toxicities have been observed, including leukopenia, rash, venous thrombosis, and intolerance to the dexamethasone. This report indicated better tolerability than thalidomide, however, 20% of subjects still stopped treatment with lenalidomide due to toxicities. We have extended our study to subjects on dialysis, using attenuated doses, with good preliminary results. A study using lenalidomide in combination with melphalan and dexamethasone is ongoing; this study is not suitable for subjects with significant prior exposure to alkylator agent.

Pomalidomide (CC4047), a 2nd generation immune-modulatory drug, has shown promising activity in phase-2 trial in combination with low-dose dexamethasone for relapsed or refractory multiple myeloma and AL amyloidosis. Responses were seen in 50% of subjects previously-failing thalidomide and/or lenalidomide in AL amyloidosis.

Given these promising results of pomalidomide in plasma cell dyscrasias, we propose a study of pomalidomide and low dose dexamethasone in persons with previously-treated AL amyloidosis.

STUDY OBJECTIVES:

Primary:

- Determine dose-limiting toxicity (DLT) and the maximum tolerated dose (MTD) of pomalidomide combined with dexamethasone in persons with previously-treated light-chain (AL)-amyloidosis.

Secondary:

- Determine the following at the MTD**:**
  - Hematological complete (CR) very good partial (VGPR) and partial (PR) rates
  - Response-duration
  - Organ response
  - Time–to-event
  - Survival

Exploratory:

- To investigate the relationship of changes in the levels of the biomarkers BNP and troponin I to frequency of specific adverse events and the occurrence of DLT.

STUDY DESIGN:

Phase-I/II dose-escalation study of pomalidomide and dexamethasone in persons with previously-treated AL-amyloidosis. During the Phase I portion the MTD will be determined based on DLTs in the first cycle. At the MTD an expanded cohort of 12 subjects will be evaluated to estimate efficacy.

The study includes a screening period, a treatment (dose escalation) period, and a follow-up period for survival. After giving written informed consent, subjects will be evaluated for eligibility for enrollment in the study and baseline evaluations will be performed. Subjects who satisfy all inclusion and exclusion criteria will begin study drug treatment with dose escalation. Standard dose escalation rules will be used.

Subjects will be monitored every cycle for safety, hematological status, and organ function during therapy or until the occurrence of progressive disease (PD).

Treatment Group Assignments and Subject Replacement

This is a dose-escalation study and dose escalation will proceed through 3 dose-levels according to standard rules in which dose levels are started sequentially after complete evaluation of the occurrence of DLT. Based on the dose escalation scheme, as many as 30 subjects could be enrolled in the study. Subjects who discontinue pomalidomide for reasons other than DLT before completing at least 2 treatment cycles are to be replaced.

Subpopulations

An additional 12 subjects will be enrolled in an expanded cohort for analysis of efficacy at each schedule studied.

Subjects in this cohort will be treated at the dose defined as the MTD for that schedule.

Schema:

Phase-I:

Pomalidomide 2 mg/day D1-21 – dose escalation to 4 mg/day by 1 mg units*
Dexamethasone 10-20 mg D1, 8, 15, 22

* Pomalidomide dosing for Phase I cohorts 1 and 2 given on days 1-28 of a 28-day cycle and changed to Days 1-21 of a 28 day cycle with Cohort 3.

This cycle will be repeated every 28 days.

Subjects will take aspirin 325 mg/day to prevent venous thrombosis whilst on-study.
A proton pump inhibitor will be used for GI prophylaxis.

Phase-II:

Pomalidomide [MTD] mg/day D1-21
Dexamethasone 10-20 mg D1, 8, 15, 22

This cycle will be repeated every 28 days.

Subjects will take aspirin 325 mg/day for prophylaxis against venous thrombosis while on study.
A proton pump inhibitor will be used for GI prophylaxis.

STUDY ENDPOINTS

Primary:

- Dose-limiting toxicity (DLT) and maximum tolerated dose (MTD) of pomalidomide in combination with dexamethasone

Secondary:

To be determined for MTD:

- Hematological complete (CR) very good partial (VGPR) and partial (PR) rates
- Response-duration
- Organ response
- Time–to-event
- Survival

Exploratory:

- relationship of changes in the levels of the biomarkers BNP and troponin I compared to frequency of specific adverse events and the occurrence of DLT

STUDY DURATION: Treatment may continue until subject experiences unacceptable toxicities or disease progression. Follow-up will take place every 3 months until disease progression, then annually for survival. Accrual ~24 months	**TOTAL SAMPLE SIZE:** 30 subjects
DOSING REGIMEN(S): Phase I portion: Pomalidomide 2 mg/day D1-21 – dose escalation to 4 mg/day in 1 mg increments in phase I* Dexamethasone 10-20 mg D1, 8, 15, 22 The above cycle will be repeated every 28 days. * Pomalidomide dosing for Phase I cohorts 1 and 2 given on days 1-28 of a 28-day cycle and changed to Days 1-21 of a 28 day cycle with Cohort 3. Phase II portion: Pomalidomide [MTD] mg/day D1-28 Dexamethasone 10-20 mg D1, 8, 15, 22 This cycle will be repeated every 28 days.	**STUDY DRUG SUPPLIES:** Celgene Corporation will supply pomalidomide as 1.0 mg and 2.0 mg

2 Schedule of Study Assessments *

Procedure	Pre-Study [1]	Cycle One*				Cycles 2, 3	Cycles* 5, 6, 8, 9, 11, 12	Cycles* 4, 7 and 10 ∞	***30 days of discontinuation From Study Drug**	**Follow-Up[8] Phase**
		Day **1**	Day **8** §	Day **15**	Day **22** §	Day 1	Day 1	Day 1		**Every 3 months**
Physical examination, vital signs, weight	X	X			X	X		X	X	X
SWOG performance status	X	X			X	X		X	X	X
CBC with differential	X	X	X[6]	X[6]	X[6]	X[6]	X[6]	X		X
Pregnancy test [2]	X[2, 3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	X[3]	
Education and counseling guidance [7]		X [7]				X[7]	X[7]	X[7]		
Sodium, chloride, CO2, Glucose	X	X	X	X	X	X	X			X
BUN, creatinine, potassium, Magnesium, phosphorous	X	X	X	X	X	X	X	X		X
ALT, AST, albumin, alk phos, bilirubin	X	X				X	X			X
calcium	X	X				X	X	X		X
Cholesterol, triglyceride, TSH	X							X		X
Total Protein, LDH, INR, PTT	X	X						X		X
BNP, uric acid	X	X	X	X	X	X	X	X		X
C-reactive protein, Beta 2-microglobulin	X							X		X
IgG, IgA, IgM	X							X		X
Serum immunofixation electrophoresis	X							X		X
Urine immunofixation electrophoresis	X							X		X
24 hour urine protein	X							X		X
Free light chain assay	X					X	X	X		X
Bone marrow biopsy and aspirate	X							X[5]		X[5]
EKG	X							X		X
ECHO	X							X[5]		X[5]
CXR	X							X[5]		X[5]
Urinalysis	X							X		X

Dispensement of Cycle 1 study drug		X								
Record adverse events			X	X	X	X	X	X	X	
Record concomitant therapies/procedures		X				X	X	X	X	
Dispense study drug for next cycle		X				X	X	X		
Perform drug accountability		X				X	X	X	X	

* Pre-cycle evaluations may be done up to 7 days prior to Day 1 to allow time for results and drug distribution. All other exams may be done +\- 4 days.

§ Phase I participants only

[1] All pre-study evaluations to be completed within 28 days of initiation of therapy except for bone marrow, which must have been repeated following any previous therapy ≥ 1 cycle. ECHO must be done within 60 days of first dose of pomalidomide.

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

[3] Pregnancy tests must occur 7 days and again within 24 hours prior to initiation of pomalidomide. 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 1: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods).

[4] If clinically indicated

[5] If needed to confirm response.

[6] CBC to be done weekly for the first cycle or until on a stable dose of pomalidomide, then day 1 of each cycle.

[7] All subjects must be registered into the POMALYST REMS™ program of Celgene Corporation, which provides education and counseling on the risks of fetal exposure, blood clots and reduced blood counts. Counseling must be provided by the according to the POMALYST REMS™ program prior to each new prescription. See Appendix 1: Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods and Appendix 1: Pomalidomide Education and Counseling Guidance Document.

[8] For responders, follow-up exams should take place every three months until disease progression. Following disease progression, follow-up evaluations should take place annually.

∞ Evaluations to be done every three cycles while on study drug.

3 Background and Rationale

3.1 Introduction

The dependence of tumor growth and metastasis on angiogenesis has been well characterized and has led to exploration of the role of anti-angiogenic drugs (both small molecules and monoclonal antibodies) in the treatment of solid tumors. Such agents have shown promise in both animal models and in preliminary studies of solid carcinomas in humans– including SCLC and non-SCLC [1,2]. Among these studies, three sets of investigators have performed preliminary evaluations of thalidomide (an anti-angiogenic drug in the IMiD class) in combination with conventional induction chemotherapy and/or as mono-therapeutic, post-induction maintenance therapy in subjects with newly diagnosed SCLC [3,4,5]. In each of these studies, some benefit with thalidomide use was detected – an increase in median survival (about 3 months overall) and/or 1- and 2-year survival relative to either parallel administration of or historic institutional control using equivalent conventional induction chemotherapy alone.

Recently, the relative roles of enhanced expression/production of the inflammatory cytokines, including both cyclooxygenase-2 (COX-2) and tumor necrosis factor-alpha (TNF-alpha), in the up-regulation of lung cancer growth, the stimulation of metastasis, the inhibition of apoptosis and in the occurrence of paraneoplastic syndromes have been identified and investigated [6,7,8]. As a result of *in vitro* and *in vivo* studies on lung and other carcinomas, inhibition of TNF-alpha and COX-2 have been identified, along with inhibition of angiogenesis, as therapeutic targets for limiting the growth, metastasis and neuro-endocrine complications of various solid carcinomas.

The emergence of immunomodulatory agents, such as thalidomide, lenalidomide and more recently CC-4047 (pomalidomide), as effective therapies has altered the therapeutic paradigm for multiple myeloma (MM). Following the approval and establishment of thalidomide-containing regimens, such as melphalan, prednisone and thalidomide (MPT) and Thal/Dex, as the standard first-line therapy for newly diagnosed MM (NDMM), lenalidomide in combination with standard high-dose dexamethasone (RD) was approved for the treatment of subjects with previously treated MM. However, even with the newly approved agents including thalidomide, lenalidomide and proteasome inhibitor such as bortezomide, MM remains an incurable disease and most subjects will eventually relapse and progress after multiple lines of different therapeutic regimens.

In addition, thalidomide, especially when combined with a corticosteroid, is effective in other diseases related to AL-amyloid including Waldentroms macroglobulinemia, Castleman disease and POEMS (polyneuritis, organomegaly, endocrinopathy, M-protein and osteosclerosis) syndrome. Substantial data indicate thalidomide combined with a corticosteroid with or without an alkylating drug is active in newly-diagnosed and progressive AL-amyloidosis with responses rates of 20-75 percent. Preliminary data indicate lenalidomide and corticosteroids are active in AL-amyloidosis including subjects failing melphalan (at all doses) and corticosteroids and also thalidomide and corticosteroids.

3.2 Pomalidomide

Pomalidomide, a thalidomide analogue, is an immune-modulatory agent that, among other anti-tumor properties, on an equimolar basis *in vitro*, displays equivalent anti-angiogenic activity, about 8-fold greater activity in stimulation of apoptosis, at least 10-fold greater activity in inhibition of cellular COX-2 production and over 4,000-fold greater activity in inhibition of cellular TNF-alpha production relative to thalidomide [9,10]. Pomalidomide has also been shown to stimulate antibody-dependent cytotoxic T-cell activity (ADCC) [9].

At tolerated doses (MTD = 2 mg QD and 5 mg QOD), pomalidomide has been shown to be active in subjects with relapsed or refractory multiple myeloma (MM) (study CC-4047-00-001) [9,11,12]. In 45 subjects who received doses of pomalidomide ranging, by cohort, up to 10 mg daily, the most commonly occurring dose-limiting toxicity (DLT) was reversible neutropenia. As with other IMiDs administered to subjects receiving concomitant systemic steroids, deep vein thrombosis (DVT) was seen (in 1subject each in this study and in its subsequent named subject supply rollover program) [9,13].

Recently, preliminary efficacy and safety data from an ongoing phase II study, led by Martha Lacy, et al, at Mayo Clinic, were published [14]. Sixty subjects with relapsed or refractory multiple myeloma were enrolled. Pomalidomide (CC-4047) was given orally at a dose of 2 mg daily on days 1-28 of a 28-day cycle and dexamethasone was given orally at a dose of 40 mg daily on days 1, 8, 15, 22 of each cycle. Subject also received aspirin 325 mg once daily for thromboprophylaxis. The study endpoints were the response rate in subjects taking pomalidomide plus dexamethasone including subjects with lenalidomide resistant refractory multiple myeloma, and safety of pomalidomide plus dexamethasone. Responses were recorded using the criteria of the International Myeloma Working Group. Thirty eight subjects achieved objective response (63%) including CR in 3 subjects (5%), VGPR in 17 subjects (28%), and PR in 18 subjects (30%). The CR + VGPR rate was 33%. Grade 3 or 4 hematologic toxicity occurred in 23 subjects (38%) and consisted of anemia in three subjects (5%), thrombocytopenia in two subjects (3%) and neutropenia in 21 (35%). Among those that developed grade 3/4 neutropenia, all first experienced the neutropenia in cycle 1-3; no new subjects experienced grade 3/4 neutropenia in cycle 4 or later. The most common non-hematological grade 3/4 toxicities were fatigue (17%) and pneumonia (8%). Other grade 3/4 non-hematological toxicities that occurred in less than 5% included diarrhea, constipation, hyperglycemia, and neuropathy. One subject (1.6%) had a thromboembolic event of deep vein thrombosis.

Similarly, pre-clinical data and the prior experience with thalidomide and lenalidomide in the treatment of subjects with myelofibrosis with myeloid metaplasia (MMM) provide the rationale for the use of pomalidomide in subjects with MMM. This is further supported by the results of a Celgene sponsored trial (MMM-001) which indicated that pomalidomide therapy at 0.5 mg or 2 mg/day +/- an abbreviated course of prednisone is well tolerated in subjects with myelofibrosis and active in the treatment of anemia [15].

Pomalidomide has been studied in AL amyloidosis at the Mayo clinic. Thirty-one subjects with previously-treated AL amyloidosis are enrolled and the data on 29 evaluable subjects were presented at ASH meeting in December 2010. Overall hematologic response rate is 38% with 8 subjects achieving PR and 3 VGPR, including subjects failing prior lenalidomide and/or thalidomide. One year overall and progression free survival are 77% and 56% respectively. Twenty one of 29 subjects experienced ≥ grade -3 AEs possibly attributed to treatment. The conclusions were that pomalidomide could provide a safe and effective therapy in previously treated subjects with AL amyloidosis, including those failing lenalidomide and/or thalidomide.

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

3.3 Rationale

AL amyloidosis is a variant plasma cell disorder in which clonal bone marrow plasma cells produce immunoglobulin light chains that misfold into fibrils that are deposited in visceral organs, leading to organ dysfunction and failure. Untreated, the disease has a median survival of only about one year. Oral treatment with melphalan and dexamethasone produces improvement in survival, with hematologic remissions and improvement in organ function. Aggressive treatment with high dose intravenous melphalan with autologous stem cell transplantation (HDM/SCT) produces complete hematologic responses (CR) in about 40% of subjects and partial responses in a similar proportion; these are frequently accompanied by stabilization or improvement in organ function. Unfortunately only about half of referred subjects are eligible for HDM/SCT. Furthermore, it has been observed by us as well as other groups that achievement of a hematologic complete response after treatment with oral melphalan and dexamethasone as well as HDM/SCT is associated with improved survival, QOL, and clinical/organ response. Thus, we continue to seek more effective regimens for subjects ineligible for aggressive treatment with HDM/SCT or not achieving a complete hematologic response to HDM/SCT or other modalities.

The advent of novel agents in the treatment of multiple myeloma has changed the therapeutic landscape of plasma cell dyscrasias. Thalidomide has been studied as a single agent and in combination with dexamethasone for the treatment of AL amyloidosis. Unfortunately, thalidomide is poorly tolerated with 50-65% of subjects experiencing grade 3 and 4 toxicities, leading to drug withdrawal in approximately half of the subjects.

We are concluding a phase II study of lenalidomide alone and in combination with dexamethasone for subjects with AL amyloidosis. This study included untreated as well as relapsed subjects after HDM/SCT. Interim analysis of the first 34 subjects suggests achievement of a complete hematologic response CR in ~30% subjects and of partial hematologic response in ~40% subjects, with most responses occurring with the lenalidomide/dexamethasone combination. A variety of toxicities have been observed, including leukopenia, rash, venous thrombosis, and intolerance to the dexamethasone. This report indicated better tolerability than thalidomide, however, 20% of subjects still stopped treatment with lenalidomide due to toxicities. We have extended our study to subjects on dialysis, using attenuated doses, with good preliminary results. A study using lenalidomide

in combination with melphalan and dexamethasone is ongoing; this study is not suitable for subjects with significant prior exposure to alkylator agent.

Pomalidomide (CC4047), a third generation immunomodulatory agent, has shown promising activity in phase II trial in combination with low-dose dexamethasone for relapsed or refractory multiple myeloma as well as AL amyloidosis. Furthermore, responses were seen in 50% of subjects who were refractory to prior IMiD in AL amyloidosis.

Given these promising results of pomalidomide in plasma cell dyscrasia, we propose a study of pomalidomide and low dose dexamethasone in the treatment of subjects with previously treated AL amyloidosis.

4 Study Objectives and Endpoints

4.1 Objectives

4.1.1 Primary objectives

- Determine dose-limiting toxicity (DLT) and the maximal tolerated dose (MTD) of pomalidomide combined with dexamethasone in subjects with previously- treated light-chain (AL)-amyloidosis

4.1.2 Secondary objectives

- Determine the following at the MTD:
    - Hematological complete (CR) very good partial (VGPR) and partial (PR) rates
    - duration of response
    - organ response
    - Time–to-event
    - Survival

4.1.3 Exploratory study objectives

- To investigate the relationship of changes in the levels of the biomarkers BNP and troponin I to frequency of specific adverse events and the occurrence of DLT

4.2 Endpoints

4.2.1 Primary Endpoint

- Maximum tolerated dose

4.2.2 Secondary Endpoints

- Hematological CR and PR
- Response-duration
- Organ response
- Time–to-event
- Survival

4.2.3 Exploratory study Endpoint

- The relationship of changes in the levels of the biomarkers BNP and troponin I to frequency of specific adverse events and the occurrence of DLT

5 Investigational Plan

5.1 Overall design

STUDY DESIGN:

Phase I/II dose-escalation study of pomalidomide and dexamethasone in persons with previously-treated AL-amyloidosis. During the Phase I portion the MTD will be determined based on DLT in the first cycle. At the MTD an expanded cohort of 12 subjects will be evaluated to estimate efficacy.

The study includes a screening period, a treatment (dose escalation) period, and a follow-up period for survival. After giving written informed consent, subjects will be evaluated for eligibility for enrollment in the study and baseline evaluations will be performed. Subjects who satisfy all inclusion and exclusion criteria will begin study drug treatment with dose escalation. Standard dose escalation rules will be used.

Subjects will be monitored every cycle for safety, hematological status, and organ function during therapy or until the occurrence of progressive disease (PD).

Treatment Group Assignments and Subject Replacement

This is a dose-escalation study and dose escalation will proceed through 3 dose-levels according to standard rules in which dose levels are started sequentially after complete evaluation of the occurrence of DLT. Based on the dose escalation scheme, as many as 30 subjects could be enrolled in the study. Subjects who discontinue pomalidomide for reasons other than DLT before completing at least 2 treatment cycles are to be replaced.

Subpopulations

An additional 12 subjects will be enrolled in an expanded cohort for analysis of efficacy at each schedule studied.

Subjects in this cohort will be treated at the dose defined as the MTD for that schedule.

Schema:

Phase I:

Pomalidomide 2 mg/day D1-21 – dose escalation to 4 mg/day by 1 mg units*
Dexamethasone 10-20 mg D1, 8, 15, 22

* Pomalidomide dosing for Phase I cohorts 1 and 2 given on days 1-28 of a 28-day cycle and changed to Days 1-21 of a 28 day cycle with Cohort 3.

This cycle will be repeated every 28 days.

Subjects will take aspirin 325 mg/day to prevent venous thrombosis whilst on-study.
A proton pump inhibitor will be used for GI prophylaxis.

Phase II:

Pomalidomide [MTD] mg/day D1-21
Dexamethasone 10-20 mg D1, 8, 15, 22

This cycle will be repeated every 28 days.

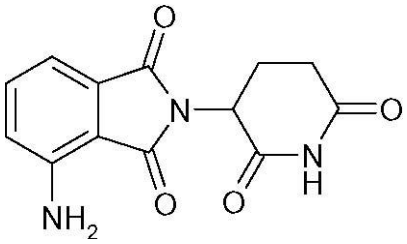
Subjects will take aspirin 325 mg/day for prophylaxis against venous thrombosis while on study. A proton pump inhibitor will be used for GI prophylaxis.

Subjects will have a toxicity evaluation, physical examination, and blood work performed according to schedule 2 while on therapy before each cycle. All subjects will return to Boston Medical Center prior to each of the first 3 cycles of therapy. The screening evaluation covers this requirement for cycle 1. A full disease evaluation will be performed at Boston Medical Center after every three cycles to determine response to treatment. Following cycle 3, subjects that are stable, may return every three months. Only one month of study drug may be supplied at a time for each cycle. A complete study calendar can be found in Section 2. Interim CBC may be performed locally. All results will be transmitted to the Clinical Trials Office for review.

5.1.1 Investigational Drug

5.1.1.1 Pomalidomide

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



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

5.1.1.2 CLINICAL PHARMACOLOGY

Mechanism of Action:

Pomalidomide is an IMiD analogue of thalidomide that, among other anti-tumor properties, on an equimolar basis in vitro, displays equivalent anti-angiogenic activity, about 8-fold greater activity in stimulation of apoptosis, at least 10-fold greater activity in inhibition of cellular COX-2 production and over 4,000-fold greater activity in inhibition of cellular TNF-alpha production relative to thalidomide [9,10]. Pomalidomide has also been shown to stimulate antibody-dependent cytotoxic T-cell activity (ADCC) [11].

5.1.1.3 Dose and tolerability:

Pomalidomide was safe at doses of up to 50 mg in a Phase I single dose study in normal, healthy male volunteers and up to 5 mg QOD or 2 mg QD in a Phase I multidose clinical study in subjects with relapsed or refractory multiple myeloma; DLTs seen in subjects receiving higher doses were predominantly hematopoetic (i.e., neutropenia), and lower grade, self-limited neutropenia was also seen in some of the 1 and 2 mg QD and 5 mg QOD recipients. In a multidose, Phase II clinical study of subjects with prostate cancer, 2 mg QD dosing was well tolerated and, unlike the multiple myeloma subjects who received 1 and 2 mg QD doses, only an overall shift to lower neutrophil counts was noted. No clinically relevant neutropenic AEs were observed, and no grade 3 or 4 neutropenic events occurred. It is, therefore, likely that subjects with solid tumors that do not extensively involve the bone marrow will have a higher pomalidomide MTD than subjects with hematologic malignancies.

5.1.1.4 Supplier(s)

Celgene Corporation will supply pomalidomide.

5.1.1.5 Dosage form

Pomalidomide will be supplied as 1.0 mg and 2.0 mg capsules for oral administration.

5.1.1.6 Packaging

Pomalidomide will be shipped to the pharmacy at the study site in individual bottles. Bottles will contain a sufficient number of capsules to last for one cycle of dosing. Study drug must be dispensed in the original packaging with the label clearly visible**. .**

5.1.1.7 Labeling

Pomalidomide investigational supplies are dispensed to the subjects in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: Caution: New drug - Limited by Federal law to investigational use. Pomalidomide should not be handled by FCBP unless wearing gloves. All bottles will contain the following warning label: "WARNING: POTENTIAL FOR HUMAN BIRTH DEFECTS."

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

5.1.1.8 Receipt of study drug

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

5.1.1.9 Storage

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.

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

5.1.1.10 Unused study drug supplies

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

5.1.1.11 Drug dispensing requirements

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

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. This is in accordance with the POMALYST REMS™ program.

5.1.1.12 Dexamethasone (Decadron®)

We will be using the oral formulation, which is available from any pharmacy. Each tablet, for oral administration, contains 0.25 mg, 0.5 mg, 0.75 mg, 1.5 mg, 4 mg or 6 mg of dexamethasone.

Dexamethasone (Decadron) is a synthetic adrenocortical steroid and is readily absorbed from the gastrointestinal tract. Chemically, dexamethasone is 9-fluoro-11b, 17, 21-trihydroxy-16a-methyl-pregna-1, 4-diene-3, 20-dione.

5.2 Screening and Eligibility

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form for entry into the study. All subjects will be screened for eligibility. Screening procedures are outlined in Section 2, Schedule of Study Assessments and unless otherwise specified, must take place within 28 days prior to initiation of therapy.

Approximately 30 subjects with previously treated AL amyloidosis will be screened for enrollment and must meet the eligibility criteria below.

Pregnancy Testing
Must follow pregnancy testing requirements as outlined in the POMALYST REMS™ program.

5.2.1 Inclusion Criteria

Subjects must meet the following inclusion/exclusion criteria to be eligible for the study.

Inclusion criteria

1. Understand and voluntarily sign an informed consent form.
2. Age ≥18 years at the time of signing the informed consent form.
3. Able to adhere to the study visit schedule and other protocol requirements.
4. Biopsy proven tissue amyloid deposits or positive fat aspirate
5. Proof of AL type (either a or b suffices)
6. Measurable plasma cell dyscrasia (a or b) AND c of the following required:
    a. Monoclonal protein in the serum or urine by immunofixation electrophoresis
    b. Plasmacytosis of bone marrow (< 30% plasma cells) with monoclonal staining for kappa or lambda light-chain isotype

c. dFLC ≥ 50 mg/L (dFLC=difference in involved and uninvolved serum free light-chain levels)

7. Must have received ≥1 prior treatment for AL amyloidosis, if it is intensive chemotherapy and an autotransplant it must be at least 3-6 months prior to enrollment on this study
8. Subjects must have recovered from the reversible side effects of any prior therapy; permanent and stable side effects/changes are acceptable. Prior treatment for AL amyloidosis with chemotherapy, thalidomide, lenalidomide or steroids is not an exclusion.
9. SWOG performance status of ≤ 2 at study entry (see Appendix 2).
10. Laboratory test results within these ranges:

    d. Neutrophil ≥ 1.5 x10e9/L;

    e. Platelets ≥100x10e9/L;

    f. Total bilirubin ≤ 1.5 mg/dL

    g. AST (SGOT) and ALT (SGPT) ≤ 2 x ULN

    h. Serum creatinine ≤ 3.0 mg/dL

11. Disease free of prior malignancies for ≥ 5 years with exception of currently treated basal cell, squamous cell carcinoma of the skin, or carcinoma "in-situ" of the cervix or breast.
12. Females of childbearing potential (FCBP)[†] must have a negative serum or urine pregnancy test with a sensitivity of at least 50 mIU/mL within 10–14 days prior to and again within 24 hours of starting pomalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking pomalidomide. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a vasectomy. All subjects must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix: 1 Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods, AND also Appendix 1: Education and Counseling Guidance Document.

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

13. Able to take aspirin (81 or 325 mg) daily as prophylactic anticoagulation (subjects intolerant to ASA may use warfarin or low molecular weight heparin or direct factor Xa inhibitors or newer anticoagulants, per preference of the patient and investigator).
14. 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.

5.2.2 Exclusion criteria

1. Subjects with secondary or familial amyloidosis

2. Subjects with multiple myeloma (≥30% plasma cells in a bone marrow biopsy specimen or lytic bone lesions)

3. Cytotoxic chemotherapy or radiation therapy ≤4 weeks of initiation of study therapy.
4. Subjects with symptomatic cardiac arrhythmias or O_2-dependent restrictive cardiomyopathy

5. Dialysis-dependent

6. Subjects with untreated or uncontrolled infections.

7. Any serious medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from signing the informed consent form.

8. Pregnant or breast feeding females. (Lactating females must agree not to breast feed while taking pomalidomide).

9. Any condition, including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study or confounds the ability to interpret data from the study.

10. Use of any other experimental drug or therapy within 28 days of initiation of study therapy.

11. Known intolerance to steroids.

12. Known hypersensitivity to thalidomide or lenalidomide.

13. The development of erythema nodosum if characterized by a desquamating rash while taking thalidomide or similar drugs.

14. Concurrent use of other anti-cancer agents or treatments.

15. Known HIV positivity is not an exclusion, unless CD4 counts <200/mcL and/or patient has multi-drug resistant HIV infections and/or other concurrent AIDS-defining conditions. HIV b-DNA < 75 copies/mL.

5.3 Visit schedule and assessments

Screening Assessments and all on study scheduled visits and assessments are outlined in Section 2 Table of Study Assessments.

At treatment discontinuation, subjects will undergo off study evaluations per the Schedule of Assessments, Section 2. In addition, a safety assessment will be done approximately 30 days post the last dose of study drug. Follow-Up contact with the subjects should occur at a minimum of every 3 months until progression, then annually.

5.4 Drug Administration

5.4.1 Treatment assignments

The Phase I portion of the study will be aimed at determining the safety profile and the MTD of Pomalidomide. A 3+3 dose escalation scheme will be implemented. Subjects will receive escalating doses of Pomalidomide orally on D1-21 in a 28-day cycle* in the absence of disease progression or unacceptable toxicity. DLTs will be assessed in Cycle 1 only. Dose escalation of Pomalidomide will continue until MTD has been identified or a maximum planned dose (4 mg/day D1-21) is determined to be safe.

* Pomalidomide dosing for Phase I cohorts 1 and 2 given on days 1-28 of a 28-day cycle and changed to Days 1-21 of a 28 day cycle with Cohort 3.

The Phase II portion of the study will begin after determination of the MTD and evaluation of the safety profile at the MTD in at least 6 subjects. The dose for administration will be informed by the results of the Phase I portion of the study. In the Phase II, eligible subjects will receive Pomalidomide at the MTD or the maximum planned dose from D1-21.

Once the MTD is defined during Phase I, patients currently receiving treatment may discuss the option with the treating investigator to continue on their current dose, or increase to the MTD, if they have not achieved a complete response.

5.4.2 Dosing regimen

The initial planned dose of pomalidomide for investigation is 2 mg/day, orally on days 1 - 21 (28 day cycle).* Dosing will be in the evening at approximately the same time each day,

either 2 hours before or 2 hours after food ingestion. Participants will be instructed to avoid smoking, as smoking can decrease the efficacy of pomalidomide. **Only enough pomalidomide for one cycle of therapy will be supplied to the subject each cycle.**

* Pomalidomide dosing for Phase I cohorts 1 and 2 given on days 1-28 of a 28-day cycle and changed to Days 1-21 of a 28 day cycle with Cohort 3.

The planned dose levels of Pomalidomide are presented below in **Table 15-1** table.

Table 15-1 Planned Study Drug Doses

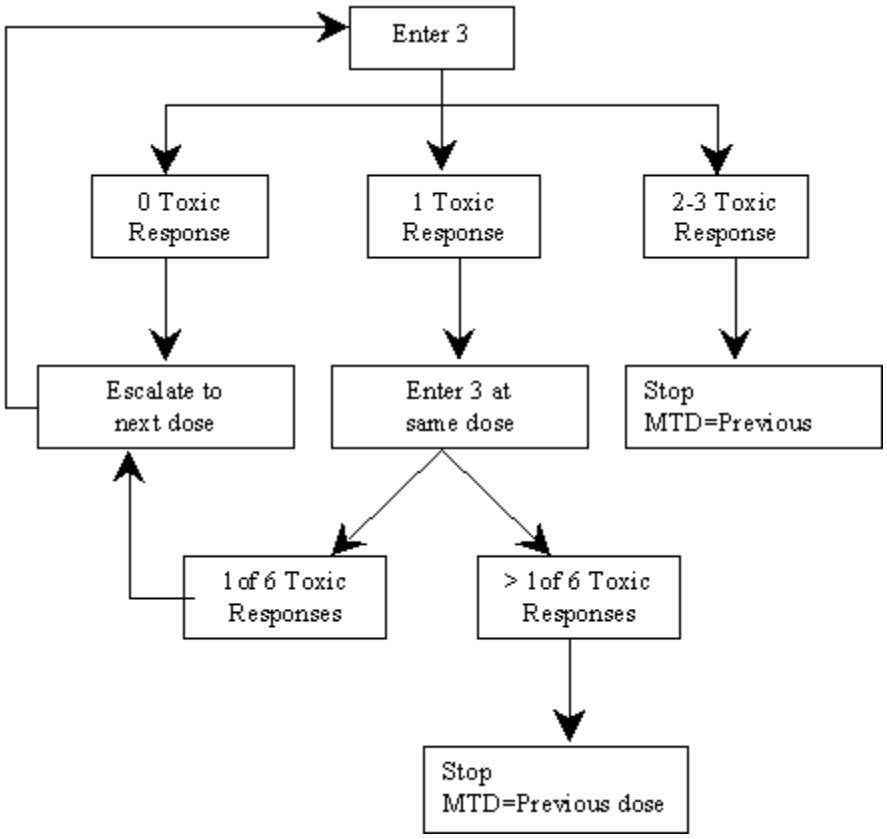
Dose Group	Pomalidomide Dose (mg/dose)	Enrollment (Number of Subjects)		
		Initial	Additional (if 1 of Initial 3 has DLT)	Expanded at MTD[a]
1	2	3[b]	3	12
2	3	3	3	
3	4	3	3	

a. Twelve additional subjects are to be enrolled in an expanded cohort for analysis of efficacy and treated at the MTD for each dosing schedule.

b. If the first 2 subjects enrolled experience DLT then this cohort is closed and further subjects will be evaluated at 1mg/day dose and the cohort expanded at that dose.

The dose escalation rules will follow the standard Fibonacci method.

Dose escalation algorithm



At least 3 subjects are to be enrolled in each dose group, beginning with the 2 mg/dose. Within each dose group, 3 subjects are to complete at least 2 treatment cycles. It is noted that if the first 2 subjects in the first cohort develop DLT, then the cohort at the 1 mg/dose dose will be defined as the MTD.

Dose escalation within a cohort is not allowed.

If after all 3 subjects complete 1 treatment cycle:

No subject experiences DLT, then enrollment at the next planned dose level may commence.

One subject experiences DLT, then 3 additional subjects are to be enrolled at the current dose level.

If 1 of 6 subjects experiences DLT, then enrollment at the next planned dose level may commence.

If 2 or more of 6 subjects experience DLT, then the previous dose is declared the MTD.

Two or more subjects experience DLT, then the previous dose is declared the MTD.

Dose escalation continues through the 3 dose levels in order to define the MTD based on the occurrence of DLT in the first cycle. Definitions of DLT and MTD are as follows:

DLT	Based on the first cycle; toxicity considered by the investigator to be related to Pomalidomide; Grade 4 thrombocytopenia or neutropenia; ≥ Grade 3 non-hematologic toxicity
MTD	The dose level at which DLT occurs in no more than 1 of 6 subjects (ie, the dose level below that at which DLT was established).

Subjects will take aspirin 325 mg/day to prevent venous thrombosis while on pomalidomide.

A proton pump inhibitor will be used for GI prophylaxis.

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, rather it should be taken as usual at the next scheduled time.

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

Subjects experiencing adverse events may need study treatment modifications (See section 5.5).

5.4.3 Special Handling Instructions

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

5.4.4 Record of administration

Accurate records will be kept of all study drug administration (including dispensing and dosing) will be made in the source documents.

5.5 Dose Continuation, Modification and *Interruption*

Subjects will be evaluated for AEs at each visit with the NCI CTCAE v4.0 (Appendix 3: NCI CTCAE v4.0) used as a guide for the grading of severity. Refer to Sections 6.5.1, 6.5.2

and 6.5.3 for instructions on beginning a new cycle of therapy and dose-modifications during a cycle of therapy.

5.5.1 Dose-Modification Guidelines

During the study, the focus of the evaluations is on the assessment of toxicity to document the occurrence of DLT. Although DLTs may occur at any point during treatment, only DLTs occurring during Cycle 1 of treatment must influence decisions regarding dose-escalation, expansion of a dose level, or evaluation of intermediate dose levels. However, DLTs occurring in later cycles may be taken into consideration for dose-escalation decisions, at the discretion of the investigators. Unless a DLT is documented to have occurred, no dose modification is allowed during Cycle 1.

In the event that a patient experiences DLT during Cycle 1, treatment should be held and the event will be counted toward the assessment of MTD for the given cohort. Patients experiencing DLTs in Cycle 1 may be restarted following recovery from toxicity at the discretion of the investigator according to the guidelines provided in Section 5.5.2. If a decision is made to restart study therapy following a DLT, the pomalidomide dose must be reduced 1 dose level. The patient will be evaluated weekly for possible toxicities that may have occurred after the previous dose(s). If multiple toxicities are noted, the dose adjustments and/or delays should be made according to the most severe toxicity guidelines.

5.5.2 Dose-Reduction Steps

Dose-reduction steps are below:

Table 1: Pomalidomide Dose Reduction Steps for Phase I and II

Starting Dose	**MTD (as determined in Phase I portion) mg daily on Days 1-28 every 28 days**
Dose Level – 1	Decrease by 1 mg daily from MTD on Days 1-21 every 28 days*
Dose Level – 2	Decrease by 2 mg daily from MTD on Days 1-21 every 28 days*
Dose Level – 3	Decrease by 3 mg daily from MTD on Days 1-21 every 28 days*

* Pomalidomide dosing for Phase I cohorts 1 and 2 given on days 1-28 of a 28-day cycle and changed to Days 1-21 of a 28 day cycle with Cohort 3.

Table 2: DEXAMETHASONE Dose Reduction Steps for Phase I and II

Starting Dose	**20 mg QD once weekly every 28 days**
Dose Level –1	10 mg QD once weekly every 28 days
Dose Level –2	4 mg QD once weekly every 28 days

Dosing will be adjusted as needed by study investigators as outlined in the tables in Section 5.5.3. If dexamethasone is permanently discontinued, the patient will continue with single agent Pomalidomide.

5.5.3 Instructions for initiation of a New Cycle

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

- The ANC is ≥ **1,000**/mm³;
- The platelet count is ≥ 50,000/mm³;
- Any pomalidomide-related rash, neuropathy or cardiac event that may have occurred has resolved to ≤ grade 1 severity;
- Any other pomalidomide-related adverse events that may have occurred have resolved to ≤ grade 2 severity. .

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of treatment will not be initiated until the toxicity has resolved as described above. If pomalidomide dosing was held during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. **If pomalidomide dosing was omitted due to an attributable toxicity (see table 3) for the remainder of the previous cycle or if the new cycle is delayed due to attributable toxicity newly encountered on the scheduled Day 1**, then the new cycle will be started with a one-level dose reduction of pomalidomide. If pomalidomide is permanently discontinued, the subject will be removed from study. If dexamethasone is permanently discontinued, the subject may continue on single-agent pomalidomide.

5.5.4 Instructions for dose modifications or interruptions during a cycle.

Table 3: Pomalidomide Dose Modifications for toxicities attributable to Pomalidomide		
NCI CTCAE Toxicity Grade	**Onset Day 2-14 of Cycle**	**Onset ≥ Day 15 of Cycle**
Grade 3 neutropenia associated with fever (temperature ≥ 38.5º C) or Grade 4 neutropenia ¥	• Hold (interrupt) pomalidomide dose. • Follow CBC weekly. • If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle. If neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the pomalidomide dose maintained ¥	• Omit pomalidomide for remainder of cycle • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level. If neutropenia is the only toxicity for which a dose reduction is required. G-CSF may be used and the pomalidomide dose maintained for the next cycle at the investigators discretion.¥
Thrombocytopenia ≥Grade 3 (platelet count < 50,000/mm³)	• Hold (interrupt) pomalidomide dose. • Follow CBC weekly • Hold prophylactic anticoagulation for thrombocytopenia (grade 3 or 4) or bleeding. Prophylactic anticoagulation can be resumed when platelet count ≥50k (≤2 grade) and no sign of bleeding. • If thrombocytopenia resolves to ≤ grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle.	• Omit pomalidomide for remainder of cycle • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level. • Hold prophylactic anticoagulation for thrombocytopenia (grade 3 or 4) or bleeding. Prophylactic anticoagulation can be resumed when platelet count ≥50k (≤2 grade) and no sign of bleeding.
Non-blistering rash **Grade 3** **Grade 4**	• If Grade 3, hold (interrupt) pomalidomide dose. Follow weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle. • Discontinue pomalidomide. Remove subject from study.	• Omit pomalidomide for remainder of cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level. • Discontinue pomalidomide. Remove subject from study.
Desquamating (blistering) rash- any Grade	• Discontinue pomalidomide. Remove subject from study.	• Discontinue pomalidomide. Remove subject from study.
Neuropathy **Grade 3** **Grade 4**	• Hold (interrupt) pomalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle. • Discontinue pomalidomide. Remove subject from study.	• Omit pomalidomide for the remainder of the cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level. • Discontinue pomalidomide. Remove subject from study.

Table 3: Pomalidomide Dose Modifications for toxicities attributable to Pomalidomide		
NCI CTCAE Toxicity Grade	**Onset Day 2-14 of Cycle**	**Onset ≥ Day 15 of Cycle**
Venous thrombosis/embolism ≥ Grade 3	• Hold (interrupt) pomalidomide and start anticoagulation; restart pomalidomide at investigator's discretion (maintain dose level).	• Omit pomalidomide for remainder of cycle. See Anticoagulation Consideration (Section 5.6.1.2)
other non-hematologic toxicity ≥ Grade 3	• Hold (interrupt) pomalidomide dose. Follow at least weekly. • If the toxicity resolves to ≤ grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle.	• Omit pomalidomide for remainder of cycle. • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level.
Hyperthyroidism or hypothyroidism ≥ Grade 2	• Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • If the toxicity resolves to ≤ grade 1 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle.	• Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. • See Instructions for Initiation of a New Cycle and reduce the dose of pomalidomide by 1 dose level.
Any attributable or non-attributable hospitalization or toxicity grade ≤ 2	• Pomalidomide may be held or continued at the discretion of the treating investigator. • Once resumed, maintain dose level.	• Pomalidomide may be held or continued at the discretion of the treating investigator. • **If held**, see Instructions for Initiation of a New Cycle and maintain dose level.

¥ As stated in the table, pomalidomide should be held for occurrence of grade 3 neutropenia with fever or grade 4 neutropenia attributable to Pomalidomide. Follow CBC weekly.

If neutropenia has resolved to ≤ grade 2 prior to Day 21, restart pomalidomide at next lower dose level and continue the cycle. If neutropenia is the only toxicity for which a dose reduction is required, G-CSF may be used and the pomalidomide dose can be maintained. In case of second occurrences of Grade 4 neutropenia or Grade 3 neutropenia with fever in the setting of GCSF, pomalidomide will be held and if neutropenia has resolved to ≤ grade 2 prior to Day 21, restart pomalidomide at next lower dose level with addition of G-CSF

Dose Modifications for Dexamethasone

Table 4: Non-hematological toxicity attributable to dexamethasone		
	Grade 1-2	**Grade 3-4**
Dyspepsia / GI	Start H2-blocker or Proton Pump Inhibitor if not already on one of these.	Hold dexamethasone and start H2-blocker or Proton Pump Inhibitor if not already on one of these. Once toxicity has decreased to Grade 0-2, resume Dex at one dosing level lower with continued H2B or PPI. If Grade 3-4 toxicity persists for more than 14

		days,endoscopy or other UGI evaluation is encouraged.
Edema	May add diuretic	Decrease dex by one dosing level, and add diuretics
Confusion/Mood Alteration	For Grade 2, decrease dexamethasone by one dosing level without holding dose	Hold dex until severity decreases to Grade 0-2, then resume dex at next lower dosing level.
Myopathy	For Grade 2-4, decrease dexamethasone by one dosing level without holding dose	
Hyperglycemia	For Grade 2, add oral hypoglycemic agents and/or insulin to control blood sugar. If hyperglycemia not able to be easily controlled, decrease dexamethasone by one dosing level without holding dose.	Add oral hypoglycemic agents and/or Insulin, and decrease dosing level by one.
Other	For Grade 2, decrease dexamethasone by one dosing level without holding dose	Hold dex until severity decreases to Grade 0-2, then resume dex at next lower

5.5.3 Treatment compliance

At all times, when dispensing study drug, research center personnel will review the instructions, printed on the packaging, with subjects. Subjects will be asked to maintain a diary to record the drug administration. Subjects will be asked to bring any unused study drug and empty study drug containers to the research center at their next visit. Research personnel will count and record the number of used and unused study drug capsules at each visit and reconcile with the subject diary.

5.6 Concomitant therapy

5.6.1 Recommended concomitant therapy

Subjects should receive full supportive care, including transfusions of blood and blood products, antibiotics, and antiemetics when appropriate.

5.6.1.2 Anti-coagulation Consideration

Pomalidomide increases the risk of thrombotic events in subjects who are at high risk or with a history a thrombosis, in particular when combined with other drugs known to cause thrombosis.

Subjects will take aspirin 325 mg/day to prevent venous thrombosis while on pomalidomide. Low molecular weight heparin may be utilized in subjects that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

5.6.2 Prohibited concomitant therapies

Concomitant use of sargramostim (GM-CSF), other anti-cancer therapies, including radiation, thalidomide, or other investigational agents is not permitted while subjects are

receiving study drug during the treatment phase of the study. G-CSF is not allowed during Phase I, Cycle 1 while evaluating for DLT. However, G-CSF is allowed for Phase II participants or following cycle 1 for Phase I participants.

5.7 Discontinuation of Study-Treatment

Treatment will continue until the occurrence of any of the following events.

- Disease progression
- Adverse event(s) that, in the judgment of the Investigator, may cause severe or permanent harm or which rule out continuation of the treatment regimen.
- Major violation of the study protocol.
- Withdrawal of consent
- Lost to follow up
- Death
- Suspected pregnancy

5.8 Follow-Up

Subjects who discontinue treatment for any reason, will be followed every 3 months until disease progression, then annually for survival, as clinically indicated. At treatment discontinuation, subjects will undergo a safety assessment approximately 30 days post the last dose of study drug. In addition off study evaluations per the Schedule of Assessments, Section 2 will be done.

6 Adverse events

6.1 Serious Adverse Event (SAE) Definition

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

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

- Suspected positive Pregnancy

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

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

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

6.2 Adverse Drug Reaction Reporting

Toxicity will be scored using CTCAE Version 4.0 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP homepage (HTTP://CTEP.INFO.NIH.GOV). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.0. All adverse clinical experiences, whether observed by the investigator or reported by the subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the subject's outcome. The investigator must evaluate each adverse experience for its relationship to the test drug and for its seriousness.

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

AEs and SAEs will be reported from the first dose of study drug through 30 days after administration of the last dose of study drug or the start of subsequent therapy for amyloidosis, whichever occurs first. All SAEs should continue to be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Pregnancies

Pregnancies occurring while the subject is on pomalidomide or within 4 weeks after the subject's last dose of pomalidomide are considered expedited reportable events. If the subject is on pomalidomide, it is to be discontinued immediately and the subject is to be instructed to return any unused portion of pomalidomide to the Investigator. The pregnancy must be reported to Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) within 24 hours of the Investigator's knowledge of the pregnancy by phone and facsimile using the SAE Form.

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

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

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

All neonatal deaths that occur within 30 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 30 days that the Investigator suspects is related to the *in utero* exposure to pomalidomide should also be reported.
In the case of a live "normal" birth, Celgene Corporation Worldwide Drug Safety Surveillance (WWDSS) should be advised as soon as the information is available.

6.2.1 Celgene Drug Safety Contact Information:

Celgene Corporation
Worldwide Drug Safety Surveillance (WWDSS)
86 Morris Avenue
Summit, N.J. 07901

Toll Free: **(800)-640-7854**
Phone: **(908) 673-9667**
Fax: **(908) 673-9115**
e-mail: drugsafety@celgene.com

6.3 Investigator Reporting Responsibilities

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

IND Annual Reports

If the FDA has granted an IND number, it is a requirement of 21 CFR 312.33, that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CRF 312.33 provides the data elements that are to be submitted in the report. The Annual Report should

be filed in the study's Regulatory Binder, and a copy provided to Celgene Corporation as a supporter of this study as follows.

Celgene Corporation
Attn: Medical Development
86 Morris Avenue
Summit, NJ 07901
Tel: (908) 673-9000

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

6.3.1 Expedited reporting by investigator to Celgene

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 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-AMYL-PI-0024) 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.
Report of Adverse Events to the Institutional Review Board
The principal Investigator is required to notify his/her Institutional Review Board (IRB) of a serious adverse event according to institutional policy.

6.3.2 Investigator Reporting to the FDA

Adverse drug reactions that are **Serious, Unlisted/unexpected, and at least possibly associated to the drug,** and that have not previously been reported in the Investigators brochure, or reference safety information document should be reported promptly to the Food and Drug Administration (FDA) in writing by each investigator/physician engaged in clinical research. A clear description of the suspected reaction should be provided along with an assessment as to whether the event is drug or disease related.

The investigator/physician shall notify the FDA by telephone or by fax of any unexpected fatal or life threatening experience associated with the use of the drug. As soon as possible, but no later than 7 calendar days after the sponsors initial receipt of the information. Each

phone call or fax shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND if applicable.

6.4 Adverse event updates/IND safety reports

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

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

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

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file (see Section 11.4 for records retention information).

7 Response-Criteria

Efficacy assessments are scheduled to occur every three months while on therapy.

7.1 Hematologic Response Criteria

CR Negative serum and urine immunofixation electrophoresis, normal serum free light chain ratio

VGPR dFLC <40 mg/L, dFLC = difference in involved and uninvolved serum free light-chain levels

PR dFLC reduction >50%, dFLC = difference in involved and uninvolved serum free light-chain levels

SD Meets neither criteria for CR, VGPR, PR or PD

PD From CR, an increase in serum M-protein to > 0.5 g/dL, an increase in the urine M-protein to > 200 mg/day, or an increase in the serum monoclonal free light chain by > 10 mg/dL (100 mg/L). From VGPR, PR or SD, an increase in the serum M-protein from the lowest level by > 50%, as long as the absolute magnitude of this increase is > 0.5 g/dL; or an increase in the urine M-protein from the lowest level by 50%, as long as the absolute magnitude of this increase is > 200 mg/day; or an increase in the serum or urine monoclonal free light chain by > 50% from the lowest level, as long as the absolute magnitude is > 10 mg/dL (100 mg/L).

Measurable disease to enter on the clinical trial

dFLC of 50 mg/L, dFLC = difference in involved and uninvolved serum free light levels

7.2 Organ Response-Criteria:

A subject will be said to have had an organ response in an involved organ if *any* of the following criteria are met, and none of the criteria in Section 10.4 are met.

Kidney: 50% reduction in 24-hour urine protein excretion in the absence of progressive renal insufficiency (defined as a 25% increase in serum creatinine, as long as that is ≥ to an absolute increase of 0.5 mg/dL). In the case of nephrotic syndrome: a decrease in proteinuria to < 1g/24h and an improvement in one of 2 extrarenal features – normalization of serum albumin or resolution of edema and/or discontinuation of diuretics in response to improvement in edema.

Heart: ≥ 2 mm reduction in the interventricular septal (IVS) thickness by echocardiogram, improvement of ejection fraction by ≥ 20% (echocardiogram must be performed at the same institution), or decrease in 2 NYHA classes without increase in diuretic need (see Appendix E for class definitions).

Liver: ≥ 50% decrease in normalization of an initially elevated alkaline phosphatase level or reduction in the size of the liver by at least 3 cm (determined by US or CT).

Neuropathy: While neurotoxicity is acceptable for determining organ involvement, it will not be adequate for assessing organ response; organ response will be indeterminable for subjects in which neurotoxicity is the only site of organ involvement.

Gastrointestinal Tract: While GI involvement is acceptable for determining organ involvement, it will not be adequate for assessing organ response: organ response will be indeterminable for subjects in which GI is the only site of organ involvement.

8 Protocol Amendments/Deviations

8.1 Protocol amendments

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

8.2 Protocol deviations

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

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

9 Data Management

9.1 Analyses and Reporting

Data will be analyzed and reported after study is completed or meaningful endpoints are reached. All subsequent data collected will be analyzed and reported in a follow-up clinical report.

9.2 Data Monitoring Committee

Toxicity and accrual monitoring will be performed on a routine basis by the study investigators as well as the multidisciplinary members of the Amyloid Treatment and Research Program at Boston University, which has over 40 years' experience in the treatment of AL amyloidosis. Subjects will undergo toxicity assessment, performance status assessment and laboratory tests before beginning each new cycle. Response assessment will be conducted every three cycles. The clinical status and laboratory reports of the study participants will be reviewed routinely by the co-investigators at the weekly meetings of the Stem Cell Transplant Program and reviewed by the Amyloid Program at weekly meetings. Dose modifications/interruptions or discontinuation will be implemented according to Section 5.5.

In addition, the BMC Cancer Center's Internal Data and Safety Monitoring Committee (DSMC) will review the protocol, and will determine review frequency based on level of risk. The protocol will be reviewed at least annually by the DSMC. Please see full DSMB Charter in Appendix 4.

9.3 Study monitoring and auditing

9.3.1 Investigator responsibilities

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

Investigators must enter study data onto CRFs or other data collection system. The Investigator will permit study-related monitoring visits and audits by Celgene or its representatives, IRB/EC review, and regulatory inspection(s) (e.g., FDA, EMEA, TPP), providing direct access to the facilities where the study took place, to source documents, to CRFs, and to all other study documents.

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

10 Statistical Plan

10.1 Overview

This is a Phase I/II study. Responses and toxicity will be compared informally to those reported lenalidomide and dexamethasone combined.

The Phase I portion of the study will be aimed at determining the safety profile and the MTD of pomalidomide. A 3+3 dose escalation scheme will be implemented. Subjects will receive escalating doses of pomalidomide orally on D1-21 in a 28-day cycle in the absence of disease progression or unacceptable toxicity.* Pomalidomide has been safely given to persons with relapsed/refractory myeloma subjects at 2 mg/day continuously in a small Phase II study. Therefore, the estimated safe starting dose of pomalidomide will be 2 mg/day continuously. DLTs will be assessed in Cycle 1 only. Dose escalation of pomalidomide will continue until MTD has been identified or a maximum planned dose (4 mg/day continuously) is determined to be safe.

* Pomalidomide dosing for Phase I cohorts 1 and 2 given on days 1-28 of a 28-day cycle and changed to Days 1-21 of a 28 day cycle with Cohort 3.

10.2 Datasets to be analyzed

Data for safety analysis will be obtained utilizing the NCI Common Terminology Criteria for Adverse Events v4.0.

DLT Based on the first cycle; toxicity considered by the investigator to be related to pomalidomide; Grade 4 thrombocytopenia or neutropenia; $\geq$ Grade 3 non-hematologic toxicity

MTD The dose level at which DLT occurs in no more than 1 of 6 subjects (ie, the dose level below that at which DLT was established).

Data to be included in the analysis for the hematologic response endpoint include evaluation of serum free light chain assay, monoclonal protein in serum or urine by immunofixation electrophoresis, percentage of plasma cells and presence of clonal dominance of kappa or lambda isotope on bone marrow biopsy.

Data for the secondary endpoint of organ response will include creatinine and 24 hour urine protein, liver span and liver function tests, mean left ventricular wall thickness, NYHA heart failure class, orthostatic vital signs and symptoms, GI symptoms and evaluation of peripheral neuropathy.

Data for the exploratory endpoint include BNP and troponin I levels.

10.3 Statistical Methodology

Determination of Sample Size
Based on the dose escalation scheme, as many as 30 subjects may be enrolled in this study.

The number of subjects enrolled will depend on the outcome of the actual dose escalation process. The dose-escalation phase consists of 3 cohorts, each with 2 to 6 subjects enrolled depending on when DLT occurs. Therefore, a minimum of 2 and a maximum of 18 subjects will be enrolled in this phase.

An additional 12 subjects will be enrolled in an expanded cohort for efficacy at each schedule. Therefore, an additional 12 subjects could potentially be enrolled.

It is expected that approximately 30 patients will be enrolled in the phase I/II portions of this study. The endpoints measured in the protocol will be overall response rate (ORR) determined by either CR, VGPR or PR and response of one or more organs. It is estimated by the principle investigator's approximate frequency of response in 18 patients (6 patients will be dosed at the MTD during the phase I portion of this trial plus the additional 12 patients at this MTD dose during the phase II portion). Using the adjusted Wald's confidence interval for the proportion and the corresponding point estimates for hypothetical data, it is expected that if 6 out of 18 have ORR then the estimated response rate would be 35.57% with a 90% confidence interval between 18.21% and 52.81% with similar estimates for organ response.

Randomization and Stratification
This is not a randomized study.

Populations for Analysis
The safety population will include all subjects who received at least 1 dose of study drug.

The additional 12 subjects enrolled in the expanded cohort for efficacy will comprise the efficacy population.

Procedures for Handling Missing, Unused, and Spurious Data
No imputation of values for missing data will be performed. Standard clinical monitoring and data management practices will be used to ensure the integrity of data.

General Methodology
In general, summary tabulations will be presented by dose group showing the number of observations, mean, standard deviation, median, minimum, and maximum for continuous variables, and the number and percent (calculated using non-missing values) per category for categorical data.

Safety Analysis

- Determination of MTD

The determination of MTD will be achieved by the results of a deterministic algorithm; thus, statistical hypothesis testing is not intended.

The evaluation of MTD will be based on data from subjects who receive pomalidomide and whose data are interpretable in the context of study drug-specific toxicity (ie, subjects should have had sufficient safety assessments performed to determine whether DLT occurred and should not have received alternate antineoplastic therapies through cycle 1). Subjects who are withdrawn from the study for reasons other than DLT before completing cycle 1 and are replaced consequently will not be included in the analysis of MTD. Subjects will be analyzed according to the dose actually received.

Pharmacokinetics/Pharmacodynamics
Not applicable.

Efficacy Analysis
The efficacy analysis will be based on confirmed hematological response and confirmed organ response. The analysis of response data at the MTD will be descriptive, consisting of 2-sided 90% confidence intervals.

Additional analyses of efficacy data at the MTD will consist of evaluations of time to hematologic response, duration of hematologic response, and time to worsening of hematologic and/or organ function. These analyses will also be descriptive in nature.

Analysis of the rates of responders for each of the other dose levels will also be presented, without calculation of confidence intervals.

Exploratory Analysis
An exploratory analysis will be conducted to investigate the relationship of changes in the levels of the biomarkers brain natriuretic peptide (BNP) and troponin I to the frequency of specific AEs and the occurrence of DLT. Additionally, the benefit, if any, of using these measures in addition to routine monitoring by ECG and echocardiogram will be explored. The frequency of conversion in immunofixation results from positive to negative will be explored and the disappearance of free light chain. Efficacy at additional doses may be explored for potential use in future Phase II clinical trials.

Interim Analysis
Interim analyses will be performed following each cohort during the Phase I portion of the study. No interim analysis is planned for the Phase II portion.

10.4 Safety evaluation

Data from all subjects who receive any study drug will be included in the safety analyses. Subjects who entered the study and did not take any of the study drug(s) and had this confirmed, will not be evaluated for safety.

The severity of the toxicities will be graded according to the NCI CTCAE v4.0 whenever possible.

10.5 Interim analyses

10.5.1 Interim analysis strategy

Accrual will be placed on hold during interim analyses during the Phase I portion while cohort toxicities are evaluated.

10.5.2 Efficacy

If none of the first four subjects treated at the MTD experience a response, consideration will be made to terminate the study. Accrual will not be placed on hold during efficacy evaluation.

10.5.3 Safety

Interim analysis will be performed following each cohort during the Phase I portion of the study.

10.6 Sample size and power considerations

11 Regulatory Considerations

11.1 Institutional Review Board/Ethics Committee approval

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

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

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

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

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

11.2 Informed consent

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

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

11.3 Subject confidentiality

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit Celgene's representatives and, when necessary, representatives of the FDA or other regulatory

authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

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

11.4 Study records requirements

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the study drug, that is copies of CRFs and source documents (original documents, data, and records [e.g., hospital records; clinical and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; SAE reports, pharmacy dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiches; photographic negatives, microfilm, or magnetic media; x-rays; subject files; and records kept at the pharmacy, at the laboratories, and at medico-technical departments involved in the clinical study; documents regarding subject treatment and study drug accountability; original signed informed consents, etc.]) be retained by the Investigator for as long as needed to comply with national and international regulations (generally 2 years after discontinuing clinical development or after the last marketing approval). The Investigator agrees to adhere to the document/records retention procedures by signing the protocol.

11.5 Premature discontinuation of study

11.5.1 Single center

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

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

11.5.2 Study as a whole

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

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

12 References

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13 Appendices

Appendix I

Pomalidomide Risks of Fetal Exposure, Pregnancy Testing Guidelines and Acceptable Birth Control Methods

Risks Associated with Pregnancy

Pomalidomide was found to be teratogenic in a developmental study in rabbits. Pomalidomide is an analogue of thalidomide. Thalidomide is a known human teratogen that causes severe life-threatening human birth defects. If Pomalidomide is taken during pregnancy, it may cause birth defects or death to an unborn baby.

Criteria for females of childbearing potential (FCBP)

This protocol defines a female of childbearing potential as a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

Counselling

For a female of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females of childbearing potential must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

- She understands the potential teratogenic risk to the unborn child
- She understands the need for effective contraception, without interruption, 28 days before starting study treatment, throughout the entire duration of study treatment, dose interruption and 28 days after the end of study treatment
- She should be capable of complying with effective contraceptive measures
- She is informed and understands the potential consequences of pregnancy and the need to notify her study doctor immediately if there is a risk of pregnancy
- She understands the need to commence the study treatment as soon as study drug is dispensed following a negative pregnancy test
- She understands the need and accepts to undergo pregnancy testing based on the frequency outlined in this protocol
- She acknowledges that she understands the hazards and necessary precautions associated with the use of pomalidomide

The investigator must ensure that females of childbearing potential:

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

For a female NOT of childbearing potential, pomalidomide is contraindicated unless all of the following are met (ie, all females NOT of childbearing potential must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

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

The effect of pomalidomide on spermatogenesis is not known and has not been studied. Therefore, male subjects taking pomalidomide must meet the following conditions (ie, all males must be counselled concerning the following risks and requirements prior to the start of pomalidomide study therapy):

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

Contraception

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

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

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

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

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

Pregnancy testing

Medically supervised pregnancy tests with a minimum sensitivity of 25 mIU/mL must be performed for females of childbearing potential, including females of childbearing potential who commit to complete abstinence, as outlined below.

Before starting study drug

Female Subjects:

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

Male Subjects:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 90 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Subjects:

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

Male Subjects:

- Counselling about the requirement for complete abstinence or condom use during sexual contact with a pregnant female or a female of childbearing potential and the potential risks of fetal exposure to pomalidomide must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in the partner of a male study subject during study participation, the investigator must be notified immediately.

Additional precautions

- Subjects 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.
- Subjects should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male subjects should not donate semen or sperm during therapy or for at least 90 days following discontinuation of study drug.
- Only enough study drug for one cycle of therapy may be dispensed with each cycle of therapy.

Pomalidomide Education and Counselling Guidance Document

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Subject Name (Print): _____ DOB: _____/_____/_____ (mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female: ☐

If female, check one:

☐ FCBP (Female of childbearing potential): sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time during the preceding 24 consecutive months)

☐ NOT FCBP

Male: ☐

Do Not Dispense study drug if:

- **The subject is pregnant.**
- **No pregnancy tests were conducted for a FCBP.**
- **The subject states she did not use TWO reliable methods of birth control (unless practicing complete abstinence of heterosexual contact) [at least 28 days prior to therapy, during therapy and during dose interruption].**

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counselled FCBP regarding the following:
   - Potential risk of fetal exposure to pomalidomide: If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. The teratogenic potential of pomalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking pomalidomide.
   - Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy , during dose interruption and 28 days after discontinuation of study drug].
   - That even if she has amenorrhea she must comply with advice on contraception

- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the subject agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 7 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the subject's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the subject missed a period or has unusual menstrual bleeding.
  - When the subject is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.
- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Pomalidomide Information Sheet to the subject.

FEMALE NOT OF CHILDBEARING POTENTIAL (NATURAL MENOPAUSE FOR AT LEAST 24 CONSECUTIVE MONTHS, A HYSTERECTOMY, OR BILATERAL OOPHORECTOMY):

1. I counselled the female NOT of childbearing potential regarding the following:
   - Potential risk of fetal exposure to pomalidomide (Refer to item #2 in FCBP)
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug and for 28 days after stopping study drug.
   - Do not break, chew, or open study drug capsules
   - Return unused study drug capsules to the study doctor.
2. Provide Pomalidomide Information Sheet to the subject.

MALE:

1. I counselled the Male subject regarding the following:
   - Potential study drug fetal exposure to pomalidomide (Refer to item #2 in FCBP).
   - To engage in complete abstinence or use a condom when engaging in sexual contact (including those who have had a vasectomy) with a pregnant female or a female of childbearing potential, while taking study drug, during dose interruptions and for 90 days after stopping study drug.
   - Males should notify their study doctor when their female partner becomes pregnant and female partners of males taking study drug should be advised to call their healthcare provider immediately if they get pregnant
   - NEVER share study drug with anyone else.
   - Do not donate blood while taking study drug and for 28 days after stopping study drug.
   - Do not donate semen or sperm while taking study drug and for 90 days after stopping study drug.
   - Do not break, chew, or open study drug capsules.
   - Return unused study drug capsules to the study doctor.
2. Provide Pomalidomide Information Sheet to the subject.

Investigator/Counsellor Name (Print): _____
(circle applicable)

Investigator/Counsellor Signature: _____ Date: _____/_____/_____
(circle applicable)

Maintain a copy of the Education and Counselling Guidance Document in the subject records.

Appendix Ib:

Pomalidomide Information Sheet

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

Please read this Pomalidomide Information Sheet before you start taking study drug and each time you get a new supply. This Pomalidomide Information Sheet does not take the place of an informed consent to participate in clinical research or talking to your study doctor or healthcare provider about your medical condition or your treatment.

What is the most important information I should know about pomalidomide?

1. **Pomalidomide may cause birth defects (deformed babies) or death of an unborn baby.** Pomalidomide is similar to the medicine thalidomide. It is known that thalidomide causes life-threatening birth defects. Pomalidomide has not been tested in pregnant women but may also cause birth defects. Pomalidomide was found to cause birth defects when tested in pregnant rabbits. **If you are a female who is able to become pregnant:**

   - **Do not take study drug if you are pregnant or plan to become pregnant**
   - **You must either not have any sexual relations with a man or use two reliable, separate forms of effective birth control at the same time:**
     - for 28 days before starting study drug
     - while taking study drug
     - during dose interruptions of study drug
     - for 28 days after stopping study drug
   - **You must have pregnancy testing done at the following times:**
     - within 10 – 14 days and again 24 hours prior to the first dose of study drug
     - weekly for the first 28 days
     - every 28 days after the first month or every 14 days if you have irregular menstrual periods
     - if you miss your period or have unusual menstrual bleeding
     - 28 days after the last dose of study drug (14 and 28 days after the last dose if menstrual periods are irregular)
   - **Stop taking study drug if you become pregnant during treatment**
     - If you suspect you are pregnant at any time during the study, you must stop study drug immediately and immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation.
   - **Do not breastfeed while taking study drug**

- The study doctor will be able to advise you where to get additional advice on contraception.

If you are a female not of childbearing potential:

In order to ensure that an unborn baby is not exposed to pomalidomide, your study doctor will confirm that you are not able to become pregnant.

If you are a male:

The effect of pomalidomide on sperm development is not known and has not been studied. The risk to the fetus in females of child bearing potential whose male partner is receiving pomalidomide is unknown at this time.

1. Male patients (including those who have had a vasectomy) must either **not have any sexual relations with a pregnant female or a female who can become pregnant,** or must use a condom during sexual contact with a pregnant female or a female that can become pregnant:
    - While you are taking study drug
    - During dose interruptions of study drug
    - For 28 days after you stop taking study drug
2. **Male patients should not donate sperm or semen** while taking study drug and for 28 days after stopping study drug.
3. **If you suspect that your partner is pregnant any time during the study, you must immediately inform your study doctor. The study doctor will report all cases of pregnancy to Celgene Corporation. Your partner should call their healthcare provider immediately if they get pregnant.**

2. **Restrictions in sharing study drug and donating blood:**
    1. **Do not share study drug with other people. It must be kept out of the reach of children and should never be given to any other person.**
    2. **Do not donate blood** while you take study drug and for 28 days after stopping study drug.
    3. **Do not break, chew, or open study drug capsules.**
    4. You will be supplied with no more than one cycle of study drug
    5. Return unused study drug capsules to your study doctor.

Additional information is provided in the informed consent form and you can ask your study doctor for more information.

Appendix II – SWOG 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 house work, 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 3 NCI CTCAE Version 4.0

TOXICITY WILL BE SCORED USING NCI CTC VERSION 4.0 FOR TOXICITY AND ADVERSE EVENT REPORTING. A COPY OF THE NCI CTCAE VERSION 4.0 CAN BE DOWNLOADED FROM THE CTEP HOMEPAGE: HTTP://EVS.NCI.NIH.GOV/FTP1/CTCAE/ABOUT.HTML. ALL APPROPRIATE TREATMENT AREAS HAVE ACCESS TO A COPY OF THE CTC VERSION

APPENDIX 4

Cancer Research Center Data Safety Monitoring Charter

Data Safety and Monitoring Program
BU/BMC Cancer Center
Boston, MA 02118
617-638-8265

Table of Contents:

Mission:
The Cancer Center Data Safety Monitoring Committee (DSMC) functions to ensure the safety of participants in investigator-initiated, interventional clinical trials conducted by BUMC Cancer Center members by monitoring clinical trial progress and the collection, validity and integrity of the data collected on clinical trials under its jurisdiction. The committee ensures compliance with FDA, NCI and IRB requirements. The policies and procedures of the Data and Safety Monitoring Committee follow NCI guidelines.

Background:
All cancer related interventional protocols from any department must be reviewed by the Cancer Center Scientific Review Committee (SRC). This includes trials that are recruiting individuals to cancer prevention or detection; treatment of disease or symptoms; and studies of cancer survivors, i.e. people who have had a previous diagnosis of cancer.

At the time it approves a new investigator-initiated, interventional protocol, the SRC assigns a category of risk that determines the level of monitoring required by the DSMC**.** The level of risk (low, moderate high) is based on a number of criteria, including the expected duration of the study based on the study design and a realistic estimate of the rate of enrollment; the nature of the study population (*e.g.,* prisoners, pregnant women); procedures to ensure the safety of subjects in accordance with the degree of risk; the complexity of methods needed to ensure the validity and integrity of the data; and planned data management systems including case report forms, records and the plan for data collection. Multiple-site studies must also have an operational plan that describes the procedures for reporting serious adverse events to the Cancer Clinical Trials Program (CCTP), IRB, FDA, and NIH, as appropriate, and plans for notifying participants of trial results and communicating relevant study information to participants' health providers (*e.g.,* cessation of drugs, changes in dosage, *etc*.)

Prior to implementation, all studies in need of internal monitoring must have a monitoring plan approved by the SRC, including frequency of reviews based on the level of risk and accrual target. Typically, high-risk studies are reviewed quarterly by the DSMC, moderate

risk studies are reviewed twice each year, and low risk studies are reviewed annually. However, each study is considered independently. Implementation of monitoring plans approved by the SRC is the responsibility of the DSMC. The DSMC Coordinator manages the logistics associated with DSMC sessions.

Two months prior to a scheduled DSMC review, the PRMS Administrator informs the principal investigator and primary study coordinator of the upcoming review. At this time, the research staff is requested to submit a completed DSMC Report Form (Appendix I) and associated documents to the PRMS Administrator (for each DSMC review).

In addition to being monitored by the DSMC, clinical studies also undergo annual auditing by the SRC (see below). Two months prior to an annual DSMC review, the PRMS Administrator informs the Principal Investigator and primary study coordinator to prepare protocol documents for audit and informs the PRMS Audit Committee that an audit is due. The Audit Committee audits 10% of charts for a given year, or a minimum of three charts, to assess fidelity to the approved protocol, study documentation, timeliness of adverse reporting, accuracy of data collection, and other variables. The audit report, which lists all major and lesser deviations from protocol, is submitted to the Principal Investigator and to the DSMC.

One month prior to the DSMC Meeting, the PRMS Administrator distributes pertinent documents to the Committee members, including.

- Completed DSMC Form (Appendix I)
- Electronic copy of the protocol
- Spreadsheet including: date of enrollment, patient initials, patient number, gender, age, race, status on study (*i.e*., active, follow-up, completed, expired)
- A copy of the Data Safety Monitoring Plan outlined in the INSPIR application.
- SAE reports, follow-up reports, and outcome reports
- Audit Committee Report (if annual review)

Responsibilities of the DSMC

- Familiarize themselves with the research protocol(s) and review proposed plans for data safety monitoring, and protocol data submitted by the research staff.
- Review annual audit report from the PRMS Audit Committee to evaluate the appropriateness of the conduct of the study.
- When applicable, review interim analyses of toxicity data prepared by the study statistician according to the data safety monitoring plan and upon special request. Recommendations regarding study modification, or termination of study accrual based on these analyses can be made at that time by the DSMC. Modifications may include dropping a treatment arm based on toxicity results, dose adjustment, increasing or decreasing sample size, *etc*.
- Provide the PI and the Cancer Center Scientific Review Committee with a written report following each DSMC meeting summarizing its review of the trial as related to the cumulative toxicities observed and any relevant recommendations related to continuing, amending or terminating accrual to the trial.

- The Committee has the authority to require amendments, to recommend suspension or termination of any research activities that fall under its jurisdiction, and to institute other requirements to improve participant safety

- Confidentiality Procedures: No communication of the deliberations or recommendations of the DSMC is allowed outside the DSMC, except as provided for in the DSM policy. It is also understood that industry studies are considered proprietary to the sponsor. Any outcome results are strictly confidential and must not be divulged to anyone who is not a member of the DSMC, except as specified in the policy.

DSMC Membership

The Chair of the DSMP is responsible for overseeing all aspects of data monitoring, ensuring the safety of participants in all clinical trials, particularly institutionally-sponsored, investigator-initiated trials, and verifying the validity and integrity of the data provided to the DSMC.

Omar Eton, MD; Hematology and Oncology (DSMC Chair)
Michael Stone, MD; Surgical Oncology
Gustavo Mercier, MD Radiology
Gregory Russo, MD, Radiation Oncology
David Baribeault, Pharm D, Investigational Pharmacy
Bhavesh Shah, Pharm D, Investigational Pharmacy
Gail Wilkes, RN Nurse Educator
Linda Frattura, BA Clinical Research Associate, Cancer Clinical Trials Program
Mary-Tara Roth, Clinical Research Resources Office
Natalie Erali, CCRP, PRMS Administrator
Douglas Faller, MD, PhD, Director, Cancer Research Center (ex officio)

Theodore Colton, ScD. Director of Cancer Biostatistics Resource (*ad hoc*)
Jack Clark, PhD (Health Policy and Management) (*ad hoc*)

The members of the multi-disciplinary DSMC include representatives from medical oncology, surgical oncology, radiology, radiation oncology, oncology nursing, pharmacy, health policy, the Boston University Clinical Research Resources Office, and the Cancer Clinical Trials Office and Pharmacy.

Meeting Schedule
DSMC meetings will be held at least every three months. Special meetings (in person, via telephone or electronic) may be convened when necessary, for urgent concerns regarding patient safety or data integrity. The PI or the Scientific Review Committee may request unplanned monitoring of a given study. Data will be collected and analyzed approximately four weeks before the DSMC meeting. A copy of all the analyses will be mailed to the DSMC members before the meeting. The timing for ending material will allow two (2) weekends for the DSMC members to review it.

Data and safety monitoring and study reviews take place until all subjects have completed any protocol-related activities and are beyond the time during which study-related adverse events may occur.

DSMC Procedures

The DSMC may vote to take one of the following actions for each protocol reviewed:

Full Approval: enrollment may continue; no outstanding questions regarding toxicity or accrual.

Conditional Approval: enrollment may continue conditional upon satisfactory response by the principal investigator to the DSMC concerns regarding toxicities and/or accrual and/or new information relevant to the trial.

Suspension: enrollment immediately suspended pending principal investigator response to the DSMC concerns regarding toxicity and/or accrual patterns.

Closure: study closed due to unacceptable toxicity and/or accrual patterns. The presence of three or more of the DSMC voting members constitutes a quorum.

All DSMC decisions are conveyed in writing to the study principal investigator and the Scientific Review Committee.

The CCTP Protocol Review and Monitoring System (PRMS) Administrator serves as recording secretary to the DSMC and is responsible for coordinating all meetings and communications.

Study principal investigators may appeal DSMC decisions in writing to the chairman of the DSMC.

Temporary or permanent suspension of any BMC investigator-initiated clinical trial by the DSMC will be reported immediately to the BUMC IRB and any relevant study collaborators (e.g. pharmaceutical companies). The monitoring plan is amended as to reflect any new monitoring requirements.

If the suspension is temporary, the BUMC IRB and any relevant study collaborators will also be notified in a timely manner regarding the resolution of the issues that caused the suspension, and the date that the suspension was lifted.

This committee was established in January, 2010 and its procedures will be continually reviewed and refined until a more permanent charter can be adopted.

BUMC Cancer Center Protocol Review and Monitoring System (PRMS)
DATA AND SAFETY MONITORING COMMITTEE REPORT FORM

Please submit this form two weeks prior to the scheduled DSMC Meeting and attach the following documents:
- Electronic copy of the protocol
- Spreadsheet including: date of enrollment, pt initials, pt number, gender, age, race, status on study
- A copy of the Data Safety Monitoring Plan outlined in the INSPIR application.
- SAE reports, follow-up reports, and outcome reports

BUMC PROTOCOL #: **Activation DATE:**

STUDY STATUS: Open to Accrual **DATE OF LAST REPORT:**

PROTOCOL TITLE			
10 Principal Investigator; Primary Research Nurse/Associate			
11 PROTOCOL ACTIVITY			
Planned Accrual Duration:			
Date First Patient Enrolled at BMC:		Local Accrual to Date / Goal: National Accrual to Date / Goal:	/ /
# Consented Since Last Report:		Accrual Since Last Report:	
# Eligible Since Last Report:		# Ineligible Since Last Report:	
12 Study Status: (include # of Patients currently active, in follow-up, completed or expired.)			
13			
14			
15 PROTOCOL-SPECIFIC INTERIM ANALYSIS (if applicable)			
16			
17			
18			
19 SAE/UPSER REPORTING SINCE LAST REPORT: List event, causality attribution, expected/not expected, patient study ID number, date of occurrence (include cycle #, Day #), and date IRB notified. Attach SAE reports, follow-up reports, and outcome reports.			
1]			
2]			
3]			
PATIENTS COMPLETED/OFF PROTOCOL SINCE LAST REPORT w **Provide reason [progression, death (include cause), toxicity (specify), completed therapy, etc]. Provide detailed supplemental information for patients off study treatment due to toxicity or death.**			
PROTOCOL DEVIATIONS/EXCEPTIONS SINCE LAST REPORT w **Include both *purposeful and accidental* variances in the approved procedures outlined for a study in its IRB approved protocol; provide date reported to Regulatory or IRB. Attach any protocol deviation forms.**			
OTHER COMMENTS			
Investigator Signature & Date:		**Data Manager Signature & Date:**	

Figure 1 shows the procedures involved in data and safety monitoring.