TITLE: Phase I/II Trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma

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TITLE: Phase I/II Trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma

CITY OF HOPE PROTOCOL NUMBER/VERSION: **IRB # 12267** **VERSION: 07**

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COH Amendment 03 personnel update Dated 12/16/2015	Version: 03
COH Amendment 04 Protocol Dated 12/17/2015	Version: 04
COH Amendment 05 Protocol Dated 08/01/2016	Version: 05
COH Amendment 06 at Continuation Title Page Dated 11/09/2016	Version: 06
COH Amendment 07 Protocol Dated 03/07/2017	Version: 07

DISEASE SITE: **Multiple Myeloma**
STAGE (*If applicable*):
MODALITY(IES):
TYPE (*e.g., Pilot, Phase I, etc.*)**:** Phase I/II

PRINCIPAL INVESTIGATOR: Amrita Krishnan, M.D.
Designs, responsible for study conduct and data analysis

COLLABORATING INVESTIGATOR(S): Joycelynne M. Palmer, Ph.D (Biostatistics)

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CLINICAL STUDY PROTOCOL

MMRC-051

COH IRB # 12267

Title:	Phase I/II trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma
Phase:	Phase I/II
Protocol Version:	Version 6.0 03/03/2017
Study Sponsor:	City of Hope National Medical Center Investigator Initiated Trial
Principal Investigator:	Amrita Krishnan, MD Lead Principal Investigator City of Hope
Collaborating Investigators:	Prashant Kapoor, MD Mayo Clinic – Rochester Joseph Mikhael, MD Mayo Clinic - Arizona Ajay Nooka, MD, MPH Winship Cancer Institute of Emory University School of Medicine Jesus G. Berdeja, MD Sarah Cannon Research Institute Center
Study Statistician	Joycelynne M. Palmer, PhD City of Hope

This is an investigator-initiated study. The lead principal investigator, Amrita Krishnan, MD (who may also be referred to as the sponsor-investigator), is conducting the study and City of Hope National Medical Center, and is acting as the study sponsor. Therefore, the legal/ethical obligations of the lead principal investigator include both those of a sponsor and those of an investigator.

Phase I/II trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma

Protocol Acceptance Form – Amendment6.0 Protocol Dated 03-Mar-2017

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practices (GCPs) and the Declaration of Helsinki, and complying with the obligations and requirements of clinical Investigators and all other requirements listed in 21 CRF part 312.

_____	_____
Principal Investigator Signature	Date
_____	_____
Print Principal Investigator Name and Title	Date

PROTOCOL SUMMARY

Protocol Title:
Phase I/II trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma
Brief Protocol Title for the Lay Public (if applicable):
Phase I/II trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma
Study Phase:
Phase I/II
Participating Sites:
▪ City of Hope ▪ Mayo Clinic: Rochester and Arizona ▪ Winship Cancer Institute of Emory University School of Medicine ▪ Sarah Cannon Research Institute Center
Rationale for this Study:
Novel drugs are needed for the treatment of relapsed or relapsed refractory multiple myeloma. The combination of proteasome inhibitor (PI) and immunomodulating (IMiD) agents has produced significant responses. Many patients are exposed to these classes of drugs earlier in the course of therapy, for patients who relapse after agents such as the PI bortezomib and the IMiD lenalidomide, newer agents are now available or in development including pomalidomide and MLN9708. Pomalidomide is an IMiD that is active even in patients who are refractory to other IMiDS such as lenalidomide. MLN9708 is a PI that has shown activity in patients refractory to bortezomib. MLN9708 has shown activity in Phase I/II trials and pomalidomide and dexamethasone have shown activity in Phase I/II and III trials. Hence combining the two agents and including dexamethasone for synergy could potentially induce responses in this refractory patient population.
Objectives:
Phase I: **Primary:** 1) To determine the recommended phase II dose (RP2D) of MLN9708 when given in combination with pomalidomide and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma. **Secondary:** 2) To evaluate the safety of MLN9708 at each dose level when given as part of a three drug combination by assessing the following: - type, frequency, severity, attribution, time course and duration of adverse events - clinical laboratory tests at various points in the study

Phase II:

Primary:

1. To estimate the response rate and to evaluate the antitumor activity of the three drug combination: MLN9708 (at the RP2D), pomalidomide and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma.

Secondary:

At the RP2D, for the three drug combination:

2. To characterize and evaluate toxicities, including type, frequency, severity, attribution, time course and duration.

3. To obtain estimates of response duration, depth of response, clinical benefit response, and survival (overall and progression-free).

Study Design:

This study will be conducted as a multicenter phase I/II trial.

The phase I portion will follow a standard 3+3 dose escalation design, to evaluate toxicities associated with MLN9708 when given in combination with pomalidomide and dexamethasone. Two doses of MLN9708, 3mg and 4 mg, will be tested in up to three possible dose levels:

Schedule: Each cycle is 28 days			
Dose Level	**Pomalidomide**	**MLN9708**	**Dexamethasone***
-1	3mg daily on days 1-21	3 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22
1	4 mg daily on days 1 - 21	3 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22
2	4 mg daily on days 1 - 21	4 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22

*: Patients >75 years, at the time of trial registration, will receive a dexamethasone starting dose of 20mg on the same set schedule.

The RP2D identified in the phase I portion of the study will be brought forward for activity evaluation.

The phase II portion of this study will implement a Gehan two-stage design to estimate the response rate and to evaluate the activity of MLN9708 when given in combination with pomalidomide and dexamethasone (Gehan, 1961).

Endpoints:

Phase I:

The primary endpoint is toxicity. Toxicity will be graded according to the NCI-Common

Terminology Criteria for Adverse Events version 4.03. Dose limiting toxicity (DLT) is defined in section 7.3 of the protocol.

Phase II:

The primary endpoint is response rate (sCR/CR/VGPR and PR) and is based on the International Myeloma Working Group (IMWG) criteria.

Sample Size:

Phase I:

The phase I study will follow a 3+3 design, to evaluate toxicities associated with MLN9708 when given in combination with pomalidomide and dexamethasone. Two doses of MLN9708 (3 mg and 4 mg) will be tested in up to three possible dose levels. In the phase I portion of this study, the total sample size will depend on the number of dose levels evaluated to determine the RP2D. While the phase I study is expected to enroll and treat 9 patients (3 patients at dose level 1, and another 6 at dose level 2-assuming the 4mg dose is well tolerated), a maximum of 18 patients could be treated (6 patients treated at each dose level.

Phase II:

The phase II portion of the study is expected to enroll a minimum of 9 and a maximum of 25 patients. The six patients treated at the RP2D in the phase I portion of the study will count toward the 25 patients required; given this, we expect to enroll only 19 new patients during the phase II trial portion. The sample size is based on the desire to achieve a (promising) target response rate of >30%.

Estimated Duration of the Study

Accrual, for both phases, is expected to be completed in 26 months; with approximately 2 patients enrolled each month. Patients will be treated in 28-day treatment cycles until disease relapse, progression or unacceptable toxicity, withdrawal of consent, or protocol specified parameters to stop treatment. Patients who discontinue study treatment for reasons other than disease relapse/progression will continue to have disease assessments per International Myeloma Working Group (IMWG) criteria until relapse or progression, initiation of new anticancer treatment, or death whichever occurs first. Patients will be followed to collect further anticancer treatment and survival information until death, loss to follow-up, withdrawal of consent, study termination or up to 24 months post treatment.

Summary of Patient Eligibility Criteria:

Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.
2. Voluntary written informed consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
3. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days 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 through 90 days after the last dose of study drug. 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 from the time of signing the informed consent form through 90 days after the last dose of study drug.

4. All patients must be registered in and must comply with all requirements of the POMALYST REMS™ program.
5. Patients must have a diagnosis of relapsed or relapsed and refractory Multiple Myeloma with a minimum of one prior regimen and a maximum of 5 prior regimens.
6. Patients must have had therapy with a proteasome inhibitor and lenalidomide and be refractory to lenalidomide according to the IMWG definition of refractory disease (progressive disease on or within 60 days of stopping lenalidomide).
7. Patients must have measurable disease defined as one of the following:
   - Serum M protein $\geq$ 0.5 g/dL
   - Urine M protein $\geq$ 200 mg/24 hours
   - Serum free light chain $\geq$ 10 mg/dL provided the FLC ratio is abnormal.
8. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2.
9. Patients must meet the following clinical laboratory criteria:
   - Absolute neutrophil count (ANC) $\geq$ 1,000/mm^3
   - Platelet count $\geq$ 75,000/μL for patients in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count $\geq$ 50,000/μL for patients in whom $\geq$ 50% of bone marrow nucleated cells are plasma cells. Platelet transfusions are not allowed within 3 days of last platelet assessment to confirm eligibility.
   - Total bilirubin $\leq$ 1.5 × the institutional upper limit of normal range (IULN).
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq$ 3 × IULN (institutional upper limit of normal range)
   - Calculated creatinine clearance $\geq$ 45 mL/min (Appendix15.2)

Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are pregnant or breastfeeding or have a positive serum pregnancy test during the screening period.
2. Failure to have fully recovered (i.e., $\leq$ Grade 1 toxicity) from the reversible effects of prior chemotherapy.
3. Prior treatment with a multidrug regimen containing pomalidomide except the 2 drug combination of pomalidomide and dexamethasone.
4. Major surgery within 14 days before enrollment.
5. Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the MLN9708.
6. Central nervous system involvement.
7. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

8. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.
9. Systemic treatment, within 14 days before the first dose of MLN9708, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's Wort.
10. Unable or unwilling to undergo antithrombotic prophylaxis.
11. Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.
12. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
13. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
14. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of MLN9708 or pomalidomide including difficulty swallowing.
15. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy with evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
16. Patient has > Grade 2 peripheral neuropathy on clinical examination during the screening period.
17. Participation in other clinical trials, including those with other investigational agents not included in this trial, within 21days of the start of this trial and throughout the duration of this trial (for all other standard therapies, no treatment within 14 days of the start of this trial).
18. Patients who are pomalidomide refractory, defined as patients who progress on or within 60 days of pomalidomide when given as a single agent or with dexamethasone.

Investigational Product Dosage and Administration:

MLN9708: 3mg or 4 mg oral; Pomalidomide: 3mg or 4mg oral; Dexamethasone: 40 mg oral (Note: Patients >75 years, at the time of trial registration, will receive a Dexamethasone dose of 20 mg on the same set schedule.)

Clinical Observations and Tests to be Performed:

Standard myeloma restaging studies (SPEP, UPEP, Bone Marrow Biopsy, Serum and Urine Immunofixation, Serum free lites, when applicable). Refer to the Table of Assessments for complete details.

Statistical Considerations:

Phase I:
The primary objective of the phase I study is to determine the recommended phase II dose (RP2D) of MLN9708 when given in combination with pomalidomide and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma.

The phase I study will follow a 3+3 design for enrollment with dose escalation, or expansion of a cohort on the basis of the occurrence of dose limiting toxicities (DLTs) during cycle 1. Two doses of MLN9708 will be tested in up to three possible dose levels (dose level -1 and dose level 1: 3mg / dose level 2: 4 mg, administered on days 1, 8 and 15 of a 28 day cycle). The highest dose level that produces ≤1/6 DLTs in cycle 1 will be the maximum tolerated dose (MTD). The RP2D of MLN9708 and pomalidomide will generally be the MTD, but it may be less than the MTD based on a review of available data/cumulative toxicities from phase I.

Analysis: Observed toxicities will be summarized in terms of type (organ affected or laboratory determination), severity, time of onset, duration, probable association with the study regimen and reversibility or outcome. Baseline information (e.g. the extent of prior therapy) and demographic information will be presented as well to describe the patients treated in this study.

Phase II:
The primary objective is to estimate the response rate and to evaluate the antitumor activity of the three drug combination: MLN9708 (at the RP2D), pomalidomide, and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma. The primary endpoint is a confirmed tumor response of sCR/CR/VGPR or PR and is based on IMWG Criteria. A single cycle of treatment will be given in a 28 day cycle. Each patient's disease status will be evaluated at baseline. Response will be assessed at the end of each cycle/just prior to the start of each cycle and is based on the IMWG criteria.

Statistics/Sample Size and Accrual: The phase II portion of this study will implement a Gehan two-stage design to estimate the response rate and to evaluate the activity of MLN9708 when given in combination with pomalidomide and dexamethasone (Gehan 1961). The phase II portion of the study is expected to enroll a minimum of 9 and a maximum of 25 patients. The six patients treated at the RP2D in the phase I portion of the study will count toward the 25 patients required; given this, we expect to enroll only 19 new patients on the phase II trial. The sample size is based on the desire to estimate the response rate with at most 10% standard error, and early stopping if the combination is unexpectedly ineffective.

At stage 1, 9 patients will be entered on the study. If 0 responses are seen in the first 9 patients treated, the study will be terminated and the true regimen response will be declared ≤30%. If at least 1 patient responds, the trial will continue to the second stage. Because patients treated during the phase I portion of the trial at the dose selected for the phase II trial will be counted (n=6), only 3 additional patients will be enrolled at stage 1. Under this design if the study regimen is >30% effective, there would be ~95.6% chance of at least one success.

At stage 2, 16 additional patients will be entered. This accrual provides for estimation of the response rate with no more than 10% standard error.

Analysis: The overall response rate will be calculated as the percent of evaluable patients that have confirmed sCR/CR/VGPR or PR; the clinical benefit response rate will be calculated as the percent of evaluable patients that have confirmed sCR/CR/VGPR/PR/ MR or SD; exact

95% confidence intervals will be calculated for these estimates. Response rates will also be evaluated based on number and type of prior therapy(ies). Time to response, duration of response, and survival will be estimated using the product-limit method of Kaplan and Meier.
Sponsor
Investigator Initiated Trial - City of Hope
Case Report Forms
This trial will utilize the Medidata RAVE® Electronic Data Capture system.

SCHEDULE OF EVENTS

PROCEDURES	**Screen**	**Cycle 1 Each cycle is 28 days**				**Cycle 2+* Each cycle is 28 days**				**End of Treatment**	**Post Study Follow Up**
	-21d to -1d	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15***	**Day 22**		
Window		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1		
Informed Consent	X										
Medical History, Demographics	X										
Concomitant Medications	X	X	X	X	X	X	X		X	X	X[11]
PE, Height[1], Weight, ECOG	X					X				X	
Toxicity Evaluation		X				X				X	
Vital Signs (HR, Temp, BP)	X	X				X				X	
12-lead ECG[3]	X[3]									X	
Education and counseling guidance document[4]	X					X				X	
CBC[5]	X	X	X	X	X	X				X	
Serum Chemistry[5]	X			X		X				X	
Neurological exam[6]	X					X				X	
PT/PTT[12]	X									X	
Pregnancy test [FCBP] [2]	X	X	X	X	X	X		X[2]		X[2]	
Extramedullary disease[7]	X					X				X	
Skeletal Survey [8]	X										
Bone Marrow Aspiration/Biopsy[9]	X					X					
Myeloma-specific lab tests[10]	X					X				X	
MLN9708 Administration		X	X	X		X	X	X			
Dexamethasone		X	X	X	X	X[13]	X[13]	X[13]	X[13]		
Pomalidomide Administration		Days 1 - 21				Days 1 – 21					

PROCEDURES	Screen	Cycle 1 Each cycle is 28 days				Cycle 2+* Each cycle is 28 days				End of Treatment	Post Study Follow Up
	-21d to -1d	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15*	Day 22		
Follow for PD and survival											X[11]

1) Measured at screening only.
2) FCBP - A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months. Pregnancy tests for FCBP must be performed within 10 to 14 days and again within 24 hours of initiation of therapy. Repeat pregnancy test every week for the first 4 weeks and then every 28 days while on therapy and during interruptions in therapy and 28 days following discontinuation of pomalidomide. Women with irregular menstruation must have pregnancy testing every 14 days while on therapy and during interruptions and 14 and 28 days after discontinuation of Pomalidomide. For Cycle 2 and forward, the D15 pregnancy test (if required) can be done locally and results faxed to the main institution.
3) ECG (12-Lead) should be performed and read locally.
4) All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. All patients enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS™ program.
5) CBC to be performed and reviewed by clinician within 24 hours of day of dosing (first day of each cycle). Alternately, a STAT CBC may be drawn on day of dosing, however should be reviewed prior to administration of investigational product(s). Serum Chemistry to be performed and reviewed by the investigator within 24 hours of day of dosing (first day of each cycle). Alternately, a STAT CMP may be drawn on day of dosing however should be reviewed by the investigator prior to administration of investigational product(s). Chemistry includes: glucose, calcium, albumin, total protein, sodium, potassium, BUN, creatinine, ALP, ALT, AST, bilirubin and uric acid (uric acid to be drawn at screening and then as needed based on tumor lysis syndrome risk). Weight and serum creatinine will be used to calculate creatinine clearance by Cockroft-Gault equation (see appendix 15.2).
6) Neurological assessment required at screening and Day 1 of Cycle 2+.
7) Extramedullary Disease: prior to study (28 days), testing required only if extramedullary disease is present, every 12 weeks (if present at screening) or upon clinical suspicion of progressive disease (if present at screening). This may include CT scan of the abdomen/pelvis, CT or x-ray of the chest, ultrasound of the liver/spleen or abdomen.
8) Skeletal survey (including skull, all long bones, pelvis and chest) with tumor measurements (measurements required if plasmacytomas are present). Also required if previous survey >28 days from study entry and at any time when clinically indicated.
9) A bone marrow aspiration and biopsy is required at screening; Repeat bone marrow biopsy/aspirate as appropriate to confirm achievement of response (aspirate only—biopsy not required).
10) Myeloma lab tests: B2Microglobulin (collected at screening only); serum immunoelectrophoresis, immunoglobulin assay, M band quantitation by immunofixation, free light chain and 24 hour urine collection for Bence Jones protein to be performed at baseline prior to study, prior to each cycle (to confirm complete response and in patients with urine only measurable disease) thereafter and at time of end of treatment (if last tests were > 3 weeks).
11) End of study follow-up to be completed every three months for two years to include second primary malignancies, new therapies for the treatment of MM only (not all concomitant medication) and survival.
12) Due to the risk of blood clots while on Pomalidomide, if patient is started on warfarin, routine monitoring of INR should occur (as per your institutuional guidelines).
13) After the patient has been on Dexamethasone over one year, the patient can discontinue Dexamethasone at their next scheduled visit.

*Additional tests to be performed at the beginning of each cycle and at any reasonable time point during treatment if indicated for monitoring of drug profile/safety or, for disease/health status at the discretion of the clinical investigator. Starting with Cycle 2 and forward, the patient is not required to come to the main hospital/institution for a Day 15 visit. The patient can be seen locally by their physician at their discretion.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
AL	amyloidosis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
βhCG	beta-human chorionic gonadotropin
BMA	bone marrow aspirate
BMB	bone marrow biopsy
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CL	clearance
C_{max}	single-dose maximum (peak) concentration
CO_2	carbon dioxide
CR	complete remission
CRA	Clinical Research Associate
CRP	C-reactive protein
CT	computed tomography
CV	cardiovascular
CYP	cytochrome P_{450}
DCC	data coordinating center
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSMC	data safety monitoring committee
ECG	electrocardiogram

Abbreviation	Term
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study (visit)
EOT	End of Treatment (visit)
FCBP	female of child bearing potential
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
Hb	hemoglobin
Hct	hematocrit
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMiDS	immunomodulatory agents
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IV	intravenous; intravenously
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	multiple myeloma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NDMM	newly diagnosed multiple myeloma
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural killer cells
NYHA	New York Heart Association

Abbreviation	Term
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression free survival
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial remission
PMT	Protocol Monitoring Team
RBC	red blood cell
RP2D	recommended phase 2 dose
RRMM	relapsed refractory multiple myeloma
SAE	serious adverse event
SD	stable disease
T_{max}	single-dose time to reach maximum (peak) concentration
TEAE	treatment emergent adverse event
TTP	time to prgression
TW	twice weekly
ULN	upper limit of the normal range
US	United States
V_d	volume of distribution in the terminal phase
VGPG	very good partial response
W	weekly
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Multiple Myeloma Background

Multiple myeloma (MM) is an incurable malignancy that is the second most common hematological malignancy. There are approximately 20,000 new cases per year and 10,000 deaths per year from MM in the United States. [1] Treatment options for relapsed MM include the following:

Bortezomib; A drug in the class of proteasome inhibitors, it was approved as monotherapy for relapsed MM.[2] Given the efficacy and tolerability of the drug it is often used in combination with agents such as alkylators (cyclophosphamide), immunomodulatory agents (IMiDS), or liposomal doxorubicin either in the upfront setting or relapsed setting. [3]

Carfilzomib: Also a proteasome inhibitor, was approved in 2012 for patients who had prior therapy with bortezomib and an IMID and were progressing on or refractory to their most recent therapy. It has less peripheral neuropathy than bortezomib and has shown responses in bortezomib refractory patients.[4] However, there are concerns with potential cardiac, pulmonary and renal side effects. Also the administration schedule of consecutive days of intravenous dosing make it a more cumbersome regimen for patients.

Lenalidomide/Thalidomide: Drugs in the class known as immunomodulatory agents. Lenalidomide in conjunction with dexamethasone is approved for relapsed myeloma. [5]

Thalidomide is also approved for myeloma therapy but in the United States, lenalidomide is used preferentially due to its more favorable side effect profile. Similar to the practice with bortezomib both drugs are now commonly used in the upfront induction setting for therapy of myeloma in conjunction with dexamethasone for synergy. [6]

Unfortunately even with the advent of these active novel agents and improved response rates of combination therapy, all patients with myeloma ultimately relapse. However, patients are living longer and hence, the goals of MM therapy are not only efficacy but also favorable toxicity profiles.[7] In addition as these novel agents are being used earlier in the course of myeloma therapy, when patients do relapse, their disease is often refractory to the approved agents. Survival for this group of patients, especially those refractory to bortezomib and lenalidomide, the so called double refractory group is especially poor. [8]

Hence new therapies for patients with relapsed disease are needed. In addition, oral therapies have the advantage of ease of administration and the potential for longer term use.

1.2 MLN9708

1.2.1 Preclinical Experience

Please refer to the current MLN9708 Investigator's Brochure (IB) and Safety Management Attachment (SMA).

1.2.2 Clinical Experience

As of 30 April 2012, 382 patients have been treated with MLN9708 across 9 enrolling, sponsor-led phase 1 or phase 1/2 studies evaluating both twice-weekly and weekly dosing schedules. MLN9708 is available as an intravenous and oral formulation. Regardless of the route of administration in the twice-weekly dosing schedule, MLN9708 is given on Days 1, 4, 8, and 11 of a 21-day cycle; in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. To date, the development of oral MLN9708 has focused on multiple myeloma [relapsed and/or refractory and newly diagnosed] and a different yet related plasma cell dyscrasia, systemic light chain (AL) amyloidosis. A clinical pharmacology study looking at drug-drug interactions, the effect of food, and bioavailability also uses the oral formulation. Details of these trials can be found in ClinicalTrials.gov and the MLN9708 IB.

1.2.3 Pharmacokinetics and Drug Metabolism

Clinical IV and PO pharmacokinetic (PK) data show that MLN9708 (measured as the biologically active boronic acid form of MLN9708 [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral MLN9708 is rapidly absorbed with a median time to first maximum plasma concentration (T_{max}) of approximately 0.5 to 2.0 hours and terminal $t_{1/2}$ after multiple dosing of approximately 5 to 7 days.[9] Results of a population PK analysis (N = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA.[10] Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for MLN9708 using the population PK analysis. See the IB for information on the PK for IV doses of MLN9708.

Metabolism appears to be the major route of elimination for MLN9708, with negligible urinary excretion of the parent drug (< 3% of dose). In vitro studies of liver microsomes show that

MLN9708 is metabolized by multiple cytochrome P450 enzymes (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes is 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). MLN9708 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. The potential for MLN9708 treatment to produce DDIs via CYP inhibition is inferred to be low; however, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor because of the potential for first-pass metabolism when MLN9708 is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of MLN9708 in human liver microsomes. MLN9708 may be a weak substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN9708 is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

1.2.4 Clinical Trial Experience Using the Oral Formulation of MLN9708

In the 7 studies actively enrolling patients to investigate oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 242 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708, either as a single agent treatment or in combination with currently clinically available treatments. Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 1-1.

Table 1-1 Ongoing Studies of Oral MLN9708

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 58	PO, twice weekly (TW), single agent	0.24-2.23 mg/m^2, TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia
C16004 RRMM N = 52	PO, weekly (W), single agent	0.24-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea
C16005 NDMM N = 65	PO, W, combination with LenDex 28 day cycle	1.68-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D*: 4.0 mg fixed (switched to fixed dosing in phase 2, relevant to 2.23 mg/m^2)
C16006 NDMM N = 28	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with melphalan and prednisone	Arm A*: 3-3.7 mg, fixed dose, TW DLT: rash, thrombocytopenia, subileus Arm B*: 5.5 mg, fixed dose, W DLT: Esophageal ulcer
C16007 RR-AL N = 6	PO, W, single agent	4-5.5 mg, fixed dose*, W MTD: 4 mg DLT: thrombocytopenia, dirrhea, dyspnea, acute rise in creatinine, cardiac arrest
C16008 NDMM N=11	PO, TW, combination with LenDex 21 day cycle	3.0-3.7 mg fixed dose* W MTD: 4 mg DLT:
C16009 Solid tumors, Lymphomas N = 22	PO, W, single agent	5.5 mg fixed dose* W
C16010 RRMM N = 1	PO, W, combination with LenDex	4.0 mg fixed dose* W
TB-MC010034 RRMM N = 5	PO, W, single agent in 1s part of study then in combination with LenDex in 2nd part	3.0 mg fixed dose* W DLT: thrombocytopenia, nausea, hypertension, diarrhea

Abbreviations: RRAL = Relapsed or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area ; DLT = dose-limiting toxicity; IV = intravenuously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RRMM = relapsed and/or refractory multiple myeloma; RPh2D = recommended phase 2 dose

* Approximate body surface area (BSA) and fixed dosing equivalence: 3 mg ~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg ~ equivalent to 2.97 mg/m^2 BSA dosing.

1.2.5 Overview of the Oral Formulation of MLN9708

The emerging safety profile indicates that oral MLN9708 is generally well tolerated with predominant toxicities largely reversible, able to be monitored by routine clinical examinations and manageable by dose reductions, discontinuation, or standard supportive care. From experience from phase 1 through 2 studies the major toxicities can be managed to allow repeat treatment cycles over periods extending beyond 24 months.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 146 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral MLN9708 Studies (C16003, C16004, C16007, and C16009) is shown in Table 1-2.

Table 1-2 Summary of Most Common (At Least 10% of Total) All Grade Treatment-Emergent Adverse Events (Oral MLN9708 Single-Agent [C16003/4/7/9] Safety Population)

Primary System Organ Class	**Preferred Term and Incidence N=146 n (%)**
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 102 (70)	Nausea 68 (47); Diarrhoea 55 (38); Vomiting 51 (35); Abdominal pain 21 (14); Constipation 21 (14)
General disorders and administration site conditions 98 (67)	Fatigue 71 (49); Pyrexia 31 (21); Oedema peripheral 15 (10)
Blood and lymphatic system disorders 77 (53)	Thrombocytopenia 60 (41); Anaemia 30 (21); Neutropenia 23 (16); Leukopenia 15 (10)
Nervous system disorders 63 (43)	Headache 20 (14); Dizziness 18 (12)
Metabolism and nutrition disorders 60 (41)	Decreased appetite 39 (27) Dehydration 21 (14)
Respiratory, thoracic and mediastinal disorders 60 (41)	Cough 22 (15); Dyspnoea 21 (14)
Skin and subcutaneous tissue disorders 60 (41)	Rash macular 17 (12)
Musculoskeletal and connective tissue disorders 56 (38)	Arthralgia 20 (14); Back pain 17 (12)
Infections and infestations 54 (37)	Upper respiratory tract infection 21 (14)

Source: MLN9708 Investigator's Brochure Edition 6

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator

In the 3 studies actively enrolling patients to investigate oral MLN9708 in combination with standard combination regimens in patients with newly diagnosed multiple myeloma, a total of 96 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 in combination with lenalidomide and dexamethasone in 2 trials (C16005 and C16008) and with melphalan and prednisone in 1 trial (C16006). The most frequent (at least 10%) adverse events occurring in the pooled safety population from Studies C16005, C16006, and C16008 is shown in Table 1-3. In combinations trials, related is defined as possibly related to any drug in the combination regimen, not just specifically related to MLN9708.

Table 1-3 Summary of Most Common (At Least 10% of Total) Treatment- Emergent Adverse Events (Oral MLN9708 Combination Agent [C16005/6/8] Safety Population)

Primary System Organ Class	**Preferred Term and Incidence N= 96 n (%)**
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 70 (73)	Nausea 32 (33); Constipation 29 (30); Vomiting 25 (26) Diarrhoea 22 (23)
General disorders and administration site conditions 64 (67)	Fatigue 37 (39); Oedema peripheral 20 (21); Pyrexia 19 (20)
Skin and subcutaneous tissue disorders 57 (59)	Rash 13 (14)
Nervous system disorders 46 (48)	Neuropathy peripheral 13 (14); Dysgeusia 12 (13) Dizziness 11 (11)
Musculoskeletal and connective tissue disorders 45 (47)	Back pain 18 (19); Muscle spasms 10 (10)
Blood and lymphatic system disorders 42 (44)	Thrombocytopenia 28 (29); Anaemia 22 (23); Neutropenia 19 (20)
Infections and infestations 40 (42)	Upper respiratory tract infection 17 (18);
Metabolism and nutrition disorders 38 (40)	Decreased appetite 11 (11)
Respiratory, thoracic and mediastinal disorders 34 (35)	Dyspnoea 13 (14); Cough 11 (11)
Psychiatric disorders 23 (24)	Insomnia 15 (16)

Source: MLN9708 Investigator's Brochure Edition 6.

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

The clinical experience with MLN9708 also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent MLN9708, when combined with established therapies, and across the malignancies studied (advanced solid tumors [11], non-Hodgkin's disease, Hodgkin's disease [12], relapsed and/or refractory multiple myeloma [RRMM;[13,14]], relapsed or refractory systemic light chain amyloidosis [RRAL; [15]], and newly diagnosed multiple myeloma [NDMM;[16,17,18]]) to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of MLN9708.

Of particular relevance to this study (C16011) is the clinical experience from Studies C16004 and C16007 in which single-agent MLN9708 is administered weekly in patients with RRMM or RRAL, respectively.

1.2.6 MLN9708 in Relapsed and/or Refractory Multiple Myeloma

Study C16004 is an open-label, dose-escalation, phase 1 study of MLN9708 administered weekly on Days 1, 8, and 15 of a 28-day cycle in adult patients with RRMM. Patients with MM enrolled in the dose-escalation component of the study have relapsed following at least 2 lines of therapy, which must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. The dose-escalation phase of the trial has completed. In this study, 2 of 3 patients experienced protocol-defined DLTs (Grade 3 rash and Grade 3 nausea, vomiting, and diarrhea) at a dose of 3.95 mg/m2. As per protocol, subsequent patients were treated at 1 dose level below (2.97mg/m2) where 1 of 6 patients experienced a DLT (Grade 3 nausea, vomiting, and diarrhea). The MTD of weekly oral MLN9708 was determined to be 2.97 mg/m2.

Once the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were enrolled in order to further evaluate the safety, tolerability, efficacy, PK, and pharmacodynamics of oral MLN9708. The MTD expansion cohorts enrolling are:

1. Relapsed and Refractory expansion cohort [refractory is defined as disease progression while on therapy or within 60 days after the last dose of therapy];

2. Carfilzomib expansion cohort

3. Proteasome Inhibitor-Naïve expansion cohort

4. Velcade-Relapsed expansion cohort

Final study results are not available for this ongoing trial, but preliminary data suggest MLN9708 has antitumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated.[19,20]

As of the 30 April 2012 data cut, these patients are considered heavily pretreated as evidenced by a median number of 4 (range 1–13) prior lines of therapy, with 66% refractory to the last line of therapy. Patients have received a median of 2 cycles of therapy (range, 1- 11). Five patients have achieved objective response: 1 patient achieved a VGPR and 4 patients achieved a PR. Additionally, 15 patients achieved durable disease stabilization for up to 9.5 months. At data cut-off, 15 patients remain on treatment; discontinuation of treatment was primarily due to progressive disease (69%).

A summary of the safety profile of patients treated in Study C16004 is outlined in Table 1-4. Overall, 92% of patients experienced a TEAE of any grade and of any cause. Peripheral neuropathy was limited to Grade 1/ 2 in 6 patients, with 3 patients reporting baseline Grade 1 PN at study entry.

Table 1-4 Study C16004, Oral MLN9708, Single Agent, Given Weekly: Most Common TEAEs as of 30 April 12 (N= 52)

Most Common (> 20%) Any Grade and Irrespective of Cause	Thrombocytopenia (54%) Fatigue (48%) Nausea (44%), diarrhea (44%) Vomiting (37%) Decreased appetite (33%) Rash* (31%) Anemia (25%) Neutropenia (23%)
Drug-Related Grade ≥ 3 in > 5% of patients	Thrombocytopenia (38%) Diarrhea and neutropenia 17% (each), fatigue and lymphopenia 10% (each), nausea and decreased appetite 8% (each) and vomiting 6%

Source: MLN9708 Investigator's Brochure Edition 6
* Rash includes preferred terms of rash macular, rash, maculo-papular, rash morbilliform, rash pruritic, pruritus,, rash erythematous, exfoliative rash, and rash popular

Dose reductions required were due to AEs that included rash, neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, dehydration, hypotension, increase in serum creatinine, abdominal pain, ileus, fatigue, and pneumonia. The AEs reported for the 5 patients who were required to discontinue treatment included Grade 2 MLN9708-related nausea/vomiting in 1 patient treated above the MTD, Grade 3 MLN9708-related diarrhea in a second patient, related Grade 3 thrombocytopenia, related Grade 2 dyspnea, and notrelated Grade 4 elevation in creatinine (1 patient each). There were no on-study deaths.

Study C16007 is evaluating single agent weekly , Day 1, 8, and 15 of a 28-day cycle, oral dosing in patients with RRAL after at least 1 prior therapy. The objectives of this study are to determine the safety, tolerability, and MTD, as well as to determine hematologic and organ response rates in this patient population. The starting dose level was selected from Study C16004 as previously described. In Study C16007 the dose was switched from the BSA-based dosing to the fixed dose, thereby the 4.0 mg fixed starting dose in Study C16007 corresponds to the 2.23 mg/m2 dose (one dose level below MTD) from Study C16004. This study is currently enrolling patients in the dose-expansion portion of the trial.

As of 30 April 2012, 14 patients have been treated in this study. At the first dose level of 4.0 mg, 1 of 6 patients experienced a protocol-defined DLT (that is, thrombocytopenia that lasted more than 2 weeks, which met the definition of a DLT due to the delay in starting Cycle 2). As per protocol, the dose was escalated to 5.5 mg for the next cohort of patients where 2 of 5 patients experienced a DLT (Grade 3 diarrhea, n=1; and Grade 2 dyspnea, Grade 2 acute rise in serum creatinine, and Grade 4 cardiac arrest, n=1). The latter patient did not appear to have cardiac AL amyloidosis by echocardiogram on study entry, but did have substantial renal involvement. After the occurrence of this DLT, diagnoses included cardiac involvement and CHF. The MTD of weekly oral MLN9708 was determined to be 4.0 mg. Following the establishment of the MTD, patients are currently being enrolled in to 1 of 2 cohorts: proteasome inhibitor naïve or proteasome inhibitor exposed.[21]

As of the 30 April 2012 data cut, the patients enrolled in the study are considered heavily pretreated, as evidenced by a median number of 3 prior lines of therapy (range 1–7), with 38%

and 46% of patients having been previously treated with bortezomib and lenalidomide, respectively. To be eligible for the study, patients must have amyloid involvement of the heart, kidney, or both; at the data cut the organ involvement distribution was 6, 4, and 4 patients, respectively. Patients have received a median of 2.5 cycles of therapy (range, 1-12). Eight patients remain on treatment. Early signs of activity have been reported. There were 11 patients who have received at least 1 cycle of therapy with completed response assessments (9 in the 4.0 mg [MTD] cohort and 2 in the 5.5 mg cohort). The overall hematologic response rate at MTD is 56% (5 patients achieved a hematologic response [4 VGPR and 1 PR]; 3 patients showed no change, and 1 patient had an early progression.

A summary of the safety profile of patients treated in Study C16007 is outlined in Table 1-5. Overall, 86% of patients experienced a TEAE of any grade and of any cause.

Table 1-5 Study C16007, Oral MLN9708, Single Agent Given Weekly Most Common TEAEs as of 30April 12 (N = 14)

Most Common (> 20%) Any Grade and Irrespective of Cause	Nausea (50%) Fatigue (36%) Thrombocytopenia (29%) Diarrhea (29%) Decreased Appetite (21%) Peripheral Edema (21%) Dyspnea (21%) Abdominal pain (21%)
Drug-Related Grade ≥ 3 in more than 3 Patients	Thrombocytopenia 5 patients, rash 3 patients, dehydration 2 patients, fatigue 2 patients

Source: MLN9708 Investigator's Brochure Edition 6

One patient discontinued study drug administration due to a TEAE (patient with DLT of acute rise in serum creatinine, dyspnea, and cardiac arrest treated at 5.5 mg, as noted above). No death has been reported.

The potential risks reported with MLN9708 use, pooled from all studies using the oral formulations, were anticipated based on preclinical data and previous experience with VELCADE and are noted in the MLN9708 IB, SMA, and ICF documents. Regardless of whether MLN9708 is administered on the once weekly or twice weekly dosing schedule, there is consistency among the type of TEAEs reported, despite some differences in the frequency and severity of the reported events. While the predominant potential toxicities may be severe in some cases, they are largely reversible, and can be managed by routine clinical monitoring and

standard medical interventions, which may include dose reductions and supportive care. Please refer to the MLN9708 IB and SMA for further information.

1.2.7 MLM9708 in Newly Diagnosed Multiple Myeloma (NDMM)

In Study C16005, MLN9708 is given weekly (Days 1, 8, and 15), in combination with lenalidomide (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22) in a 28-day cycle. Enrollment to this study is closed.

Clinical data as of 30 April 2012 is available. The MTD in Study C16005 was determined to be 2.97 mg/m^2 given weekly in a 28-day cycle with LenDex. The DLTs were urticarial rash, dizziness, nausea, orthostatic hypotension, vomiting, diarrhoea, and syncope. The recommended phase 2 dose (RP2D) estimation was established following evaluation of the available data from the phase 1 portion of the trial which included, but was not limited to, analyses of efficacy results and adverse events (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, and treatment discontinuation). Given that the dose of MLN9708 at 2.97 mg/m^2 compromised the maximal dosing of lenalidomide and that the dose of 2.23 mg/m^2 is very tolerable and clinically active, Millennium designated 2.23 mg/m^2 as the RP2D after evaluation of the data and discussion with investigators. The RP2D of 2.23 mg/m^2 has been translated into a fixed dose of 4.0 mg based on the results from the population PK analysis. Enrollment in this study has been completed; final study results are not available, but preliminary data suggests oral MLN9708 given weekly plus lenalidomide and dexamethasone in a 28-day cycle appears well tolerated with manageable toxicity and encouraging antitumor activity.

In Study C16005, 15 of 15 (100%) patients in the dose escalation portion of the study experienced at least 1 TEAE irrespective of grade or causality. At the MTD across all dose expansion cohorts 49 of 53 patients (including 3 patients from the dose escalation cohort [92%]) reported at least 1 TEAE irrespective of grade or causality. In the MTD cohorts, fatigue was the most common AE reported (38%). Other common AEs reported include nausea (32%), constipation (30%), upper respiratory infection (23%), and peripheral oedema (21%). Skin toxicity, primarily erythematous rash, occurred in 62% of patients (of note, rash is an overlapping toxicity with MLN9708 and lenalidomide). Peripheral neuropathy was reported in 13% of patients; Grade 3 in 1 patient.

A summary of the overall safety profile of patients treated in Study C16005 is outlined in Table 1-6. Overall, 100% of 65 patients experienced at least one TEAE of any grade and of any cause.

Table 1-6 Study C16005: Oral MLN9708 Given Weekly in Combination With Lenalidomide and Dexamethasone, Most Common TEAEs as of 30 April 2012

Most Common (> 20%) Any Grade and Irrespective of	Fatigue (37%)

Cause	Nausea (34%)
	Constipation (31%)
	Vomiting (28%)
	Diarrhoea (26%)
	Thrombocytopenia (23%)
	Upper respiratory tract infection (22%)
	Anaemia and oedema peripheral (20% each)
Drug-Related[a] Grade ≥ 3 in ≥ 2 Patients	Nausea, vomiting (n=3 each)
	Thrombocytopenia, lymphopenia, rash pruritic (n=2 each)

Source: MLN9708 Investigator's Brochure Edition 6.

a Related means to ANY drug in the study drug combination.

The most common drug-related SAEs reported in Study C16005 as of 30 April 2012 include pneumonia, infection, diverticulitis, localised infection, gastrointestinal haemorrhage, respiratory syncytial virus (RSV) pneumonia faecaloma, pyrexia, pneumonia respiratory syncytial viral, non-cardiac chest pain, peripheral oedma, asthenia, hyponatraemia vomiting, diarrhoea, nausea, chest pain, dehydration, anemia, dizziness, peripheral sensory neuropathy, orthostatic hypotension, embolism, muscular weakness, acute renal failure, blood creatinine increased, maculopapular rash, atrial fibrillation, syncope, hypotension, and deep vein thrombosis, and back pain.

As of the clinical data cutoff, 4 patients have discontinued treatment due to TEAEs including gastrointestinal haemorrhage, angioedema, syncope, and RSV pneumonia.

One death was reported for a patient with RSV pneumonia; the event was deemed by the investigator to be related to treatment with MLN9708.

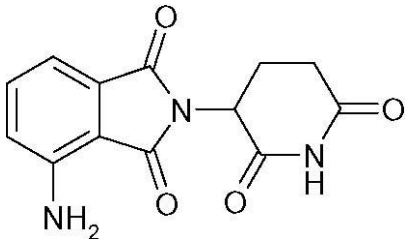
1.2.7.1 Clinical Trial Experience Using the Intravenous Formulation of MLN9708

See the IB for descriptions of the 2 ongoing studies investigating IV MLN9708 in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

1.3 Pomalidomide

Pomalidomide is a thalidomide analogue indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate.

POMALYST is an immunomodulatory antineoplastic agent. The chemical name is (RS)-4-Amino-2-(2,6-dioxo-piperidin-3-yl)-isoindoline-1,3-dione and it has the following chemical structure:



POMALYST is available in 1 mg, 2 mg, 3 mg and 4 mg capsules for oral administration. Each capsule contains pomalidomide as the active ingredient and the following inactive ingredients: mannitol, pregelatinized starch and sodium stearyl fumarate. The 1 mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink and black ink. The 2 mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3 and white ink. The 3 mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide and white ink. The 4 mg capsule shell contains gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2 and white ink.

1.3.1 Mechanism of Action

Pomalidomide, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic activity. In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide demonstrated anti-angiogenic activity in a mouse tumor model and in the in vitro umbilical cord model.

1.3.2 Pharmakokinetics

Absorption

Following administration of single oral doses of POMALYST, the Cmax for pomalidomide occurs at 2 and 3 hours post dose. The systemic exposure (AUC) of pomalidomide increases in

an approximately dose proportional manner. In patients with multiple myeloma who received POMALYST 4 mg daily alone or in combination with dexamethasone, pomalidomide steady-state drug exposure was characterized by AUC(T) of 400 ng.hr/ mL and maximum plasma concentration (Cmax) of 75 ng/mL. Following multiple doses, pomalidomide has an accumulation ratio of 27 to 31 %.

Distribution

Pomalidomide has a mean apparent volume of distribution (Vd/F) between 62 and 138 L at steady state. Pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67% of plasma level at 4 hours post-dose (~Tmax) after 4 days of once daily dosing at 2 mg. Human plasma protein binding ranges from 12% to 44% and is not concentration dependent.

Metabolism

Pomalidomide is primarily metabolized in the liver by CYP1A2 and CYP3A4. In vitro, CYP1A2 and CYP3A4 were identified as the primary enzymes involved in the CYP-mediated hydroxylation of pomalidomide, with additional minor contributions from CYP2C19 and CYP2D6.

Elimination

Pomalidomide is eliminated with a median plasma half-life of approximately 9.5 hours in healthy subjects and approximately 7.5 hours in patients with multiple myeloma. Pomalidomide has a mean total body clearance (CL/ F) of 7-10 L/ hr.

Following a single oral administration of [14C]-pomalidomide (2 mg) to healthy subjects, approximately 73% and 15% of the radioactive dose was eliminated in urine and feces, respectively, with approximately 2% and 8% of the radiolabeled dose eliminated unchanged as pomalidomide in urine and feces.

1.3.3 Non-clinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies examining the carcinogenic potential of pomalidomide have not been conducted. One of twelve monkeys dosed with 1 mg/kg of pomalidomide (an exposure approximately 15-fold of

the exposure in patients at the recommended dose of 4 mg/per day) developed acute myeloid leukemia in a 9-month repeat-dose toxicology study.

Pomalidomide was not mutagenic or clastogenic in a battery of tests, including the bacteria reverse mutation assay (Ames test), the in vitro assay using human peripheral blood lymphocytes and the micronucleus test in orally treated rats administered doses up to 2000 mg/kg/day.

In a fertility and early embryonic development study in rats, drug-treated males were mated with untreated or treated females. Pomalidomide was administered to males and females at doses of 25 to 1000 mg/kg/day. When treated males were mated with treated females, there was an increase in post-implantation loss and a decrease in mean number of viable embryos at all dose levels. There were no other effects on reproductive functions or the number of pregnancies. The lowest dose tested in animals resulted in an exposure (AUC) approximately 100-fold of theexposure in patients at the recommended dose of 4 mg/day. When treated males on this study were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females.

Pomalidomide does not inhibit or induce CYP450 enzymes or any of the transporters in vitro.

1.3.4 Clinical Studies

Multiple Myeloma

The trial that led to the recent approval of pomalidimide was a Phase 2, multicenter, randomized open label study in patients with relapsed multiple myeloma who were refractory to their last myeloma therapy and had received lenalidomide and bortezomib. Patients were considered relapsed if they had achieved at least stable disease for at least one cycle of treatment to at least one prior regimen and then developed progressive disease. Patients were considered refractory if they experienced disease progression on or within 60 days of their last therapy. A total of 221 patients were randomized to receive pomalidomide alone or pomalidomide with Low dose Dex. In Trial 1, the safety and efficacy of pomalidomide 4 mg, once daily for 21 of 28 days, until disease progression, were evaluated alone and in combination with Low dose Dex (40 mg per day given only on Days 1, 8, 15 and 22 of each 28-day cycle for patients 75 years or younger, or 20mg per day given only on Days 1, 8, 15 and 22 of each 28-day cycle for patients greater than 75 years of age). Patients in the pomalidomide alone arm were allowed to add Low dose Dex upon disease progression.

Most common adverse reactions (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper- respiratory tract infections, back pain and pyrexia (6.1).

A recent phase III randomized trial comparing pomalidomide plus dexamethasone, to high-dose dexamethasone alone in patients with relapse and refractory MM, demonstrated higher response rates, PFS and OS in the pomalidomide arm. Ten percent (10%) of patients treated on the dexamethasone alone arm achieved an objective response and 31% of the patients on the combination arm with pomalidomide and low-dose dexamethasone achieved a response; odds ratio [OR] 4·22 [2·35 –7·58] p<0·0001 . [26] The treatment regimens most commonly used in Europe are very different from those used in the United States, as patient access to many of the novel agents is more limited in Europe. None of the patients enrolled/treated in that trial had been previously treated with carfilzomib or pomalidomide. For this trial, where MLN9708 will be added to pomalidomide and dexamethasone, patients with prior exposure to either of these agents would not be excluded. As many patients (>50%) are likely to have been previously treated with one or both of these agents we consider a response rate of 30% sufficient efficacy to justify further development.

1.4 Study Rationale

Pomalidomide is the newest immunomodulatory drug that is chemically a combination of thalidomide and lenalidomide. It has been studied in phase I-III trials for patients with relapsed myeloma. It has shown activity even in lenalidomide refractory patients and phase III trials have demonstrated superior overall and progression free survival (OS/PFS) compared to high dose dexamethasone. [22,23]

MLN9708 is a next generation small molecule 20-s proteasome inhibitor generated with the aim of improving the efficacy seen with bortezomib in MM but further improvement in drug administration. It has shown activity in the relapsed and relapsed/refractory MM setting including bortezomib refractory patients. [24] Therefore given the synergy seen with IMIDS and proteasome inhibitors as well as the activity of both compounds in relapsed MM, this becomes an attractive combination for study in the relapsed/relapsed refractory setting.

Dosing Justification

As mentioned above, the standard FDA approved dose of pomalidomide is 4mg days 1-21. Maximum response is seen when it is combined with dexamethasone. Because of an impetus in myeloma therapy to be relatively steroid sparing, the generally accepted dose of dexamethasone

is a " Low dose" weekly dosing of 40mg. Data generated from the MLN9708 plus lenalidomide and dexamethasone trial confirmed the tolerability of this new proteasome inhibitor with an IMID. The RP2D of MLN9708 is 4mg d1,8,15. However, the potential for overlapping hematologic toxicity especially in a more advanced disease population with pomalidomide (which tends to be more myelosuppressive than lenalidomide) in conjunction with MLN9708 led to the choice of an initial dose of 3mg for MLN9708. Because of the synergy between IMIDS and proteasome inhibitors we would still expect to see activity at this dose.

1.5 Potential Risks and Benefits

Please refer to the current MLN9708 Investigator's Brochure (IB) and the Package Insert for pomalidomide.

MLN9708 is a modified dipeptide boronic acid proteasome inhibitor similar to VELCADE, which has a known safety profile [VELCADE PI]. The most frequent AEs reported to date in the ongoing MLN9708 phase 1 studies were anticipated based on preclinical data and previous experience with VELCADE, and are noted in the IB, and the informed consent documents. However, it is possible that MLN9708 will have toxicities that were not previously observed in or predicted from such sources. Patients will be monitored closely for anticipated toxicities.

The toxicity profile of MLN9708 and pomalidomide in combination with dexamethasone is unknown and will be evaluated in this trial.

MLN9708 shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials [11,12,13,14,16,17,18].

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

2. STUDY OBJECTIVES

2.1 Study Objectives (Phase I)

2.1.1 Primary:

1. To determine the recommended phase II dose (RP2D) of MLN9708, when given in combination with pomalidomide and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma.

2.1.2 Secondary:

2. To evaluate the safety of MLN9708 at each dose level when given as part of a three drug combination by assessing the following:

- type, frequency, severity, attribution, time course and duration of adverse events

- clinical laboratory tests at various points in the study

2.2 Study Objectives (Phase II)

2.2.1 Primary:

1. To estimate the response rate and to evaluate the antitumor activity of the three drug combination: MLN9708 (at the RP2D), pomalidomide and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma.

2.2.2 Secondary:

At the RP2D, for the three drug combination:

2. To characterize and evaluate toxicities, including type, frequency, severity, attribution, time course and duration.

3. To obtain estimates of response duration, depth of response, clinical benefit response, and survival (overall and progression-free).

3. STUDY ENDPOINTS

3.1 Primary Endpoints

Phase I:

The primary endpoint is toxicity. Toxicity will be graded according to the NCI-Common Terminology Criteria for Adverse Events version 4.03. A DLT will be defined as any of the following toxicities that are at least possibly related to either Pomalidomide or MLN9708 and occur during cycle 1:

- Grade 4 neutropenia
- Grade 3 neutropenia with fevers $\geq$ 38.5°C
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with bleeding

- Grade 3 or higher non-hematological toxicity will be considered dose limiting, with the following exceptions: diarrhea, fatigue, nausea or vomiting will only be considered dose limiting if, after 48 hours it has not recovered to <Grade 3 (despite maximal medical therapy), allergic reaction/hypersensitivity, or electrolyte/metabolic toxicity unable to be corrected to <Grade 1 or baseline within 48 hours will be considered dose limiting.
- Delay in starting cycle 2 on the scheduled day 1 for > 7 days due to treatment related toxicity
- Any dose modification or delay during cycle 1, except modifications/delays done in response to hypo- hyperthyroidism <=Grade 2, herpes zoster infection, all considered idiopathic or intrinsic to the underlying myeloma.

Phase II:

The primary activity endpoint is response rate (confirmed sCR/CR/VGPR or PR), based on the International Myeloma Working Group (IMWG) criteria, calculated as the number of responders divided by the number of evaluable patients. Confirmation of sCR/CR/VGPR or PR assessed by IMWG criteria.

Secondary activity endpoints for this study are as follows:

- Duration of response, defined as the time interval from the date of first documented response (sCR/CR/VGPR or PR) to documented disease relapse, progression or death whichever occurs first.

- Clinical benefit response, based on the International Myeloma Working Group (IMWG) criteria, calculated as the number of responders plus those with a minimal response (MR) or stable disease (SD) divided by the number of evaluable patients. Confirmation of sCR/CR/VGPR/PR/MR or SD assessed by IMWG criteria.

- Overall survival, defined as the time interval from date of first dose of study drug to date of death from any cause.

- Progression-free survival, defined as the time interval from date of first dose of study drug to first documented disease relapse, progression or death from any cause, whichever occurs first.

4. STUDY DESIGN

4.1 Overview of Study Design

4.1.1 Phase I:

The phase I portion of the study is based on a 3 + 3 dose escalation design, to evaluate toxicities associated with MLN9708 when given in combination with pomalidomide and dexamethasone. Two doses of MLN9708 (dose level -1 and dose level 1: 3mg; dose level 2: 4mg) will be tested in up to three possible dose levels. Based on previous combination trials of MLN9708, the 4mg dose of MLN9708 is expected to be well tolerated. Given that this is the first study to combine MLN9708, with dexamethasone and pomalidomide, patients will initially be treated at a 3mg dose. The maximum tolerated dose (MTD) will be established by evaluating dose limiting toxicity (DLT) during cycle 1. The recommended phase II dose (RP2D) of MLN9708 and pomalidomide will generally be the MTD, but it may be less than the MTD based on a review of available data/cumulative toxicities from phase I. Patients will be treated with oral MLN9708 on days 1, 8, and 15 of each 28 day cycle and with Dexamethasone on days 1, 8, 15 and 22 of each 28 day cycle. Pomalidomide will be given on days 1-21 of each 28 day cycle. The dose of MLN9708 and Pomalidomide administered will depend on the dose level assignment; the dose of dexamethasone will be fixed (Patients >75 years, at the time of trial registration, will receive a Dexamethasone starting dose of 20 mg on the same set schedule).

Phase II

Patients who enroll during the phase II portion of the trial will be treated at the same dose and schedule of MLN9708, pomalidomide and dexamethasone determined safe during the phase I study (the RP2D).

4.2 Number of Patients

The phase I study is expected to enroll and treat 9 patients; 3 patients at dose level 1, and another 6 treated at dose level 2 -assuming the 4mg dose of MLN9708 is well tolerated. The phase II portion of the trial is expected to enroll a minimum of 9 and a maximum of 25 patients. The six patients treated at the RP2D in the phase I portion of the study will count toward the 25 patients required; given this, we expect to enroll only 19 new patients on the phase II trial.

4.3 Duration of Study

Accrual, for both phases, is expected to be completed in 26 months; with approximately 2 patients enrolled each month. Patients will be treated in 28-day treatment cycles until disease relapse, progression or unacceptable toxicity, withdrawal of consent, or protocol specified parameters to stop treatment. Patients who discontinue study treatment for reasons other than disease relapse/progression will continue to have disease assessments per International Myeloma Working Group (IMWG) criteria until relapse or progression, initiation of new

anticancer treatment, or death whichever occurs first. Patients will be followed to collect further anticancer treatment and survival information until death, loss to follow-up, withdrawal of consent, study termination or up to 24 months post treatment.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.

2. Voluntary written informed consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

3. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting pomalidomide or MLN9708 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 or MLN9708 through 90 days after the last dose of study drug. 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 from the time of signing the informed consent form through 90 days after the last dose of study drug. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure.

4. All patients enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS™ program.

5. Patients must have a diagnosis of relapsed or relapsed and refractory Multiple Myeloma with a minimum of one prior regimen and a maximum of 5 prior regimens.

6. Patients must have had therapy with a proteasome inhibitor and lenalidomide and be refractory to lenalidomide according to the IMWG definition of refractory disease (progressive disease on or within 60 days of stopping lenalidomide).

7. Patients must have measurable disease defined as **one** of the following:

a. Serum M protein ≥ 0.5 g/dL

b. Urine M protein ≥ 200 mg/24 hours

c. Serum free light chain ≥ 10 mg/dL provided the FLC ratio is abnormal.

8. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.

9. Patients must meet the following clinical laboratory criteria:

- Absolute neutrophil count (ANC) ≥ 1,000/mm^3
- Platelet count ≥ 75,000/μL for patients in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count ≥ 50,000/μL for patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells. Platelet transfusions are not allowed within 3 days of last platelet assessment to confirm eligibility.
- Total bilirubin ≤ 1.5 × the institutional upper limit of the normal range (IULN).
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × IULN.
- Calculated creatinine clearance ≥ 45mL/min (see Appendix 15.2).

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are pregnant or breastfeeding or have a positive serum pregnancy test during the screening period.
2. Failure to have fully recovered (ie, ≤ Grade 1 toxicity) from the reversible effects of prior chemotherapy.
3. Prior therapy with a combination regimen containing pomalidomide except the 2 drug combination of pomalidomide and dexamethasone.
4. Major surgery within 14 days before enrollment.
5. Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the MLN9708.

6. Central nervous system involvement.

7. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

8. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

9. Systemic treatment, within 14 days before the first dose of MLN9708, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's Wort.

10. Unable or unwilling to undergo antithrombotic prophylaxis.

11. Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

12. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

13. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.

14. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of MLN9708 or pomalidomide including difficulty swallowing.

15. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy with evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

16. Patient has > Grade 2 peripheral neuropathy on clinical examination during the screening period.

17. Participation in other clinical trials, including those with other investigational agents not included in this trial, within 21days of the start of this trial and throughout the duration of this trial (for all other standard therapies, no treatment within 14 days of the start of this trial).
18. Patients who are pomalidomide refractory, defined as patients who progress on or within 60 days of pomalidomide when given as a single agent or with dexamethasone.

6. PATIENT ENROLLMENT

Phase I Dose Escalation Portion – Prior to discussing protocol entry with the patient, contact the City of Hope Data Coordinating Center to ensure that a treatment slot on the protocol is available.

Phase I and II Patient Enrollment

The screening period for a particular patient commences when the patient signs the informed consent. Consent must be signed before any study-specific tests may be performed. After a patient has been screened and has successfully fulfilled all eligibility criteria, the site representative will email the inclusion/exclusion checklist and all other required source documentation to the City of Hope Data Coordinating Center. In order to ensure privacy/security, please ensure that you type #secure# in the subject line of all correspondence related to the trial/patient:

Lupe Duarte, CCRC
Multiple Myeloma Project Manager
Phone: 626-256-4673 x 63968
Fax: 626 301-8422
Email: dcc@coh.org

A unique patient number will be assigned at that time that will be used to identify the patient throughout the clinical study and must be used on all study documentation related to that patient. Patients will be assigned to a dose level at enrollment. Prior to accepting the registration, the COH DCC staff member will verify the following:

1. IRB approval at the registering institution
2. Patient eligibility
3. Existence of a signed consent form
4. Existence of a signed authorization for use and disclosure of protected health information (if applicable).

Treatment cannot begin prior to registration and must begin ≤ 7 days after registration. Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule.

7. STUDY TREATMENT

7.1 Dose and Schedule

The phase I study will follow a standard 3 + 3 dose escalation design, to evaluate toxicities associated with MLN9708 when given in combination with pomalidomide and dexamethasone. Two doses of MLN9708 (3 mg and 4 mg) will be tested in up to three possible dose levels.

7.2 Dose Levels to be Tested

Schedule: Each cycle is 28 days			
Dose Level	**Pomalidomide**	**MLN9708**	**Dexamethasone***
-1	3mg daily on days 1-21	3 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22
1	4 mg daily on days 1 - 21	3 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22
2	4 mg daily on days 1 - 21	4 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22

*: Patients >75 years, at the time of trial registration, will receive a Dexamethasone dose of 20 mg on the same set schedule.

7.3 Dose Limiting Toxicity/Unacceptable Toxicity

Dose Limiting Toxicity (DLT) is defined as any of the following toxicities that are at least possibly related to either Pomalidomide or MLN9708 that occur during cycle 1. Toxicity will be graded according to the NCI-Common Terminology Criteria for Adverse Events, Version 4.03.

Note: The Phase II portion of the study will use the same definition to define unacceptable toxicity.

For the purposes of this study, DLT will be defined as:

- Grade 4 neutropenia
- Grade 3 neutropenia with fevers ≥ 38.5°C
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with bleeding
- Grade 3 or higher non-hematological toxicity will be considered dose limiting with the following exceptions: diarrhea, fatigue, nausea or vomiting will only be considered dose limiting if, after 48 hours it has not recovered to <Grade 3 (despite maximal medical therapy), allergic reaction/hypersensitivity, or electrolyte/metabolic toxicity unable to be corrected to <Grade 1 or baseline within 48 hours will be considered dose limiting.
- Delay in starting cycle 2 on the scheduled day 1 for > 7 days due to treatment related toxicity
- Any dose modification or delay of MLN9708 or Pomalidomide during cycle 1, except modifications/delays done in response to hypo- hyperthyroidism <=Grade 2, herpes zoster infection, all considered idiopathic or intrinsic to the underlying myeloma.

7.4 Dose Escalation/Expansion

DLT incidence will be based on toxicity events encountered during the first cycle of treatment with the combination of MLN9708, pomalidomide and dexamethasone.

Dose de-escalation, escalation or cohort expansion will only take place after 3 patients are fully assessed using the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 4.03 following the completion of cycle 1.

Dose escalation will occur according to the following rules:

- If zero out of 3 evaluable patients has a DLT in cycle 1 then the next dose level of combination therapy will be tested.
- If 1 out of 3 evaluable patients has a DLT in cycle 1, three additional patients will be assessed at the same dose level of combination therapy.
- If 2 out of 3 patients have a DLT in cycle 1, dose escalation will cease and the next lower dose level of combination therapy will be expanded. Note: If 2 of 3 experience DLT on dose level -1, the trial will be stopped.
- If 1 out of 6 evaluable patients has a DLT in cycle 1, then dose escalation to the next dose level of combination therapy will continue.

- If 2 or more out of 6 patients have a DLT in cycle 1, dose escalation will cease and the next lower dose level of combination therapy will be expanded. Note: If 2 of 6 experience DLT on dose level -1 the trial will be stopped.

The highest dose level that produces ≤1/6 DLTs in cycle 1 will be the maximum tolerated dose (MTD).

Note: Patients may continue therapy unless there is unacceptable toxicity, disease progression or withdrawl of consent.

7.5 Recommended Phase II Dose (RP2D)

The MTD will be based on the assessment of DLT during cycle 1 (see section 7.4). The MTD will be defined as the highest dose at which ≤ 1/6 patients in a cohort experience DLT. The recommended phase II dose (RP2D) of MLN9708 and pomalidomide will generally be the MTD, but it may be less than the MTD based on a review of available data/cumulative toxicities from phase I.

7.6 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of study drug should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of dose.

7.6.1 MLN9708 Administration

Patients should be instructed to swallow MLN9708 capsules whole, with water, and not to break, chew, or open the capsules. MLN9708 should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

7.6.2 Pomalidomide Administration

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. Pomalidomide capsules may be taken with water.

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 at the next scheduled time point. Similarly, if the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

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

Pomalidomide (POMALYST®) will be provided to research patients 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 patients enrolled into this trial, and all research patients 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.

Special Handling Instructions

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

7.6.3 Dexamethasone Administration

Dexamethsone is commercially available and commercial supplies will be used for this study.

Oral dexamethasone will be given on an outpatient basis. Missed doses of dexamethasone will not be made up. Similarly, if the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose. Procedures for dose reductions and delays are summarized in Section 7.9.2.

7.6.4 Growth Factor Administration

For the Phase I portion of the study, growth factors, granulocyte colony stimulating factor [G-CSF], may be given prophylactically for at least two days on days 21 – 26 during or beyond cycle 2. For the Phase II portion of the study, G-CSF may be given prophylactically for at least two days on days 21-26 during or beyond cycle 1. It will be administered subcutaneously at a dose of 5ug/kg or per institutional standard practice dosing either daily or every other day for a minimum of two doses. If patients experience neutropenia or dosing delays, we would recommend consideration of growth factor in subsequent cycles.

7.7 Dose Modification Guidelines

Patients will be evaluated for adverse events at each visit with the NCI Common Toxicity Criteria, Version 4.03 used as a guide for the grading of severity.

As defined in section 7.3, during the phase I portion of the study, any toxicity related dose modification or delay of MLN9708 or Pomalidomide during cycle 1 except modifications/delays done in response to hypo- hyperthyroidism <=Grade 2, herpes zoster infection, all considered idiopathic or intrinsic to the underlying myeloma is a DLT. No dose escalations are permitted in any given patient once a dose level has been assigned. While patients experiencing DLT during Cycle 1 may continue on therapy, if toxicity can be managed according to the dose modification guidelines outlined below, the DLT event will contribute to the assessment of MTD for that given cohort. Patients will be considered evaluable for toxicity if they receive any study drug. Patients will be considered evaluable for dose limiting toxicity if they receive at least 75% of both Pomalidomide and MLN9708 and are followed for the full 28 days during cycle 1 or experience a DLT. For the phase II portion, as part of the primary analysis, patients will be considered evaluable for response if they are eligible, have baseline disease assessments, and receive any protocol treatment. As part of a secondary analysis, patients will be considered evaluable for response if they have baseline disease assessments, receive at least 75% of both Pomalidomide and MLN9708 during the first cycle of therapy and have had their disease re-evaluated.

Dose modifications may be performed in all subsequent cycles of treatment regardless of which phase of study the patient is enrolled on. If toxicities cannot be managed by dose modification or the patient cannot tolerate the lowest dose of study drug, the patient is to be discontinued from study treatment. However, patients that have achieved a plateau of response to study

therapy will continue to adhere to the schedule of assessments followed during the treatment phase of the study even though study drug has been discontinued.

7.8 Dose Reduction Steps

7.8.1 Dose Reduction Steps for Pomalidomide

Pomalidomide Dose Reduction Steps			
Starting Dose	**Daily on Days 1 – 21 every 28 days**		
4.0 mg	3.0 mg	2.0 mg	1.0 mg
3.0 mg	2.0 mg	1.0 mg	-
2.0 mg	1.0 mg	-	-
1.0 mg	-	-	-

7.8.2 Dose Reduction Steps for MLN9708

MLN9708 Dose Reduction Steps			
Starting Dose	**Daily on Days 1, 8 and 15 every 28 days**		
4.0 mg	3.0 mg	2.3 mg	1.5 mg
3.0 mg	2.3 mg	1.5 mg	-

7.8.3 Dose Reduction Steps for Dexamethasone

Dexamethasone Dose Reduction Steps**		
Starting Dose	**Days 1, 8, 15 and 22 every 28 days**	
40 mg	20 mg	12 mg
20 mg*	12 mg	6 mg
12 mg	-	-

*: Patients >75 years, at the time of trial registration, will receive a dexamethasone starting dose of 20 mg on the same set schedule.

**: After the patient has been on Dexamethasone over one year, the patient can discontinue Dexamethasone at their next scheduled visit.

- Dexamethasone may be permanently discontinued for toxicity at the discretion of the investigator but the patient can remain on study therapy with pomalidomide and MLN9708 if tolerated.

- After the patient has been on Dexamethasone over one year, the patient can discontinue Dexamethasone at their next scheduled visit.

7.9 Dose Modification Guidelines for Treatment Related Toxicity

For recommended comcomitant therapy to reduce the risk/severity of potential adverse events refer to Section 7.11. For recommendations on management of adverse events refer to section 7.12. In addition, the table below provides guidelines for dose modification based on toxicity. Dose modifications different from those recommended may be made in consultation with the Lead Principal Investigator based on investigators assessment of toxicity attribution and management of individual patients.

7.9.1 Dose Modification for MLN9708 and Pomalidmide During a Cycle of Therapy

Treatment modifications due to MLN9708 and Pomaliomide related AEs during a cycle of therapy are outlined below.

CTCAE Category	AGENTS	Toxicity During a Cycle
Hematologic Toxicity during a cycle of therapy		
≥ Grade 3 neutropenia associated with fever (temperature ≥ 38.5C) or Grade 4 neutropenia	**Pomalidomide**	Hold dose. Follow CBC weekly. Use of G-CSF is allowed and recommended. If neutropenia resolved to ≤ grade 2 within the cycle, resume pomalidomide and continue through the scheduled end of the cycle. If not resolved to ≤ grade 2, omit for remainder of cycle and reduce the dose of pomalidomide by one dose level at the start of the next cycle. Omitted doses are not made up. Granulocyte colony stimulating factor [G-CSF], may be used prophylactically on days 21 – 26. Section7.6.4

	MLN9708	Hold dose. Follow CBC weekly. If neutropenia resolves to ≤ grade 2 resume treatment on schedule day of cycle. However, if the Day 8 or 15 dose is held, that dose should be omitted and treatment should continue with next scheduled dose (i.e., if Day 8 is skipped, the next dosing day is Day 15) resume MLN9708 at same dose. If neutropenia dose not resolve to ≤ Grade 2 during the cycle and any 2 doses were held due to toxicity then reduce the MLN9708 dose by one level at the start of the next cycle. Granulocyte colony stimulating factor [G-CSF],) may be used prophylactically on days 21 – 26.
Platelet count < 25,000/mm^3 or G3 thrombocytopenia with bleeding	**Pomalidomide**	Hold dose. Follow CBC weekly. Use of platelet transfusions is allowed to proceed with dosing. If thrombocytopenia resolved to < grade 2 within the cycle, resume pomalidomide and continue through the scheduled end of the cycle. If not resolved to ≤ grade 2, omit for remainder of cycle and reduce the dose of pomalidomide by one dose level at the start of the next cycle. Omitted doses are not made up.
	MLN9708	Hold dose. Follow CBC weekly. If thrombocytopenia resolves to ≤ grade 2 resume treatment on schedule day of cycle. However, if the Day 8 or 15 dose is held, that dose should be omitted and treatment should continue with next scheduled dose (i.e., if Day 8 is skipped, the next dosing day is Day 15) resume MLN9708 at same dose. If thrombocytopenia dose not resolve to ≤ Grade 2 during the cycle and any 2 doses were held due to toxicity then reduce the MLN9708 dose by one level at the start of the next cycle.
For recurrent episodes of hematologic toxicity, MLN9708 and/ or pomalidomide may be dose reduced together or independently at the investigaotrs discretion to manage toxicity.		
Non-Hematologic toxicity during a cycle of therapy		
RASH **Grade 2 or 3**	**Pomalidomide**	Hold pomalidomide and MLN9708. Follow weekly. Implement supportive therapy (see section 7.11.2)

	MLN9708	If the toxicity resolves to ≤ grade 1, restart MLN9708 and pomalidomide and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of pomalidomide by one dose level at the start of the next cycle. Omitted doses are not made up. For subsequent occurances, alternate dose reductions with MLN9708 and pomalidomide.
Non-blistering rash Grade 4		Discontinue pomalidomide and MLN9708. Withdraw participant from the study.
Desquamating (blistering) rash-any Grade or Erythema multiforme ≥ Grade 3	**Pomalidomide/ MLN9708**	Discontinue treatment. Withdraw participant from study.
Hyperthyroidism or Hypothyroidism	**Pomalidomide**	Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart pomalidomide at investigator's discretion. For toxicity attributable to pomalidomide, reduce the dose by one dose level.
Neuropathy **Grade 2 peripheral neuropathy with pain or Grade 3**	**Pomalidomide MLN9708**	Hold MLN9708. Follow weekly. If the toxicity resolves to ≤ grade 1(or baseline), restart MLN9708 at next lower dose level and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of MLN9708 one dose level at the start of the next cycle. Omitted doses are not made up. For recurrent Grade 2 peripheral neuropathy with pain or grade 3 neuropathy, hold treatment. If the toxicity resolves to ≤ grade 1(or baseline), reduce pomalidomide and /or MLN9708 at investigators discretion.
Grade 4		Discontinue teatment. Withdraw participant from study.
Herpes Zoster reactivation any grade	**Pomalidomide MLN9708**	Hold MLN9708 and pomalidomide until lesions are dry. Initiate antiviral therapy (maintain dose level).
Venous	**Pomalidomide/**	Hold therapy and start full anticoagulation as

Thrombosis/Embolism ≥ Grade 3	**MLN9708**	appropriate; restart at investigator's discretion (maintain dose level).
Other Pomalidomide or MLN9708 related non-hematologic toxicity Grade ≥ 3 **Grade 4 related non-hematologic toxicity**	**Pomalidomide MLN9708**	Determine attribution of toxicity and hold both pomalidomide and MLN9708. Follow at least weekly. If toxicity resolves to ≤ grade 1 or baseline, resume therapy with one level dose reduction. Consider permanent discontinuation of therapy. Exceptions may be made following discussion with the Lead Principal Investigator for patients that are experiencing clinical benefit.

Once MLN9708 or pomalidomide is reduced for any toxicity, the dose may not be re-escalated.

7.9.2 Dexamethasone Dose Modification Guidelines*

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1–2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone and do not resume
Cardiovascular	Edema >Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration > Grade 2 (interfering with	Hold dexamethasone until symptoms resolve. Restart with one dose level

	function +/- interfering with activities of daily living)	reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone dose by one dose level. If weakness persists despite above measures, decrease dose by one dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

7.10 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm3.
- Platelet count must be ≥ 75,000/mm^3 or > =50,000/mm^3 for patients with baseline platelets ≥50,000/mm^3 but <75,000/mm^3.
- All other nonhematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re evaluate. The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the Principal Investigator.

7.11 Concomitant Medications

7.11.1 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study. A drug/drug interaction (DDI) with a strong inhibitor would increase MLN2238 (metabolite of MLN9708) exposure.

- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient to use. A DDI with a strong inducer would decrease MLN2238 (metabolite of MLN9708) exposure.

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

Please refer to a complete listing of prohibited medications, strong CYP3A and CYP1A2 inhibitors that can be found via the following link: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

The dietary supplements St John's wort and Ginkgo biloba are not permitted.

The following procedures are prohibited during the study:

- Any antineoplastic treatment with activity against MM except for drugs in this treatment regimen.
- Radiation therapy (the requirement for local radiation therapy generally indicates disease progression).
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study drug dosing.
- Adjuvant hormone therapy for breast or prostate cancer.

7.11.2 Permitted/Recommended Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator and is strongly recommended.

- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. Intravenous fluids should be given to prevent volume depletion.

- Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.

- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.

- Concomitant treatment with bisphosphonates will be permitted, as appropriate.

- Patients who experience worsening neuropathy from baseline may be observed for recovery, and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.

- Supportive measures consistent with optimal patient care may be given throughout the study.

- Fluid deficits should be corrected before and throughout treatment.

7.11.3 Required/Recommended Concomitant Therapy

- Pomalidomide increases the risk of thromboembolism. Anti-coagulation prophylaxis is required after an assessment of each patient's underlying risk factors, unless there is an excess risk of bleeding.

- Antiviral therapy such as acyclovir is recommended for herpes prophylaxis.

- For the Phase I portion of the study, growth factors, granulocyte colony stimulating factor [G-CSF], may be given prophylactically for at least two days on days 21 – 26 during or beyond cycle 2. For the Phase II portion of the study, G-CSF may be given prophylactically for at least two days on days 21-26 during or beyond cycle 1. It will be administered subcutaneously at a dose of 5ug/kg or per institutional standard practice dosing either daily or every other day for a minimum of two doses. If patients experience neutropenia or dosing delays, we would recommend consideration of growth factor in subsequent cycles.

- Allopurinol is recommended for patients with high tumor burden due to the possibility of tumor lysis syndrome.

7.11.4 Pregnancy

It is not known what effects MLN9708 has on human pregnancy or development of the embryo or fetus. Pomalidomide can cause fetal harm when administered during pregnancy. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Females of child bearing potential* and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

A female of child bearing potential is any 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).

7.11.4.1 Females

Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control simultaneously (one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings or implants) or partner's vasectomy and one additional effective contraceptive method – male latex or synthetic condom, diaphragm or cervical cap. Contraception must begin 4 weeks prior to initiating treatment, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of pomalidomide or 90 days following discontinuation of MLN9708. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

Females of reproductive potential must have 2 negative pregnancy tests before initiating therapy. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing pomalidmide and MLN9708. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. Treatment with pomalidomide and MLN9708 must be discontinued during this evaluation. 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.

7.11.4.2 Males

Pomalidomide is present in the semen of males who take pomalidomide. The effects of MLN9708 are unknown. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking pomalidomide or MLN9708 and for up to 28 days after discontinuing pomalidomide or 90 days after discomtinuation of MLN9708, even if they have undergone a successful vasectomy. Male patients taking pomalidmide or MLN9708 must not donate sperm. 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.

7.12 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with MLN9708 treatment. Management guidelines regarding these events are outlined below. Further details of management of MLN9708 AEs are described the MLN9708 IB.

Prophylaxis Against Risk of Infection

If lymphopenia is noted, patients may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir or valacyclovir may be initiated as clinically indicated. Other antivirals are also acceptable.

Nausea and/or Vomiting

Standard anti-emetics, including 5-HT3 antagonists, are recommended for emesis occurring upon treatment initiation; prophylactic anti-emetics may also be considered. Dexamethasone should not be administered as an anti-emetic. Fluid deficits should be corrected before initiation of study drug and during treatment.

Diarrhea

Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficits should be corrected before initiation of treatment and during treatment. Prophylactic antidiarrheals are not generally recommended.

Erythematous Rash With or Without Pruritus

As with VELCADE, rash with or without pruritus has been reported with MLN9708, primarily at the higher doses tested. The rash may range from some erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body or more generalized, has been transient and has resolved either spontaneously or with standard symptomatic measures such as oral or topical steroids and/or antihistamines. Prophylactic measures should also be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone $\leq$ 10 mg per day or equivalent) is permitted. A rare risk is Stevens-Johnson Syndrome, a severe, life-threatening or deadly rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice.

Thrombocytopenia

Thrombocytopenia has been reported to date primarily at the higher doses tested. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Thrombocytopenia nadirs commonly recover without intervention by the beginning of the next scheduled cycle. MLN9708 administration should be modified as noted as per dose modification recommendations when thrombocytopenia occurs. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

Neutropenia has been reported with MLN9708 and pomalidomide. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable with G-CSF Neutropenic nadirs commonly recover without intervention by the beginning of the next scheduled cycle or with a short delay in treatment. MLN9708 administration should be modified when neutropenia occurs, as noted in the dose modification recommendations. Given that MLN9708 will be administered in combination with pomalidomide, with overlapping toxicity of neutropenia, G-CSF will be used prophylactically in this protocol.

Fluid Deficits

Dehydration should be avoided because MLN9708 may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported with MLN9708. Fluid deficits should be corrected before initiation of study drug and during treatment and as needed during therapy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) induced prevalence of nephrotoxicity is relatively low; however, given the wide use of these agents many persons are at risk, including for example, patients with cardio-renal disease, dehydration, and the aging kidney. NSAIDs should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function. Until further information is available, intake of NSAIDs while on this protocol should be avoided.

Hypotension

Symptomatic hypotension and orthostatic hypotension have been reported with MLN9708. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome (PRES) has been reported with MLN9708. While this case ultimately resolved, PRES has also been reported rarely with another proteasome inhibitor, Velcade. PRES is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Prompt diagnosis and initiation of antihypertensive and anticonvulsant therapy are important to prevent irreversible end-organ damage.

Anticoagulation Consideration

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

Consideration should be given to the requirement of aspirin (81 or 325 mg) or some other form of prophylaxis as deemed appropriate. Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

8. STUDY DRUG

8.1 Packaging and Labeling

8.1.1 MLN9708

The study drug MLN9708 capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

MLN9708 capsules should be stored unopened at 2°C to 8°C (36°F-46°F). The capsules are individually packaged in cold form foil-foil blisters in a child-resistant package. The 0.5-, 2.3-, 3.0-, and 4.0 mg capsules are supplied as a 1 x 3 blister card in a child-resistant cardboard wallet.

8.1.2 Pomalidomide

Pomalidomide capsules will be provided by Celgene Corporation as 1.0, 2.0, 3.0 and 4.0 mg capsules for oral administration.

Pomalidomide (POMALYST®) will be provided to research patients 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 patients enrolled into this trial, and all research patients 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.

Pomalidomide investigational supplies are dispensed to the patients in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: Caution: New drug - Limited by Federal law to investigational use. 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.

8.2 Storage, Handling, and Accountability

MLN9708 and pomalidomide are anticancer drugs and as with other potentially toxic compounds caution should be exercised when handling MLN9708 and pomalidomide capsules.

8.2.1 MLN9708

Upon receipt at the investigative site, MLN9708 should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, MLN9708 capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because MLN9708 is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of MLN9708, including that MLN9708 is to be taken as intact capsules.

Investigational MLN9708 (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

8.2.2 Pomalidomide

Care should be exercised in handling of pomalidomide. Pomalidomide capsules should not be opened or crushed. If powder from pomalidomide contacts the skin, wash the skin immediately and thoroughly with soap and water. If pomalidomide contacts the mucous membranes, flush thoroughly with water.

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

Storage
At the study site, all pomalidomide 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.

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

Only enough pomalidomide capsules for 1 cycle of therapy may be provided to the patient

each cycle.

9. STUDY COMPLIANCE

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

9.1 Treatment Assignment

Patients will be assigned at the time of enrollment (per section 6.0) to a given dose level during the phase I portion of the study or to the recommended phase II dose as determined during the phase I portion of the study.

9.2 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Lack of Protocol adherence
- Lost to follow-up
- Progressive disease
- Study termination

At the time of withdrawal, all study procedures outlined for the End of Treatment visit should be completed. The primary reason for patient's withdrawal from the study will be recorded in the source documents and CRF.

The Lead Principal Investigator or designee must be notified within 24 hours if a patient is withdrawn from the study by the Data Coordinating Center or designee.

If the reason for withdrawal is the occurrence of an AE, the Investigator will follow the patient until such events resolve, stabilize, and according to the Investigator's judgment, there is no need of further follow up.

10. STATISTICAL AND QUANTITATIVE ANALYSES

10.1 Statistical Methods

10.1.1 Determination of Sample Size

Phase I: The phase I study will follow a 3+3 design, to evaluate toxicities associated with MLN9708 when given in combination with pomalidomide and dexamethasone. Two doses of MLN9708 (dose level -1 and dose level 1: 3 mg; dose level 2: 4 mg) will be tested in up to three possible dose levels; there will be no dose reductions below the 3mg dose of MLN9708. In the phase I portion of this study, the total sample size will depend on the number of dose levels evaluated to determine the maximum tolerated dose (MTD). While the phase I study is expected to enroll and treat 9 patients (3 patients treated on dose level 1 and 6 additional patients treated at dose level 2 -assuming the 4mg dose is well tolerated), a maximum of 18 patients could be treated (6 patients per dose level). The highest dose level that produces ≤1/6 DLTs in cycle 1 will be the MTD. (See section 7.4 for dose expansion/escalation rules.) The recommended phase II dose (RP2D) of MLN9708 and pomalidomide will generally be the MTD, but it may be less than the MTD based on a review of available data/cumulative toxicities from phase I.

Phase II: For this trial, where MLN9708 will be added to pomalidomide and dexamethasone, patients with prior exposure to either of these agents would not be excluded, unlike the patients treated on the randomized phase III study of comparing pomalidomide plus dexamethasone, to high-dose dexamethasone alone. As many patients (>50%) are likely to have been previously treated with one or both of these agents we consider a response rate of 30% sufficient efficacy to justify further development.[26] In addition, the estimation of response in this refractory/high-risk population is of equal importance. Given this, the phase II portion of the trial, will use a Gehan two stage design (Gehan, 1961). The phase II trial is expected to enroll a minimum of 9 and a maximum of 25 patients. The six patients treated at the RP2D in the phase I portion of the study will count toward the 25 patients required. Given this, we expect to enroll only 19 new patients on the phase II trial. The sample size is based on the desire to estimate the response rate with at most 10% standard error, and early stopping if the combination is unexpectedly ineffective. The primary endpoint is confirmed tumor response (sCR/CR/VGPR or PR).

At stage 1, 9 patients will be entered on the study. If 0 responses are seen in the first 9 patients treated, the study will be terminated and the true regimen response will be declared ≤30%. If at least 1 patient responds, the trial will continue to the second stage. Because patients treated during the phase I portion of the trial at the dose selected for the phase II trial will be counted

(n=6), only 3 additional patients will be enrolled at stage 1. Under this design if the study regimen is >30% effective, there would be ~95.6% chance of at least one success. At stage 2, 16 additional patients will be entered. This accrual provides for estimation of the response rate with no more than 10% standard error.

10.1.2 Populations for Analysis

Phase I (Evaluable for Toxicity): Patients will be considered evaluable for toxicity if they receive any study drug. Patients will be considered evaluable for dose limiting toxicity if they receive at least 75% of both Pomalidomide and MLN9708 and are followed for the full 28 days during cycle 1 or experience a DLT. All patients who are not evaluable for dose limiting toxicity will be replaced.

Phase II (Evaluable for Toxicity): Patients will be considered evaluable for toxicity if they receive any study drug. Patients in Phase II will not be replaced based on toxicity.

Phase I and II (Evaluable for Response): For the phase II portion, as part of the primary analysis, patients will be considered evaluable for response if they are eligible, have baseline disease assessments, and receive any protocol treatment. As part of a secondary analysis, patients will be considered evaluable for response if they have baseline disease assessments, receive at least 75% of both Pomalidomide and MLN9708 during the first cycle of therapy and have had their disease re-evaluated. Patients will have their response classified according to the IMWG response criteria. All patients in phase II and those treated at the RP2D in phase I, who are not evaluable for response will be replaced.

10.1.3 Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including age, gender, medical history, and prior therapy, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median (range) will be provided. For categorical variables, patient counts and percentages will be provided.

10.1.4 Efficacy Analysis

A primary activity endpoint is not defined for the Phase I study. The primary activity endpoint for the Phase II study is response rate. Response rates (overall, clinical benefit) and depth of response will be calculated as the percent of evaluable patients that have confirmed sCR/CR/VGPR or PR (overall) or sCR/CR/VGPR/PR/MR or SD (clinical benefit), exact 95% confidence intervals will be calculated for these estimates. Response rates will also be evaluated

based on number and type of prior therapy(ies). Response defined as per modified IMWG criteria. Time to response, duration of response, and survival (overall and progression-free) will be estimated using the product-limit method of Kaplan and Meier.

10.1.5 Safety Analysis and Stopping Rules for Excessive Toxicity

Toxicity information recorded will include the type, severity, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity.

The following table will be consulted as relevant toxicities are encountered. The early stopping rule for safety/toxicity will be assessed for each patient after cycle 1. The expected rate of unacceptable toxicity should not be ≥33%. Note: Unacceptable toxicity is defined in section 7.3 of the protocol. See the table below for detailed early stopping rules. These rules are in addition to the quarterly review of all toxicities submitted to the COH DSMC. Patients with ongoing toxicity (cycle 1 toxicity persisting beyond day +28) will be followed until resolution or stability. If more than the specified number of patients has significant treatment related toxicities, patient accrual will be halted and a full review of the data by the Data Safety Monitoring Committee (DSMC) will be mandated. Patient accrual will not resume until approved by the DSMC to do so.

# of patients treated at phase II dose	# of patients with unacceptable toxicity to halt enrollment[1]	Given the following toxicity rates, cumulative probability of early stopping:		
		15%	33%	45%
6	2	0.22	0.64	0.84
12	4	0.24	0.73	0.92
18	6	0.25	0.78	0.95
[1]: For each unacceptable toxicity, halt enrollment and evaluate if the cumulative # of patients reaches or exceeds the specified limits.				

We recognize that these stopping rules represent the overall stoping rules including the patient evaluated on a given dose during the Phase I portion. As such, these rules represent the stopping probabilities of a dose with the above toxicity rates, including stopping during the phase I dose finding portion. Once the MTD has been selected, and additional patients are accrued (presumably at the MTD), the probability of early stopping is less (e.g. 26% of chance of early stopping at 12 patients if the true probability of unacceptable toxicity is 33%, and a 44% chance

of early stopping at 18 patients in that scenario). This represents the probability of early stopping conditional on passing the criteria for MTD selection (0 or 1 out of 6).

11. DATA AND SAFETY MONITORING

11.1 Definition of Risk Level

This is a Risk Level 4 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx. City of Hope is sponsor of this IND.

11.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Monitoring Team (PMT) consisting of the PI, Collaborating Investigator, CRC/protocol nurse, statistician and COH Data Coordinating Center staff is responsible for monitoring the data and safety of this study, including implementation of the stopping rules for safety and efficacy.

Beginning with the enrollment of the first patient, the PMT will meet weekly or bi-weekly via teleconference for patient and protocol management issues.

This study will utilize the Phase I tracking log to monitor data and safety for dose escalation, recording doses administered, and resultant adverse events**.** The tracking log will contain dose levels administered, DLT-defining adverse events, and documentation that the data from a dose level is complete before dose escalation. Those data and safety elements will be reported to the COH DSMC as applicable within the PMT report, which will be submitted quarterly from the anniversary date of activation, as noted in Table 1 below.

Table 1: City of Hope PMT Reporting Timelines for the DSMC

Risk Level	Phase	Standard Reporting Requirement
RL 1, RL2, and Compassionate Use Studies	No reports required	
3	I	Every 3 months from activation date, as indicated in MIDAS

3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS
4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

During periods of active protocol enrollment, quarterly reports of all protocol activity will be submitted to the DSMC and will include:

1) The number of patients screened, enrolled and treated.
2) Cohort status updates.
3) List of AEs (including SAEs/UPs).
4) Protocol deviations.

Annual continuation reports will be made to the IRB, Cancer Protocol Review and Monitoring Committee (CPRMC) at COH and to the Food and Drug Administration (FDA). These reports will be made available to participating institutions (as requested).

11.3 Definitions

11.3.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation. For serious pre-treatment events, the investigator must determine both the intensity of the event and the relationship of the event to the study procedures.

11.3.2 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has

increased in severity or frequency since the administration of study drug. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

11.3.3 Unexpected Adverse Event [21 CFR 312.32 (a)]

An AE is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the AE.

11.3.4 Expected Adverse Event

Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the AE.

11.3.5 Serious Adverse Event (SAE) [21 CFR 312.32] is defined as any expected or unexpected AE that, at any dose, results in any of the following outcomes:

- Results in **death**.
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (except scheduled hospitalizations for non-acute, unrelated cause such as an elective surgery);

- Results in **persistent or significant disability or incapacity** (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect.**
- **Secondary malignancy**, or
- Any other **AE that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above** (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

11.3.6 Unanticipated problem – Any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action

criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

AEs which are serious must be reported to Celgene and Millennium Pharmacovigilance (or designee) from the date the participant signs Informed Consent through 30 days after administration of the last dost of pomalidomide or MLN9708. Any SAE that occurs at any time after completion of MLN9708/pomalidmide treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium/Celgene Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium/Celgene Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should 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). Each Investigator is also responsible for reviewing their institutional guidelines and reporting locally based on those guidelines (i.e., unanticipated problems).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

11.2 Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting

electronically in iRIS (http://iris.coh.org). Participating institutions will submit to the COH Data Coordinating Center.

Serious Adverse Events - **All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).**

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the continuation reports and PMT reports (see Table 2 below).

Table 2: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timelines to DSMC for AE/SAEs
Investigator Initiated Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

An event determined by the IRB of record to be an Unanticipated Problem (UP) will be communicated to the Investigator and COH DSMC through the COH IRB Operations Director. The DSMC will review the case and make a determination as to whether the

study will be suspended, terminated, amended, or allowed to continue without amendment.

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

The Sponsor-Investigator and the COH Data Coordinating Center must be notified by phone, fax or of the occurrence of any SAE or Unanticipated Problem within 24 hours of the investigator, designee, or site personnel's knowledge of the event. To report an SAE/UP, the site representative must complete the Notification of Unanticipated Problem/Serious Adverse Event/Pregnancy Form (attached as an Appendix 15.3) and MEDWATCH 3500A form , then fax or scan/email the forms (as noted below) using secure email (#secure# in subject line of email):

City of Hope Data Coordinating Center

Fax Number: 626 301-8422

COH DCC email: dcc@coh.org (always use #secure# in subject line)

Telephone reports must be followed by a written report within 24 hours. Follow-up reports must be submitted in a timely fasion as additional information becomes available.

The Investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local institutional regulations, of all SAEs. The Sponsor-Investigator, the City of Hope Data Coordinating Center and/or

Millennium/Celgene may request additional source documentation pertaining to the SAE. If a patient is permanently withdrwawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report as well as the Study Discontinuation case report form.

The investigator is responsible for reporting serious adverse events that occur from the signing of the study specific consent through the duration of the post-therapy adverse event collection period to the City of Hope Data Coordinating Center (see section above for submission guidelines), as indicated when using MLN9708 and Pomalidomide within 24 hours of becoming aware of the SAE. Notification can be made via phone or telefacsimile using the MEDWATCH 3500A form. The Sponsor-Investigator, through the COH DCC, will report to Millennium and Celgene within 24 hours.

SAE and Pregnancy Reporting Contact Information - Millennium

Millennium Pharmacovigilance Designee, PPDI, PVG:

The COH DCC will fax the MEDWATCH 3500A form (Millennium Pregnancy Form attached as Appendix 15.4.4 when reporting pregnancy) within 24 hours to:

Cognizant

Contact Information:

Fax Number: 1-800-963-6290

Email: TakedaOncoCases@cognizant.com

SAE and Pregnancy Reporting Contact Information – Celgene

The Sponsor-Investigator through the COH DCC will inform Celgene in writing using the MEDWATCH 3500A of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (PO-MM-PI-0062) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to

Celgene should be attached to the SAE and retained with the patient records.

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115/Email: drugsafety@celgene.com

ADDITIONAL REPORTING REQUIREMENTS

Serious Adverse Events meeting the requirements for expedited reporting to the FDA, as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500Afor Mandatory Reporting which can be found at:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

The City of Hope Data Coordinating Center will work with participating institutions to obtain the required serious adverse event report forms including any follow up information.

The IND is held by COH, and the Sponsor-Investigator or designee, including the City of Hope Data Coordinating Center will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI and COH DCC with the preparation of the report and submit the report to the FDA in accordance with the following:

- any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)];
- any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

Sponsor-investigator or designee must also provide Millennium/Celgene Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study or study drug(s), including, but not limited to, telephone conversation logs within 24 hours of such communication.

Adverse Events of Special Interest (AESIs) are a subset of AEs that are to be reported to Millennium on a quarterly basis by the sponsor-investigator. These adverse events will be captured using Medidata RAVE, the electronic data capture system used for data collection for this trial as part of routine data collection. A report will be generated and submitted to Millennium on a quarterly basis by the City of Hope Data Coordinating Center. Millennium will provide the current list of AESIs and updates to the list will be distributed to the sponsor-investigator as appropriate.

The highest grade of non-Serious Adverse Events of Special Interest (AESIs) observed in patients will be reported. AESIs are defined as:

1. Neuropathy
    - Neuropathy peripheral
    - Peripheral sensory neuropathy
    - Polyneuropathy
    - Paraesthesia
    - Hyperaesthesia
    - Burning sensation
    - Oral pain
    - Paraesthesia oral
    - Muscle spasms
    - Muscular weakness
2. Hematologic Toxicities
3. Rash
    - Rash

- Rash macular
- Rash maculo-papular
- Rash generalized
- Rash pruritic
- Pruritus
- Rash erythematous
- Erythema
- Rash popular
- Skin exfoliation
- Exfoliative rash

4. Respiratory Complaints
    - Pneumonia
    - Pneumonitis
5. Renal toxicity
    - Blood creatinine increased
    - Blood creatinine abnormal
    - Blood urea decreased
    - Renal failure acute
    - Renal failure
    - Renal impairment
6. Hypotension
    - Orthostatic hypotension
    - Presyncope
    - Syncope
7. New Primary Malignancy
    - For all myeloma studies, new primary malignancies must be reported for at least two years from the Clinical Trial patient's first dose of MLN9708.

Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on MLN9708 or pomalidomide, or within 90 days of the patient's last dose of therapy), are considered immediately reportable events. MLN9708 and pomalidomide are to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported. The investigator must notify the sponsor-investigator and the COH DCC immediately by phone and by completing and faxing the Notification of Unanticipated Problem/Serious Adverse Event/Pregnancy Form (attached as an Appendix 15.3). The sponsor-investigator through the COH DCC will be responsible for notifying Millennnium Pharmacovigilence(through Millennium Pregnancy Form attached as Appendix 15.4.4)//Celgene Drug Safety.

The female patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female patient until completion of the pregnancy, and must notify the sponsor-investigator and the COH DCC immediately phone and by completing by completing and faxing the Notification of Unanticipated Problem/Serious Adverse Event/Pregnancy Form (attached as an Appendix 15.3). The sponsor-investigator through the COH DCC will be responsible for notifying Millennnium Pharmacovigilence(through Millennium Pregnancy Form attached as Appendix 15.4.4)//Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE. The investigator must notify the sponsor-investigator and the COH DCC immediately phone and by completing by completing and faxing the Notification of Unanticipated Problem/Serious Adverse Event/Pregnancy Form (attached as an Appendix 15.3). The sponsor-investigator through the COH DCC will be responsible for

notifying Millennnium Pharmacovigilence(through Millennium Pregnancy Form attached as Appendix 15.4.4)//Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to MLN9708 and pomalidomide should also be reported. The investigator must notify the sponsor-investigator and the COH DCC immediately phone and by completing by completing and faxing the Notification of Unanticipated Problem/Serious Adverse Event/Pregnancy Form (attached as an Appendix 15.3). The sponsor-investigator through the COH DCC will be responsible for notifying Millennnium Pharmacovigilence(through Millennium Pregnancy Form attached as Appendix 15.4.4)//Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

Male Patients

If a female partner of a male patient taking MLN9708 or pomalidomide becomes pregnant, the male patient should notify the Investigator immediately, and the pregnant female partner should be advised to call their healthcare provider immediately.

12. ADMINISTRATIVE REQUIREMENTS

12.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.2 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will be conducted only at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator. Millennium/Celgene requests that informed consent documents be reviewed by Millennium/Celgene or designee prior to IRB submission.

This study must have the approval of a properly constituted IRB or IEC. Before the investigational drug is shipped to the Site Investigator, the Site Investigator or designee will provide the COH DCC with a copy of the IRB/IEC approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The COH DCC will be responsible for obtaining annual IRB/IEC reapproval throughout the duration of the study. Copies of the Investigator's annual report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be submitted to the COH DCC.

The Site Investigator is also responsible for notifying their IRB/IEC of any significant adverse events that are serious, unanticipated and/or unexpected.

The COH DCC will provide study sites with any investigational new drug (IND) safety reports generated, changes to the Investigator's Brochure IB, and any safety updates. The Site Investigator is responsible for immediately notifying their IRB/IEC of any such updates.

The Lead Principal Investigator along with the COH DCC will initiate in writing any substantive changes to this protocol as a protocol amendment. The amendment will be submitted to the IRB/IEC, together with a revised informed consent, if applicable. Written documentation of IRB/IEC approval must be received before the amendment is implemented. Upon completion of the trial, the Site Investigator must provide the IRB/IEC with a summary of the trial's outcome.

12.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

The City of Hope Data Coordinating Center will provide the Site Investigator with a sample consent form. Local and/or institutional requirements may require disclosure of additional information in the informed consent. Any changes to the consent form must be submitted to the COH DCC for approval, prior to submission to the IRB/IEC. The IRB/IEC will review the consenf form for approval. A copy of the approved form must be submitted to the COH DCC prior to initiation of the study.

Before implementing any study procedure, informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the patient or the patient's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the patient or patient's legally authorized representative. The original signed consent must be maintained by the Site Investigator and available for inspection by the COH DCC, its designated representatives, or regulatory authority at any time.

12.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. If requested, the investigator will grant monitor(s) and auditor(s) from City of Hope, Millennium/Celgene or its designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

The investigator/institution will permit direct access to source data and documents by the COH DCC staff, its designees, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

12.5 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium/Celgene and written IRB approval/favorable opinion from City of Hope (as the sponsor) prior to implementation, except when the

modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to Millennium/Celgene and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

12.6 Study Documentation and Archives

12.6.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Site Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

12.6.2 Case Report Form Completion

All data will be collecting using COH data collection forms via an electronic data capture system, Medidata RAVE. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Site Investigator or designee in a timely fashion.

All data will be submitted as follows:

- **Eligibilty Checklist:** the participating institutions at the registering site will have completed and faxed this form at the time of registration.
- **On-Study/Baseline Forms:** completed on-study forms are due within two weeks of registration.
- **Treatment Forms (Cycle Forms):** completed forms are due within 2 weeks of completion of a cycle (unless needed sooner for DLT assessment during Phase I). The City of Hope Data Coordinating center will communicate with site staff if forms are needed sooner.

- **Adverse Event Collection:** completed adverse events are due within two weeks of a cycle (unless needed sooner for DLT assessment during Phase I). The City of Hope Data Cooridnating center will communicate with site staff if forms are needed sooner.

- **Response/Off Treatment/Off Study/Follow-Up:** forms will be completed each time a patient is evaluated for response, comes off treatment, new follow-up information is obtained or comes off study.

12.7 Archival of Records

According to 21 CFR 312.62I, the Site Investigators shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the Site Investigator shall retain these records until 2 years after the investigation is discontinued and the FDA or applicable regulatory authorities are notified.

The Site Investigator must retain protocols, amendments, IRB/IEC approvals, copies of the Form FDA1572, signed and dated consent forms, medical records, case report forms, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

12.8 Study Monitoring and Data Collection

Following initiation of the study site, remote monitoring will be completed by the COH DCC. The Site Investigator will allocate sufficient time for the designated site staff to submit source documentation as required to complete remote monitoring.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate , complete, and verificable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol, amendment(s), ICH GCP, FDA CFR, and any other applicable regulatory requirements.

The COH DCC will submit a prepare a written report after each remote monitoring timepoint or trial related communication. Reports shall include a summary of what the monitor reviewed

remotely and significant findings, deviations and deficiencies, conclusions, actions taken or to be taken to ensure site compliance.

City of Hope's Data Coordinating Center, regulatory authorities, the IRB and/or Millennium/Celgene may request access to all source documents, data capture records, and other study documentation for on-site audit, inspection and remote monitoring. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

12.9 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records for each respective drug/company, MLN9708 for Millennium and pomalidomide for Celgene indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium/Celgene or a designee or disposal of the drug (if applicable and if approved by Millennium/Celgene) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers. Accountability records will need to be submitted to the COH DCC as requested.

12.10 MLN9708 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints, call MedComm Solutions at 877-674-3784 (877 MPI DRUG) (US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium.

12.11 Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Millennium/Celgene, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium/Celgene by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the drug

12.12 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s).

13. USE OF INFORMATION

All information regarding MLN9708 supplied by Millennium and pomalidomide by Celgene to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium/Celgene. It is understood that there is an obligation to provide Millennium/Celgene with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of MLN9708 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium/Celgene, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

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15. APPENDICES

15.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

15.2 Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140\text{–age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

15.3 NOTIFICATION OF UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT/PREGNANCY

City of Hope Data Coordinating Center
Department of Clinical Research Information Support

NOTIFICATION OF UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT/PREGNANCY
For Use by Participating Institutions Only

THIS FORM ALONG WITH A COPY OF THE MEDWATCH 3500A FORM MUST BE SUBMITTED TO THE DATA COORDINATING CENTER AT CITY OF HOPE WITHIN 24 HOURS OF KNOWLEDGE OF ONSET OF SERIOUS ADVERSE EVENT, UNANCTICIPATED PROBLEM OR KNOWLEDGE OF PREGNANCY (MEETING REPORTING CRITERIA DESCRIBED IN PROTOCOL). SCAN/EMAIL DOCUMENT TO DCC@COH.ORG (PLEASE USE #SECURE# IN SUBJECT LINE OF ANY CORRESPONDENCE)

COH IRB #12267 - Participating Site IRB # _____

Phase I/II trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma

Participating/Treating Institution: _____

Reporter: _____Phone #:_____

Email: _____

PATIENT INFORMATION Pt Study ID: _____

UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT/PREGNANCY INFORMATION

Serious Adverse Event/Unanticipated Problem: _____

Grade: _____ Was this a dose limiting toxicity? _____

Attribution to MLN9708 (Unrelated, Unlikely, Possible, Probable, or Definite): _____

Attribution to Pomalidome (Unrelated, Unlikely, Possible, Probable, or Definite): _____

Start Date of SAE/UP: ____/____/____

REPORTING INFORMATION
Has the event been reported to the following?

Via Fax to Data Coordinating Center (COH) __ No __ Yes Date: __ __ / __ __ / __ __
Phone: 626-256-4673x63968/Email: dcc@coh.org (use #secure# in subject line)

Participating Site Institutional IRB? __ No __ Yes Date: __ __ / __ __ / __ __

SCAN/EMAIL THIS FORM AND THE MEDWATCH 3500A FORM OR PREGNANCY FORM TO DCC@COH.ORG (USE #SECURE# IN SUBJECT LINE)

15.3.1 Millennium Pregnancy Reporting Form

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form

Report Type: ◯ Initial ◯ Follow-up | Date of Report: ___/___/_____ (DD MM Yr)

REPORTER INFORMATION: (Please forward if an alternative physician is more appropriate)

Reporter name: _____ Title: _____

Address: _____ Telephone No.: _____ Fax No. _____

City, State/Province: _____ Postal Code: _____ Country: _____

FATHER'S INFORMATION ❒ Father Unknown

Initials: _____ Date of Birth: ___/___/_____ (DD MM Yr) or Age: _____ years

Participating in an MPI clinical study? ❒ No ❒ Yes
If no, what company product was taken: _____
If yes, please provide: Study drug: _____ Protocol No: _____
Center No: _____ Patient No: _____

Medical / Familial / Social History
(i.e. Include chronic illnesses: specify, familial birth defects/genetic/chromosomal disorders; habitual exposure: specify, alcohol/tobacco; drug exposure: specify, substance abuse and medication use. Please include drug treatment prior to or around the time of conception and/or during pregnancy)

Race: _____
Occupation: _____
Number of children: _____

MOTHER'S INFORMATION:

Initials: _____ Date of Birth: ___/___/_____ (DD MM Yr) or Age: _____ years

Participating in an MPI clinical study? ❒ No ❒ Yes
If no, what company product was taken: _____
If yes, please provide: Study drug: _____ Protocol No: _____
Center No: _____ Patient No: _____

Race: _____
Occupation: _____

Medical / Familial / Social History
(i.e. Include alcohol/tobacco and substance abuse; complications of past pregnancy, labor/delivery, fetus/baby; illnesses during this pregnancy; assisted conception: specify; other disorders including familial birth defects/genetic/chromosomal disorders; method of diagnosis consanguinity, etc.)

Number of previous pregnancies: Full term ____ Pre-term ____
Outcomes of previous pregnancies:
(Please indicate number of occurrences)

- Spontaneous abortion: _____
- Therapeutic abortion: _____
- Elective abortion: _____
- Other: _____
- Normal live birth: _____
- Children born with defects: _____
- Stillbirth: _____
- Outcome unknown: _____

MOTHER'S DRUG EXPOSURE INFORMATION

Please include medical prescriptions, vaccinations, medical devices, OTC products, pregnancy supplements (such as folic acid, multivitamins)

Product Name	Dosage	Route administered to patient	Date of first use (DD/MM/Yr)	Date of end treatment (DD/MM/Yr)	Indication	Contraindicated to pregnancy
			(__/__/____)	(__/__/____)		○Yes ○No ○Unk
			(__/__/____)	(__/__/____)		○Yes ○No ○Unk
			(__/__/____)	(__/__/____)		○Yes ○No ○Unk
			(__/__/____)	(__/__/____)		○Yes ○No ○Unk

CURRENT PREGNANCY INFORMATION

Period at exposure: _____ weeks Trimester (1) (2) (3)
Date of last menstrual period: ___/___/____ DD MM Yr ❒ Unknown

Pregnancy Status

○ Pregnancy Ongoing
Estimated date of delivery: ___/___/____ DD MM Yr
○ Live Birth
○ Stillbirth
○ Early Termination
- ○ Spontaneous abortion*
- ○ Therapeutic abortion*
- ○ Elective abortion*
- ○ Other*:_____

If box is checked, please note reason in "Additional Details" section below

Fetal/Neonatal Status

❒ Normal
❒ Birth defect (structural/chromosomal disorder)*
❒ Other (non-structural, premature birth, intrauterine death/stillbirth)*

If box is checked, please note details in "Additional details" section below

Additional Details:

Is there evidence of a defect from a prenatal test? ❒Yes ❒No

If yes, indicate which test(s) showed evidence of birth defect:

❒Ultrasound ❒Amniocentesis ❒Maternal Serum-Alpha-Fetoprotein
❒Chorionic Villi Sampling ❒Human Chorionic Gonadotropin ❒Other:_____

Please specify details of defect(s), disorder(s), and/or other anomaly(ies): _____

What are the defect(s) attributed to:_____

Infant Information:

Gestational weeks at birth or at termination: _____weeks

Date of birth or termination: ___/___/_____ (DD MM Yr)

If multiple births (e.g. twins), indicate number: ____

(Please complete separate form for each child)

Birth Order (1, 2, 3, etc.) _____

Breast-fed: ❒Yes ❒ No ❒ Unk

Method of delivery: ❒ Normal vaginal ❒ Caesarean section

❒ Other: _____

Sex: ❒ Male ❒ Female ❒ Unk

Length: _____ ❒ cm ❒ in

Weight: _____ ❒ g ❒ lbs

Head circumference: _____ ❒ cm ❒ in

Apgar score (0-10) at 1 minute: ____ ❒ Unk

Apgar score (0-10) at 5 minute: ____ ❒ Unk

Resuscitation required: ❒ Yes ❒ No ❒ Unk

Admission to intensive care required:

❒ Yes ❒ No ❒ Unk

Additional Notes:

_____

_____

_____

Please attach RELEVANT LABORATORY TESTS AND PROCEDURES (e.g. results of ultrasounds, amniocentesis, chorionic villi sampling, or miscellaneous testing as applicable). In the case of an abnormal evolution or outcome, please send copies of results of all relevant laboratory testing and procedures, including pathology results of products of conception and or autopsy reports if applicable. Please submit any additional relevant information on a separate sheet.

Investigator signature: _____ Date: ___/___/_____ (DD MM Yr)

Investigator Name: _____

e-Pregnancy Form (27 November 2013)

15.4 International Myeloma Working Group Response Criteria[27]

Response[1]	*IMWG criteria*
sCR	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
PR	• 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable,[3] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable Disease	• Not meeting criteria for CR, VGPR, PR or progressive disease
MR	• 25% but < 49% reduction of serum M protein *and* reduction in 24 hour urine M-

	protein by 50 to 89% which still exceeds 200 mg per 24 hr • In addition to the above criteria, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progressive disease	Increase of ≥ 25% from lowest response value in any one of the following: • Serum M-component (the absolute increase must be ≥ 0.5 g/dL) and/or • Urine M-component (the absolute increase must be ≥ 200 mg/24h) and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

1. Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473;

All response categories (CR, sCR, VGPR, and PD) require two consecutive assessments made at anytime before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ I gm/dl are sufficient to define response if starting M-component is ≥ 5 g/dl.

IMWG clarification for coding PD: Clarified that Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that 25% increase refers to M protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.

Appendix 15.5: City of Hope Data Coordinating Center Plan

City of Hope
Data Coordinating Center

City of Hope has been designated to oversee this trial as the Data Coordinating Center.

This document will serve as guidance as to the responsibilities of the Data Coordinating Center, as well as those of the participating sites.

City of Hope Data Coordinating Center Responsibilities

There are multiple responsibilities associated with serving in the capacity of a data coordinating center. The City of Hope Data Coordinating Center within the Division of Clinical Research Information Support (CRIS) has adequate resources and expertise to carry out these responsibilities:

1. Assist with the design and development of the initial protocol, subsequent amendments and template informed consent documents for use at each participating institution (as applicable).
2. Selecting appropriately qualified participating sites/principal investigators (as applicable).
3. Ascertaining each protocol is reviewed and approved by the IRB at the participating site prior to enrollment of subjects at that site.
4. Ensuring, if the study is federally funded, that each collaborating institution holds an applicable OHRP-approved Federal Wide Assurance (FWA).
5. Collecting and maintaining critical documents for the Trial Master File from participating investigators, e.g. resume/CV, medical license, certification of completion of training (as applicable), laboratory certifications and laboratory norms, financial disclosure forms, etc. Maintaining the file throughout the course of the trial.
6. Distribution of Regulatory Document Binder template to participating sites. A standardized regulatory document template will be sent out to the sites that includes filing of all essential documents for the trial. A standard table of contents and tabbed dividers will be provided to the participating site prior to the protocol initiation meeting.
7. Storing and/or managing data and data and safety monitoring.
8. Protecting the confidentiality of data received from participating sites in accordance with HIPAA.
9. Ensuring informed consent is obtained and documented from each subject in compliance with US regulations.
10. Maintaining documentation of all participating site IRB approvals for the protocol (including all subsequent amendments). Ensuring that participating sites are using the correct version of the protocol and consent document.
11. Assuring that all relevant IRB correspondence (continuing review and amendments) and study status changes are communicated to all participating sites in a timely basis.
12. Providing study specific training to the research personnel at the participating site, both at trial initiation and throughout the course of the trial (re-training as needed). Training will include but not be limited to: protocol background, inclusion/exclusion, registration procedures, treatment schema, dose modification guidelines, AE/SAE/UP reporting guidelines, investigator/staff responsibilities, subsequent amendment changes, etc. The training will be documented and will be continuous throughout the course of the trial.
13. Developing and providing protocol specific case report forms for each participating site (paper and/or EDC). Training of staff on case report forms at study initiation. Continued training of participating site staff if any new changes occur to case report forms during length of study.
14. Centrally registering/randomizing subjects and tracking subject enrollment for all subjects.
15. Tracking, reporting and maintaining documentation of all serious adverse events and

unanticipated problems and dissemination of the information to participating sites for submission to their local committees (as applicable).

16. Providing periodic updates to study sponsor and participating sites on subject enrollment, general study progress, and relevant scientific advances either via email distribution or via teleconferences.
17. Preparation and coordination of teleconferences on an as needed basis (may be weekly, bi-weekly, monthly or quarterly).
18. Primary liaison for participating sites with continuous and frequent communication via email and/or teleconference to ensure protocol is running smoothly, questions have been answered and documenting any issues. Addressing issues with study sponsor immediately.
19. Documenting receipt, shipment and storage of study specimens, drugs and/or devices (if applicable).
20. Conducting continuous quality assurance checks of database, as well as protocol adherence on periodic basis (remote).
21. Monitoring, on a periodic basis, either onsite or remotely of the participating sites to assess research study progress and compliance with the IRB approved protocol.
22. Securing compliance at participating sites that are not adhering to the current version of the research protocol and/or good clinical research practices.
23. Terminating the involvement, if necessary, of non-compliant investigators and reporting such action to the IRB.

Responsibilities of the Participating Site Principal Investigators

1. Signs Form FDA 1572 to acknowledge responsibilities as defined by the regulations.
2. Provides the Data Coordinating Center and/or sponsor with required information that either attest to the absence of financial interests or arrangements as described in the Code of Federal Regulations (21. CFR 54.4) and reported on form FDA 3454 that is completed by the sponsor or provides the sponsor a complete and accurate disclosure of financial interests and arrangements as described in the regulations (21. CFR 54.4) and reported on form FDA 3455 that is completed by the sponsor.
3. Supervises members of the research team that are qualified by their education and training to accept these responsibilities for study related activities not directly performed by the PI.
4. Ensures the safety and welfare of study subjects by being knowledgeable about ongoing study protocols and investigator articles.
5. Participates as appropriate in the hiring and training of individuals recruited as members of the research team.
6. Ensures that specific sponsor requirements of the PI are fulfilled as requested.
7. Meets with the data coordinating center's and/or sponsors' representative as appropriate to discuss planned and ongoing studies. Participates in regularly scheduled teleconferences to discuss site specific information, including but not limited to: patient status, data collection, adverse event reporting, etc.
8. Ensures the participating site completes required data collection in a timely fashion and/or as spelled out in protocol.
9. Meets with auditors (sponsor, FDA, etc.) at the conclusion of their audits to review

findings (if applicable).

Each participating sites individual investigator must adhere to the following requirements in order to participate in the conduct of clinical trials with City of Hope:

- To review the Belmont report, Ethical principles and Guidelines for the Protection of Human Subjects of Research, the U.S. Department of Health and Human Services (DHHS) and FDA regulations for the protection of human subjects at 45 CFR 46, 21 CFR50, 56, 312 and 812; the COH Federal Wide Assurance; and, the COH institutional policies and procedures for the protection of human subjects, located at the COH IRB website through the COH Intranet (a copy will be distributed to participating sites).
- To understand and accept the responsibility to comply with the standards and requirements stipulated in the above documents and in the study protocol and to protect the rights and welfare of human subjects involved in research.
- To comply with all other applicable federal, international, state and local laws, regulations, and policies that may provide additional protection for human subjects participating in research.
- To abide by all determinations of the COH IRB and to accept the final authority and decisions of the COH IRB, including but not limited to directives to terminate participation in designated research activities.
- To complete any educational training required by the COH (including by the Data Coordinating Center) and/or the COH IRB prior to initiating research.
- To report promptly to the COH DCC any proposed changes in the research. These must be reviewed and approved by the COH IRB.
- To NOT initiate changes in the research without prior COH IRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects.
- To report promptly to the COH PI any serious adverse events and/or unanticipated problems involving risks to subject or other as defined in the protocol and in accordance with COH policies and procedures.
- To obtain, document and maintain records of informed consent for each subject (when responsible for enrolling subjects) or each subject's legally authorized representative as required under DHHS and FDA regulations (or any other national procedural standards) as stipulated by the COH IRB.
- To acknowledge and agree to cooperate in the COH IRB's responsibility for initial and continuing reviews, record keeping and for internal and external research regulatory reporting requirements.
- To provide all information requested by the COH IRB in a timely fashion.
- To comply with all applicable FA regulations and fulfill all investigator responsibilities, including those described at 21 CFR 312 (IND regulations) and 812 (IDE regulations) when conducting research involving FDA regulated.
- To NOT enroll patients in research prior to review and approval by the COH IRB of the protocol and then subsequent review/approval at the participating site.
- To acknowledge that he/she is primarily responsible for safeguarding the rights and welfare of each research subject and that the subject's rights and welfare must take precedence over the goals and requirements of the research.
- To inform the COH/PI of important changes taken regarding membership status

of the participating site, investigators and other research staff personnel.

- To agree to communicate with the COH/PI in a timely manner.
- To agree that COH Data Coordinating Center staff will train current and/or new research personnel in protocol management and data collections.
- To agree to on-site and/or remote monitoring of all relevant data by COH Data Coordinating Center staff to assure compliance with protocol requirements and quality of the data. This will entail submission of all source documentation as requested by the COH DCC.
- To agree to remote review of source documentation as requested by the COH DCC staff.
- To participate in weekly teleconference calls (if applicable), to attend a quarterly group meeting (if applicable) and to attend an annual group meeting (if applicable), put together by the COH DCC.
- To submit all required data according to the protocol data submission schedule in a timely manner.
- To notify immediately the COH Data Coordinating Center upon notification of any external audit.

Responsibilities of the Participating Site Study Coordinator, Clinical Research Associate and/or Data Manager

1. Responsible for the sound conduct of the clinical trial, including but not limited to recruitment, screening, enrollment, treatment and follow-up of eligible subjects according to protocol requirements (e.g., subject follow-up, case report form completion in a timely fashion and reporting of adverse events, unanticipated problems).
2. Responsible for the maintenance of accurate and complete documentation including signed informed consent forms, source documentation, subject logs and study-related communications.
3. Responsible for the organizational management of all aspects of the trial including but not limited to overseeing timeliness in completing case report forms, reporting serious adverse events, managing caseload and managing study files.
4. Communicates all protocol-related issues/problems to the appropriate team members, including but not limited to questions regarding the conduct of the clinical trial, concern regarding possible Serious Adverse Events/Adverse Events/Unanticipated Problems (SAE/AE/UP) or subject compliance.
5. Develops organizational aids and checklists to facilitate patient recruitment and enrollment as well as the collection of complete and accurate study data.
6. Enrolls subjects in studies and manages their participation according to ethical, regulatory and protocol-specific requirements.
7. Tracks study enrollment.
8. Maintains study files for each study subject.
9. Maintains confidentiality of study subject's identity.
10. Participates in quality assurance activities (onsite and/or remote monitoring visits (including submission of de-identified source documents for remote monitoring), internal audits, sponsor audits, FDA audits.

Responsibilities of the Participating Site Regulatory Office and/or Designee

1. Responsible for protocol submission – initial protocol, informed consent and subsequent amendments.
2. Responsible for communication to the City of Hope Data Coordinating Center any questions related to the regulatory document submission process at their participating site.
3. Maintains the regulatory documentation and regulatory files for each applicable research project at the participating site.
4. Maintains the Regulatory Document Binder distributed by City of Hope's Data Coordinating Center locally. Ensures all documentation is up to date and filed in a timely fashion.
5. Submits institutional review board approvals for initial protocol submission as well as subsequent amendments to the City of Hope Data Coordinating Center.
6. If applicable, submits serious adverse events and/or unanticipated problems to their local regulatory committees, and sends appropriate copies to the Data Coordinating Center as spelled out in the protocol.

Required Documents to be Sent by Participating Site to the City of Hope Data Coordinating Center Prior to Site Activation

1. Participating site's Investigational Review Board (IRB) approval letter for initial protocol and consent form. All correspondence between the IRB and study site will be maintained at the study site in the regulatory binder.
2. Completed FDA1572 that includes all investigators who will participate in the clinical trial along with current signed and dated CV, copy of medical license for each investigator and Human Subjects Research and HIPAA training records and certifications.
    a. FDA1572 will be updated if changes/additions occur and a copy is to be sent to the Data Coordinating Center.
3. Financial Disclosure (FDA3455)
4. Delegation of Authority Form
    a. The delegation of authority form will be completed for all study personnel which will include the name, signature, and initials of all personnel signing Case Report Forms (CRFs), whether paper or in EDC.
5. Laboratory Certification
    a. The participating site will submit to the Data Coordinating Center all laboratory certifications from their institution as well as a copy of the normal ranges. A copy of the laboratory director's CV and medical license will also be submitted and kept on file.
6. Local IRB membership list
7. The Data Coordinating Center will complete a trial initiation checklist indicating all requirements for the study (including training of participating site) and the regulatory binder have been met prior to initiation/activation of the study at the participating site. A template for what is to be filed will be sent to each participating site. The site will maintain documents and send copies to the COH DCC.

Training:

COH Data Coordinating Center staff will be responsible for training research personnel at every participating site.

The COH Data Coordinating Center will also provide participating sites with a complete study roster that includes who to contact for any questions. This roster will be updated (as needed) throughout the course of the trial and distributed to sites.

Training will be conducted either on-site and/or at City of Hope or via teleconference. The following training will be completed at different time-points and/or as needed:

- Initial training of current research personnel during site initiation visit (via teleconference) on protocol management and data collection;
- Interim training on data collection on new case report forms as specified per protocol.
- Subsequent training of any new staff at participating sites.

Training components will include, but are not limited to protocol management, screening procedures, inclusion/exclusion criteria, randomization, study calendar, study procedures, investigational product, treatment plan, AE monitoring, dose modification, guidelines of SAE reporting, data submission schedule, eligibility checklist, informed consent process/documentation of informed consent (when applicable), and data collection training on all CRFs as required per protocol. This may include training on GCP guidelines to ensure compliance with all applicable rules and regulations. Training will also include review of all items needed in regulatory binder.

Data Collection Instruments:

1. Data for this trial will be collected using Medidata RAVE, City of Hope's electronic capture system.
2. Medidata RAVE is a web based, password protected system. It is fully compliant with global regulatory requirements, including 21CRF Part 11 compliant.
3. Participating staff will be required to complete an Account Activation Form (AAF) to obtain access to the Medidata RAVE system once IRB approval documentation is received.
4. Participating site staff will obtain log in information once they fax in the required AAF.
5. Once their AAF is received, the participating site staff will receive their individual login information.
6. The participating site staff (whether Principal Investigator or the staff collecting data at site) are required to take an eLearning Module within Medidata RAVE in order to obtain full access.
7. The participating site staff will receive training via teleconference by COH DCC staff to review eCRFs that are specific to this protocol. Continuous training will be offered to participating sites if any amendments affect changes to the eCRFs during the course of the trial.
8. The eCRFs within Medidata RAVE for this trial will have detailed instructions in the form of Help Text that provide instructions for completing each required field on each form.
9. Participating sites will be required to complete data collection within Medidata RAVE in a timely manner. Data will be expected to be completed within 2 weeks of each subject visit (or as per the study protocol – if needed sooner).
    a. The Data Coordinating Center will run monthly data expectation reports that will list any outstanding and overdue data.
    b. The Data Coordinating Center will send via email to the participating site a report monthly on any missing and/or overdue data forms. The participating site will be required to complete the missing and/or overdue data forms within 1 week of receipt of the report.
    c. If the data is not completed, the Data Coordinating Center will reach out to the participating site's Principal Investigator and site staff to ensure prompt completion of data.
    d. If any issues continue, the Data Coordinating Center will communicate with the sponsor with the hope to reach out to the participating sites in order to resolve any

issues.

10. Query reports will be generated on a monthly basis by the Data Coordinating Center.
    a. The Data Coordinating Center will send via email to the participating site a report monthly on any outstanding queries. The participating site will be required to complete the queries within 2 weeks of receipt of the report.
    b. If the queries have not been resolved in a timely manner, the Data Coordinating Center will reach out to the participating site's Principal Investigator and site staff to ensure prompt resolution of the queries and/or to discuss an extension on the due date.
    c. If the queries have not been completed in a timely manner, after discussion with the participating site's Principal Investigator and site staff, the Data Coordinating center will communicate with the sponsor with the hope of resolving any issues.

General Instructions for Completing Case Report Forms:

1. All data recorded on case report forms must be verifiable in the source documents maintained at the participating site. Source documents refer to all notes and reports contained in the subject's medical record.
2. When completing the initial eligibility checklist, participating sites are asked to print and use black ink.
3. The subject must not be identified by name on any study document. If a form such as a radiographic report or lab report is submitted, the subject's name must be obliterated and replaced with the subject's initials and registration number.
4. All dates must be verifiable by source documents.

Data Transmission:

1. Registration documents including eligibility checklist, demographics and corresponding source documentation will be sent to the Data Coordinating Center via fax or via City of Hope's Secure Mail system in order to ensure proper registration/randomization of each subject. As this information may contain identifiers (patient name, medical record number, date of birth, sex, race, ethnicity, zip code as required for internal registration), it is imperative that participating sites either fax this data OR use the Secure Mail route by typing #secure# in the email subject line. All participating sites will be sent out the City of Hope Secure Mail guide.
2. All subjects will be granted a protocol specific number (i.e., COH-001, CED-001) that will be assigned by the COH Data Coordinating Center.
3. Subsequent data collection then will take place via the web-based Medidata RAVE system. Participating sites will need to ensure they have the capability and access to a computer and the internet in order to complete data collection.
4. The Data Coordinating Center will at times need to contact the participating site to obtain information but will always refer to the protocol specific patient number.

Data Analysis:

Joycelynne M. Palmer, PhD, is responsible for data analysis. Details regarding the study design

and planned analyses can be found in section 10.0 of the protocol document.

Quality Assurance and Monitoring

1. The COH Data Coordinating staff will monitor each protocol conducted at participating sites to verify that the rights and well-being of human subjects are protected, the reported trial data are accurate, complete and verifiable from source documents, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s) with the GCP and with applicable regulatory requirements. The COH Data Coordinating Center will determine the appropriate extent and nature of the monitoring based on considerations such as study objective, purpose, design, complexity, blinding, size and endpoints of the trial. A trial may require onsite monitoring at the participating site or may be subject to remote monitoring. Remote monitoring will involve the participating site submitting de-identified source documentation to the COH Data Coordinating Center. Monitoring of that data will be done at COH by assuring the data captured onto CRFs is the same as the source documentation submitted.
2. Each IRB approved protocol will undergo monitoring evaluations by the COH Data Coordinating Center staff at varying time points as determined by the Division of Clinical Research Information Support. A trial may require onsite monitoring at the participating site or may be subject to remote monitoring. Remote monitoring will involve the participating site submitting de-identified source documentation to the COH Data Coordinating Center. Monitoring of that data will be done at COH by assuring the data captured onto CRFs is the same as the source documentation submitted.
3. In addition, COH research personnel from the Office of Clinical Research Auditing & Monitoring may audit protocol compliance at participating sites at intervals decided by the coordinating center and their office. Auditing is dependent upon the protocol's phase, accrual rate, IND status, and results of previous evaluations.
4. Participating sites will be informed of intended monitoring evaluations in a timely manner prior to the proposed visit and/or request for remote monitoring. When informed of an impending monitoring evaluation (either onsite or remotely) by COH staff, the participating site is required to prepare for the visit by including but not limited to: 1) providing adequate, private space for COH staff to conduct the evaluation, 2) having a contact person available for periodic questions, 3) providing the medical record or applicable documentation for each subject monitored on the day of the visit, 4) providing an organized collection of regulatory documents pertaining to the study, 5) flagging all source documents pertinent to data collections; and/or 6) de-identifying and submitting to the Data Coordinating Center all source documentation for subjects. Following any evaluation, an estimate of the next monitoring visit (whether onsite or remote) will be given to the participating site staff.
5. The DCC will compare the subject's records and other supporting documents with the data entered on the CRFs (paper or electronic).
6. The DCC will ensure:

    a. That the information recorded is complete and accurate.

b. That there are no omissions of specific data elements such as the administration to any subject of concomitant test articles or the development of an intercurrent illness.
c. Missing visits and examinations are noted in the records.
d. Subjects failing to complete the study and the reason for each failure are noted.
e. There is an original fully executed informed consent document in the subject record.
f. That study subjects initial (and subsequently thereafter, if applicable) met protocol mandated eligibility criteria for study participation.
g. That proper procedures were followed in obtaining informed consent from study subjects, as dictated by local regulatory guidelines (and may be subject to differences internationally).
h. That source data/documents and other trial records are accurate, complete, up-to-date and maintained.
i. That the participating site investigator provides all the required reports, notification, applications and submissions.
j. That these documents are accurate, completely, timely, legible and dated.

7. The Data Coordinating center will specifically verify that:

    a. The data required by the protocol are reported accurately on the CRF and are consistent with the source data/documents.
    b. Any dose and/or therapy modifications are well documented for each of the trial subjects.
    c. Adverse events, serious adverse events, concomitant medications and inter-current illnesses are reported in the CRFs in accordance with the protocol.
    d. That study procedures were performed in adherence to the protocol document and that deviations from written procedures were discovered and properly reported to the IRB.

8. The findings from the visit (whether on-site or remote) will be presented to the participating site in the form of a detailed, written report. This report will include a summary of what was reviewed and any findings concerning significant deficiencies and actions recommended for compliance. The report will be provided to appropriate participating site staff within 21 days of the evaluation completion. The participating site staff is required to provide a written response to the findings with the corrective plan of actions within 14 days upon receipt of the report (if corrective action is suggested).

Adverse Event/Serious Adverse Event/Unanticipated Problem Reporting

1. The Data Coordinating Center will be responsible for tracking, reporting and maintaining documentation of all serious adverse events and unanticipated problems and dissemination of the information to participating sites.
2. The Data Coordinating Center will be responsible for reporting of adverse event data to the study sponsor (as required).
3. The participating sites are responsible for reporting all adverse events as required in

Section 11.0 of the protocol, as well as to report per their local institutional guidelines.

4. The Data Coordinating Center will be responsible for distributing DSMC findings/updates/reviews to the participating sites for submission as per their local guidelines (if applicable).

CITY OF HOPE MEDICAL CENTER
1500 E. DUARTE ROAD
DUARTE, CA 91010

DEPARTMENT OF HEMATOLOGY AND HEMATOPOIETIC CELL TRANSPLANTATION

TITLE: Phase I/II Trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma

CITY OF HOPE PROTOCOL NUMBER/VERSION: **IRB # 12267** **VERSION: 07**

DATE(S)/ OF AMENDMENT(S)/REVISION(S):

COH Initial Protocol Dated 11/01/2013	Version: 00
COH Amendment 01 Protocol Dated 05/12/2014	Version: 01
COH Amendment 02 Protocol Dated 03/23/2015	Version: 02
COH Amendment 03 personnel update Dated 12/16/2015	Version: 03
COH Amendment 04 Protocol Dated 12/17/2015	Version: 04
COH Amendment 05 Protocol Dated 08/01/2016	Version: 05
COH Amendment 06 at Continuation Title Page Dated 11/09/2016	Version: 06
COH Amendment 07 Protocol Dated 03/07/2017	Version: 07

DISEASE SITE: **Multiple Myeloma**
STAGE (*If applicable*):
MODALITY(IES):
TYPE (*e.g., Pilot, Phase I, etc.*)**:** Phase I/II

PRINCIPAL INVESTIGATOR: Amrita Krishnan, M.D.
Designs, responsible for study conduct and data analysis

COLLABORATING INVESTIGATOR(S): Joycelynne M. Palmer, Ph.D (Biostatistics)

PARTICIPATING CLINICIANS: Haris Ali, M.D., Ahmed Aribi, M.D., Elizabeth Budde, M.D., Robert Chen, M.D., Stephen Forman, M.D., Myo Htut, M.D., Chatchada,Karanes, M.D., Samer Khaled, M.D., Auayporn Nademanee, M.D.**,** Nitya Nathwani, M.D., Ryotaro Nakamura, M.D., Margaret O'Donnell, M.D., Pablo Parker, M.D., Leslie Popplewell, M.D., Michael Rosenzweig, M.D., Tanya Siddiqi, M.D., David Snyder, M.D., Anthony Stein, M.D., Eileen Smith, M.D., Amandeep Salhotra, M.D. Ji-Lian Cai, M.D., Leonard Farol, M.D., Ricardo Spielberger, M.D., George Somlo, M.D., Alex Herrera, M.D., Matthew Mei, M.D., Haris Ali, M.D., Jasmine Zain, M.D., Ibrahim Aldoss, M.D., Monzr Al Malki M.D.,

CLINICAL STUDY PROTOCOL

MMRC-051

COH IRB # 12267

Title:	Phase I/II trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma
Phase:	Phase I/II
Protocol Version:	Version 6.0 03/03/2017
Study Sponsor:	City of Hope National Medical Center Investigator Initiated Trial
Principal Investigator:	Amrita Krishnan, MD Lead Principal Investigator City of Hope
Collaborating Investigators:	Prashant Kapoor, MD Mayo Clinic – Rochester Joseph Mikhael, MD Mayo Clinic - Arizona Ajay Nooka, MD, MPH Winship Cancer Institute of Emory University School of Medicine Jesus G. Berdeja, MD Sarah Cannon Research Institute Center
Study Statistician	Joycelynne M. Palmer, PhD City of Hope

This is an investigator-initiated study. The lead principal investigator, Amrita Krishnan, MD (who may also be referred to as the sponsor-investigator), is conducting the study and City of Hope National Medical Center, and is acting as the study sponsor. Therefore, the legal/ethical obligations of the lead principal investigator include both those of a sponsor and those of an investigator.

Phase I/II trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma

Protocol Acceptance Form – Amendment6.0 Protocol Dated 03-Mar-2017

I have read this protocol and agree to conduct the study as outlined herein, in accordance with Good Clinical Practices (GCPs) and the Declaration of Helsinki, and complying with the obligations and requirements of clinical Investigators and all other requirements listed in 21 CRF part 312.

_____	_____
Principal Investigator Signature	Date
_____	_____
Print Principal Investigator Name and Title	Date

PROTOCOL SUMMARY

Protocol Title:
Phase I/II trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma
Brief Protocol Title for the Lay Public (if applicable):
Phase I/II trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma
Study Phase:
Phase I/II
Participating Sites:
▪ City of Hope ▪ Mayo Clinic: Rochester and Arizona ▪ Winship Cancer Institute of Emory University School of Medicine ▪ Sarah Cannon Research Institute Center
Rationale for this Study:
Novel drugs are needed for the treatment of relapsed or relapsed refractory multiple myeloma. The combination of proteasome inhibitor (PI) and immunomodulating (IMiD) agents has produced significant responses. Many patients are exposed to these classes of drugs earlier in the course of therapy, for patients who relapse after agents such as the PI bortezomib and the IMiD lenalidomide, newer agents are now available or in development including pomalidomide and MLN9708. Pomalidomide is an IMiD that is active even in patients who are refractory to other IMiDS such as lenalidomide. MLN9708 is a PI that has shown activity in patients refractory to bortezomib. MLN9708 has shown activity in Phase I/II trials and pomalidomide and dexamethasone have shown activity in Phase I/II and III trials. Hence combining the two agents and including dexamethasone for synergy could potentially induce responses in this refractory patient population.
Objectives:
Phase I: **Primary:** 1) To determine the recommended phase II dose (RP2D) of MLN9708 when given in combination with pomalidomide and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma. **Secondary:** 2) To evaluate the safety of MLN9708 at each dose level when given as part of a three drug combination by assessing the following: - type, frequency, severity, attribution, time course and duration of adverse events - clinical laboratory tests at various points in the study

Phase II:

Primary:

1. To estimate the response rate and to evaluate the antitumor activity of the three drug combination: MLN9708 (at the RP2D), pomalidomide and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma.

Secondary:

At the RP2D, for the three drug combination:

2. To characterize and evaluate toxicities, including type, frequency, severity, attribution, time course and duration.

3. To obtain estimates of response duration, depth of response, clinical benefit response, and survival (overall and progression-free).

Study Design:

This study will be conducted as a multicenter phase I/II trial.

The phase I portion will follow a standard 3+3 dose escalation design, to evaluate toxicities associated with MLN9708 when given in combination with pomalidomide and dexamethasone. Two doses of MLN9708, 3mg and 4 mg, will be tested in up to three possible dose levels:

Schedule: Each cycle is 28 days			
Dose Level	**Pomalidomide**	**MLN9708**	**Dexamethasone***
-1	3mg daily on days 1-21	3 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22
1	4 mg daily on days 1 - 21	3 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22
2	4 mg daily on days 1 - 21	4 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22

*: Patients >75 years, at the time of trial registration, will receive a dexamethasone starting dose of 20mg on the same set schedule.

The RP2D identified in the phase I portion of the study will be brought forward for activity evaluation.

The phase II portion of this study will implement a Gehan two-stage design to estimate the response rate and to evaluate the activity of MLN9708 when given in combination with pomalidomide and dexamethasone (Gehan, 1961).

Endpoints:

Phase I:

The primary endpoint is toxicity. Toxicity will be graded according to the NCI-Common

Terminology Criteria for Adverse Events version 4.03. Dose limiting toxicity (DLT) is defined in section 7.3 of the protocol.

Phase II:

The primary endpoint is response rate (sCR/CR/VGPR and PR) and is based on the International Myeloma Working Group (IMWG) criteria.

Sample Size:

Phase I:

The phase I study will follow a 3+3 design, to evaluate toxicities associated with MLN9708 when given in combination with pomalidomide and dexamethasone. Two doses of MLN9708 (3 mg and 4 mg) will be tested in up to three possible dose levels. In the phase I portion of this study, the total sample size will depend on the number of dose levels evaluated to determine the RP2D. While the phase I study is expected to enroll and treat 9 patients (3 patients at dose level 1, and another 6 at dose level 2-assuming the 4mg dose is well tolerated), a maximum of 18 patients could be treated (6 patients treated at each dose level.

Phase II:

The phase II portion of the study is expected to enroll a minimum of 9 and a maximum of 25 patients. The six patients treated at the RP2D in the phase I portion of the study will count toward the 25 patients required; given this, we expect to enroll only 19 new patients during the phase II trial portion. The sample size is based on the desire to achieve a (promising) target response rate of >30%.

Estimated Duration of the Study

Accrual, for both phases, is expected to be completed in 26 months; with approximately 2 patients enrolled each month. Patients will be treated in 28-day treatment cycles until disease relapse, progression or unacceptable toxicity, withdrawal of consent, or protocol specified parameters to stop treatment. Patients who discontinue study treatment for reasons other than disease relapse/progression will continue to have disease assessments per International Myeloma Working Group (IMWG) criteria until relapse or progression, initiation of new anticancer treatment, or death whichever occurs first. Patients will be followed to collect further anticancer treatment and survival information until death, loss to follow-up, withdrawal of consent, study termination or up to 24 months post treatment.

Summary of Patient Eligibility Criteria:

Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.
2. Voluntary written informed consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.
3. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days 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 through 90 days after the last dose of study drug. 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 from the time of signing the informed consent form through 90 days after the last dose of study drug.

4. All patients must be registered in and must comply with all requirements of the POMALYST REMS™ program.
5. Patients must have a diagnosis of relapsed or relapsed and refractory Multiple Myeloma with a minimum of one prior regimen and a maximum of 5 prior regimens.
6. Patients must have had therapy with a proteasome inhibitor and lenalidomide and be refractory to lenalidomide according to the IMWG definition of refractory disease (progressive disease on or within 60 days of stopping lenalidomide).
7. Patients must have measurable disease defined as one of the following:
   - Serum M protein $\geq$ 0.5 g/dL
   - Urine M protein $\geq$ 200 mg/24 hours
   - Serum free light chain $\geq$ 10 mg/dL provided the FLC ratio is abnormal.
8. Eastern Cooperative Oncology Group (ECOG) performance status and/or other performance status 0, 1, or 2.
9. Patients must meet the following clinical laboratory criteria:
   - Absolute neutrophil count (ANC) $\geq$ 1,000/mm^3
   - Platelet count $\geq$ 75,000/μL for patients in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count $\geq$ 50,000/μL for patients in whom $\geq$ 50% of bone marrow nucleated cells are plasma cells. Platelet transfusions are not allowed within 3 days of last platelet assessment to confirm eligibility.
   - Total bilirubin $\leq$ 1.5 × the institutional upper limit of normal range (IULN).
   - Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq$ 3 × IULN (institutional upper limit of normal range)
   - Calculated creatinine clearance $\geq$ 45 mL/min (Appendix15.2)

Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are pregnant or breastfeeding or have a positive serum pregnancy test during the screening period.
2. Failure to have fully recovered (i.e., $\leq$ Grade 1 toxicity) from the reversible effects of prior chemotherapy.
3. Prior treatment with a multidrug regimen containing pomalidomide except the 2 drug combination of pomalidomide and dexamethasone.
4. Major surgery within 14 days before enrollment.
5. Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the MLN9708.
6. Central nervous system involvement.
7. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

8. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.
9. Systemic treatment, within 14 days before the first dose of MLN9708, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's Wort.
10. Unable or unwilling to undergo antithrombotic prophylaxis.
11. Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.
12. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.
13. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.
14. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of MLN9708 or pomalidomide including difficulty swallowing.
15. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy with evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.
16. Patient has > Grade 2 peripheral neuropathy on clinical examination during the screening period.
17. Participation in other clinical trials, including those with other investigational agents not included in this trial, within 21days of the start of this trial and throughout the duration of this trial (for all other standard therapies, no treatment within 14 days of the start of this trial).
18. Patients who are pomalidomide refractory, defined as patients who progress on or within 60 days of pomalidomide when given as a single agent or with dexamethasone.

Investigational Product Dosage and Administration:

MLN9708: 3mg or 4 mg oral; Pomalidomide: 3mg or 4mg oral; Dexamethasone: 40 mg oral (Note: Patients >75 years, at the time of trial registration, will receive a Dexamethasone dose of 20 mg on the same set schedule.)

Clinical Observations and Tests to be Performed:

Standard myeloma restaging studies (SPEP, UPEP, Bone Marrow Biopsy, Serum and Urine Immunofixation, Serum free lites, when applicable). Refer to the Table of Assessments for complete details.

Statistical Considerations:

Phase I:
The primary objective of the phase I study is to determine the recommended phase II dose (RP2D) of MLN9708 when given in combination with pomalidomide and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma.

The phase I study will follow a 3+3 design for enrollment with dose escalation, or expansion of a cohort on the basis of the occurrence of dose limiting toxicities (DLTs) during cycle 1. Two doses of MLN9708 will be tested in up to three possible dose levels (dose level -1 and dose level 1: 3mg / dose level 2: 4 mg, administered on days 1, 8 and 15 of a 28 day cycle). The highest dose level that produces ≤1/6 DLTs in cycle 1 will be the maximum tolerated dose (MTD). The RP2D of MLN9708 and pomalidomide will generally be the MTD, but it may be less than the MTD based on a review of available data/cumulative toxicities from phase I.

Analysis: Observed toxicities will be summarized in terms of type (organ affected or laboratory determination), severity, time of onset, duration, probable association with the study regimen and reversibility or outcome. Baseline information (e.g. the extent of prior therapy) and demographic information will be presented as well to describe the patients treated in this study.

Phase II:
The primary objective is to estimate the response rate and to evaluate the antitumor activity of the three drug combination: MLN9708 (at the RP2D), pomalidomide, and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma. The primary endpoint is a confirmed tumor response of sCR/CR/VGPR or PR and is based on IMWG Criteria. A single cycle of treatment will be given in a 28 day cycle. Each patient's disease status will be evaluated at baseline. Response will be assessed at the end of each cycle/just prior to the start of each cycle and is based on the IMWG criteria.

Statistics/Sample Size and Accrual: The phase II portion of this study will implement a Gehan two-stage design to estimate the response rate and to evaluate the activity of MLN9708 when given in combination with pomalidomide and dexamethasone (Gehan 1961). The phase II portion of the study is expected to enroll a minimum of 9 and a maximum of 25 patients. The six patients treated at the RP2D in the phase I portion of the study will count toward the 25 patients required; given this, we expect to enroll only 19 new patients on the phase II trial. The sample size is based on the desire to estimate the response rate with at most 10% standard error, and early stopping if the combination is unexpectedly ineffective.

At stage 1, 9 patients will be entered on the study. If 0 responses are seen in the first 9 patients treated, the study will be terminated and the true regimen response will be declared ≤30%. If at least 1 patient responds, the trial will continue to the second stage. Because patients treated during the phase I portion of the trial at the dose selected for the phase II trial will be counted (n=6), only 3 additional patients will be enrolled at stage 1. Under this design if the study regimen is >30% effective, there would be ~95.6% chance of at least one success.

At stage 2, 16 additional patients will be entered. This accrual provides for estimation of the response rate with no more than 10% standard error.

Analysis: The overall response rate will be calculated as the percent of evaluable patients that have confirmed sCR/CR/VGPR or PR; the clinical benefit response rate will be calculated as the percent of evaluable patients that have confirmed sCR/CR/VGPR/PR/ MR or SD; exact

95% confidence intervals will be calculated for these estimates. Response rates will also be evaluated based on number and type of prior therapy(ies). Time to response, duration of response, and survival will be estimated using the product-limit method of Kaplan and Meier.
Sponsor
Investigator Initiated Trial - City of Hope
Case Report Forms
This trial will utilize the Medidata RAVE® Electronic Data Capture system.

SCHEDULE OF EVENTS

PROCEDURES	**Screen**	**Cycle 1 Each cycle is 28 days**				**Cycle 2+* Each cycle is 28 days**				**End of Treatment**	**Post Study Follow Up**
	-21d to -1d	**Day 1**	**Day 8**	**Day 15**	**Day 22**	**Day 1**	**Day 8**	**Day 15***	**Day 22**		
Window		± 1	± 1	± 1	± 1	± 1	± 1	± 1	± 1		
Informed Consent	X										
Medical History, Demographics	X										
Concomitant Medications	X	X	X	X	X	X	X		X	X	X[11]
PE, Height[1], Weight, ECOG	X					X				X	
Toxicity Evaluation		X				X				X	
Vital Signs (HR, Temp, BP)	X	X				X				X	
12-lead ECG[3]	X[3]									X	
Education and counseling guidance document[4]	X					X				X	
CBC[5]	X	X	X	X	X	X				X	
Serum Chemistry[5]	X			X		X				X	
Neurological exam[6]	X					X				X	
PT/PTT[12]	X									X	
Pregnancy test [FCBP] [2]	X	X	X	X	X	X		X[2]		X[2]	
Extramedullary disease[7]	X					X				X	
Skeletal Survey [8]	X										
Bone Marrow Aspiration/Biopsy[9]	X					X					
Myeloma-specific lab tests[10]	X					X				X	
MLN9708 Administration		X	X	X		X	X	X			
Dexamethasone		X	X	X	X	X[13]	X[13]	X[13]	X[13]		
Pomalidomide Administration		Days 1 - 21				Days 1 – 21					

PROCEDURES	Screen	Cycle 1 Each cycle is 28 days				Cycle 2+* Each cycle is 28 days				End of Treatment	Post Study Follow Up
	-21d to -1d	Day 1	Day 8	Day 15	Day 22	Day 1	Day 8	Day 15*	Day 22		
Follow for PD and survival											X[11]

1) Measured at screening only.
2) FCBP - A female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months. Pregnancy tests for FCBP must be performed within 10 to 14 days and again within 24 hours of initiation of therapy. Repeat pregnancy test every week for the first 4 weeks and then every 28 days while on therapy and during interruptions in therapy and 28 days following discontinuation of pomalidomide. Women with irregular menstruation must have pregnancy testing every 14 days while on therapy and during interruptions and 14 and 28 days after discontinuation of Pomalidomide. For Cycle 2 and forward, the D15 pregnancy test (if required) can be done locally and results faxed to the main institution.
3) ECG (12-Lead) should be performed and read locally.
4) All patients must be counseled about pregnancy precautions, risks of fetal exposure and other risks. All patients enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS™ program.
5) CBC to be performed and reviewed by clinician within 24 hours of day of dosing (first day of each cycle). Alternately, a STAT CBC may be drawn on day of dosing, however should be reviewed prior to administration of investigational product(s). Serum Chemistry to be performed and reviewed by the investigator within 24 hours of day of dosing (first day of each cycle). Alternately, a STAT CMP may be drawn on day of dosing however should be reviewed by the investigator prior to administration of investigational product(s). Chemistry includes: glucose, calcium, albumin, total protein, sodium, potassium, BUN, creatinine, ALP, ALT, AST, bilirubin and uric acid (uric acid to be drawn at screening and then as needed based on tumor lysis syndrome risk). Weight and serum creatinine will be used to calculate creatinine clearance by Cockroft-Gault equation (see appendix 15.2).
6) Neurological assessment required at screening and Day 1 of Cycle 2+.
7) Extramedullary Disease: prior to study (28 days), testing required only if extramedullary disease is present, every 12 weeks (if present at screening) or upon clinical suspicion of progressive disease (if present at screening). This may include CT scan of the abdomen/pelvis, CT or x-ray of the chest, ultrasound of the liver/spleen or abdomen.
8) Skeletal survey (including skull, all long bones, pelvis and chest) with tumor measurements (measurements required if plasmacytomas are present). Also required if previous survey >28 days from study entry and at any time when clinically indicated.
9) A bone marrow aspiration and biopsy is required at screening; Repeat bone marrow biopsy/aspirate as appropriate to confirm achievement of response (aspirate only—biopsy not required).
10) Myeloma lab tests: B2Microglobulin (collected at screening only); serum immunoelectrophoresis, immunoglobulin assay, M band quantitation by immunofixation, free light chain and 24 hour urine collection for Bence Jones protein to be performed at baseline prior to study, prior to each cycle (to confirm complete response and in patients with urine only measurable disease) thereafter and at time of end of treatment (if last tests were > 3 weeks).
11) End of study follow-up to be completed every three months for two years to include second primary malignancies, new therapies for the treatment of MM only (not all concomitant medication) and survival.
12) Due to the risk of blood clots while on Pomalidomide, if patient is started on warfarin, routine monitoring of INR should occur (as per your institutuional guidelines).
13) After the patient has been on Dexamethasone over one year, the patient can discontinue Dexamethasone at their next scheduled visit.

*Additional tests to be performed at the beginning of each cycle and at any reasonable time point during treatment if indicated for monitoring of drug profile/safety or, for disease/health status at the discretion of the clinical investigator. Starting with Cycle 2 and forward, the patient is not required to come to the main hospital/institution for a Day 15 visit. The patient can be seen locally by their physician at their discretion.

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LIST OF ABBREVIATIONS AND GLOSSARY OF TERMS

Abbreviation	Term
AE	adverse event
AESI	adverse event of special interest
AL	amyloidosis
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANC	absolute neutrophil count
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the plasma concentration versus time curve
AUC_{τ}	area under the plasma concentration versus time curve from zero to next dose
BCRP	breast cancer resistance protein
βhCG	beta-human chorionic gonadotropin
BMA	bone marrow aspirate
BMB	bone marrow biopsy
BSA	body surface area
BUN	blood urea nitrogen
CBC	complete blood count
CFR	Code of Federal Regulations
CHF	congestive heart failure
CL	clearance
C_{max}	single-dose maximum (peak) concentration
CO_2	carbon dioxide
CR	complete remission
CRA	Clinical Research Associate
CRP	C-reactive protein
CT	computed tomography
CV	cardiovascular
CYP	cytochrome P_{450}
DCC	data coordinating center
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DSMC	data safety monitoring committee
ECG	electrocardiogram

Abbreviation	Term
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EDC	electronic data capture
EOS	End of Study (visit)
EOT	End of Treatment (visit)
FCBP	female of child bearing potential
FDA	United States Food and Drug Administration
GCP	Good Clinical Practice
G-CSF	granulocyte colony stimulating factor
GGT	gamma glutamyl transferase
Hb	hemoglobin
Hct	hematocrit
HIV	human immunodeficiency virus
IB	Investigator's Brochure
IC_{50}	concentration producing 50% inhibition
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	independent ethics committee
IMiDS	immunomodulatory agents
IMWG	International Myeloma Working Group
IRB	Institutional Review Board
IV	intravenous; intravenously
KPS	Karnofsky Performance Status
LDH	lactate dehydrogenase
LFT	liver function test(s)
MedDRA	Medical Dictionary for Regulatory Activities
Millennium	Millennium Pharmaceuticals, Inc., and its affiliates
MM	multiple myeloma
MRI	magnetic resonance imaging
MTD	maximum tolerated dose
NDMM	newly diagnosed multiple myeloma
NCI	National Cancer Institute
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural killer cells
NYHA	New York Heart Association

Abbreviation	Term
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PFS	progression free survival
Pgp	P-glycoprotein
PK	pharmacokinetic(s)
PO	*per os*; by mouth (orally)
PR	partial remission
PMT	Protocol Monitoring Team
RBC	red blood cell
RP2D	recommended phase 2 dose
RRMM	relapsed refractory multiple myeloma
SAE	serious adverse event
SD	stable disease
T_{max}	single-dose time to reach maximum (peak) concentration
TEAE	treatment emergent adverse event
TTP	time to prgression
TW	twice weekly
ULN	upper limit of the normal range
US	United States
V_d	volume of distribution in the terminal phase
VGPG	very good partial response
W	weekly
WBC	white blood cell
WHO	World Health Organization

1. BACKGROUND AND STUDY RATIONALE

1.1 Multiple Myeloma Background

Multiple myeloma (MM) is an incurable malignancy that is the second most common hematological malignancy. There are approximately 20,000 new cases per year and 10,000 deaths per year from MM in the United States. [1] Treatment options for relapsed MM include the following:

Bortezomib; A drug in the class of proteasome inhibitors, it was approved as monotherapy for relapsed MM.[2] Given the efficacy and tolerability of the drug it is often used in combination with agents such as alkylators (cyclophosphamide), immunomodulatory agents (IMiDS), or liposomal doxorubicin either in the upfront setting or relapsed setting. [3]

Carfilzomib: Also a proteasome inhibitor, was approved in 2012 for patients who had prior therapy with bortezomib and an IMID and were progressing on or refractory to their most recent therapy. It has less peripheral neuropathy than bortezomib and has shown responses in bortezomib refractory patients.[4] However, there are concerns with potential cardiac, pulmonary and renal side effects. Also the administration schedule of consecutive days of intravenous dosing make it a more cumbersome regimen for patients.

Lenalidomide/Thalidomide: Drugs in the class known as immunomodulatory agents. Lenalidomide in conjunction with dexamethasone is approved for relapsed myeloma. [5]

Thalidomide is also approved for myeloma therapy but in the United States, lenalidomide is used preferentially due to its more favorable side effect profile. Similar to the practice with bortezomib both drugs are now commonly used in the upfront induction setting for therapy of myeloma in conjunction with dexamethasone for synergy. [6]

Unfortunately even with the advent of these active novel agents and improved response rates of combination therapy, all patients with myeloma ultimately relapse. However, patients are living longer and hence, the goals of MM therapy are not only efficacy but also favorable toxicity profiles.[7] In addition as these novel agents are being used earlier in the course of myeloma therapy, when patients do relapse, their disease is often refractory to the approved agents. Survival for this group of patients, especially those refractory to bortezomib and lenalidomide, the so called double refractory group is especially poor. [8]

Hence new therapies for patients with relapsed disease are needed. In addition, oral therapies have the advantage of ease of administration and the potential for longer term use.

1.2 MLN9708

1.2.1 Preclinical Experience

Please refer to the current MLN9708 Investigator's Brochure (IB) and Safety Management Attachment (SMA).

1.2.2 Clinical Experience

As of 30 April 2012, 382 patients have been treated with MLN9708 across 9 enrolling, sponsor-led phase 1 or phase 1/2 studies evaluating both twice-weekly and weekly dosing schedules. MLN9708 is available as an intravenous and oral formulation. Regardless of the route of administration in the twice-weekly dosing schedule, MLN9708 is given on Days 1, 4, 8, and 11 of a 21-day cycle; in the weekly dosing schedule, the drug is given on Days 1, 8, and 15 of a 28-day cycle. To date, the development of oral MLN9708 has focused on multiple myeloma [relapsed and/or refractory and newly diagnosed] and a different yet related plasma cell dyscrasia, systemic light chain (AL) amyloidosis. A clinical pharmacology study looking at drug-drug interactions, the effect of food, and bioavailability also uses the oral formulation. Details of these trials can be found in ClinicalTrials.gov and the MLN9708 IB.

1.2.3 Pharmacokinetics and Drug Metabolism

Clinical IV and PO pharmacokinetic (PK) data show that MLN9708 (measured as the biologically active boronic acid form of MLN9708 [MLN2238]) has multi-exponential disposition with a rapid initial phase that is largely over by 4 hours. Oral MLN9708 is rapidly absorbed with a median time to first maximum plasma concentration (T_{max}) of approximately 0.5 to 2.0 hours and terminal $t_{1/2}$ after multiple dosing of approximately 5 to 7 days.[9] Results of a population PK analysis (N = 137) show that there is no relationship between body surface area (BSA) or body weight and clearance (CL). Also, based on stochastic simulations for fixed dose, exposures are independent of the individual patient's BSA.[10] Based on these data, a recommendation was made for fixed dosing in clinical trials. An absolute bioavailability of 67% was determined for MLN9708 using the population PK analysis. See the IB for information on the PK for IV doses of MLN9708.

Metabolism appears to be the major route of elimination for MLN9708, with negligible urinary excretion of the parent drug (< 3% of dose). In vitro studies of liver microsomes show that

MLN9708 is metabolized by multiple cytochrome P450 enzymes (CYPs) and non-CYP enzymes/proteins. The rank order of relative biotransformation activity of the 5 major human CYP isozymes is 3A4 (34.2%) > 1A2 (30.7%) > 2D6 (14.7%) > 2C9 (12.1%) > 2C19 (< 1%). MLN9708 is not an inhibitor of CYPs 1A2, 2C9, 2C19, 2D6, or 3A4, nor is it a time-dependent inhibitor of CYP3A4/5. The potential for MLN9708 treatment to produce DDIs via CYP inhibition is inferred to be low; however, there may be a potential for DDIs with a concomitant strong CYP3A4 or CYP1A2 inhibitor because of the potential for first-pass metabolism when MLN9708 is administered via the PO route and because of the moderate contribution of CYP3A4- and CYP1A2-mediated metabolism of MLN9708 in human liver microsomes. MLN9708 may be a weak substrate of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), and multidrug resistance associated protein (MRP2) efflux pump transporters. MLN9708 is not an inhibitor of P-gp, BCRP, and MRP2. The potential for DDIs with substrates or inhibitors of P-gp, BCRP, and MRP2 is, therefore, inferred to be low.

1.2.4 Clinical Trial Experience Using the Oral Formulation of MLN9708

In the 7 studies actively enrolling patients to investigate oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 242 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708, either as a single agent treatment or in combination with currently clinically available treatments. Information regarding the ongoing studies, patient populations, and doses investigated are included in Table 1-1.

Table 1-1 Ongoing Studies of Oral MLN9708

Trial/ Population	Description	Doses Investigated
C16003 RRMM N = 58	PO, twice weekly (TW), single agent	0.24-2.23 mg/m^2, TW MTD: 2.0 mg/m^2 DLT: rash, thrombocytopenia
C16004 RRMM N = 52	PO, weekly (W), single agent	0.24-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: rash, nausea, vomiting, diarrhea
C16005 NDMM N = 65	PO, W, combination with LenDex 28 day cycle	1.68-3.95 mg/m^2, W MTD: 2.97 mg/m^2 DLT: nausea, vomiting, diarrhea, syncope RP2D*: 4.0 mg fixed (switched to fixed dosing in phase 2, relevant to 2.23 mg/m^2)
C16006 NDMM N = 28	PO, TW (Arm A- 42 day cycle) and W (Arm B- 28 day cycle), combination with melphalan and prednisone	Arm A*: 3-3.7 mg, fixed dose, TW DLT: rash, thrombocytopenia, subileus Arm B*: 5.5 mg, fixed dose, W DLT: Esophageal ulcer
C16007 RR-AL N = 6	PO, W, single agent	4-5.5 mg, fixed dose*, W MTD: 4 mg DLT: thrombocytopenia, dirrhea, dyspnea, acute rise in creatinine, cardiac arrest
C16008 NDMM N=11	PO, TW, combination with LenDex 21 day cycle	3.0-3.7 mg fixed dose* W MTD: 4 mg DLT:
C16009 Solid tumors, Lymphomas N = 22	PO, W, single agent	5.5 mg fixed dose* W
C16010 RRMM N = 1	PO, W, combination with LenDex	4.0 mg fixed dose* W
TB-MC010034 RRMM N = 5	PO, W, single agent in 1s part of study then in combination with LenDex in 2nd part	3.0 mg fixed dose* W DLT: thrombocytopenia, nausea, hypertension, diarrhea

Abbreviations: RRAL = Relapsed or refractory Primary systemic light chain (AL) amyloidosis; BSA = body surface area ; DLT = dose-limiting toxicity; IV = intravenuously; LenDex = lenalidomide plus dexamethasone; MTD = maximum tolerated dose; NDMM = newly diagnosed multiple myeloma; PO = orally; RRMM = relapsed and/or refractory multiple myeloma; RPh2D = recommended phase 2 dose

* Approximate body surface area (BSA) and fixed dosing equivalence: 3 mg ~ equivalent to 1.68 mg/m^2 BSA dosing; 4.0 mg ~ equivalent to 2.23 mg/m^2 BSA dosing; and 5.5 mg ~ equivalent to 2.97 mg/m^2 BSA dosing.

1.2.5 Overview of the Oral Formulation of MLN9708

The emerging safety profile indicates that oral MLN9708 is generally well tolerated with predominant toxicities largely reversible, able to be monitored by routine clinical examinations and manageable by dose reductions, discontinuation, or standard supportive care. From experience from phase 1 through 2 studies the major toxicities can be managed to allow repeat treatment cycles over periods extending beyond 24 months.

In the 4 ongoing studies (C16003, C16004, C16007, and C16009) investigating single-agent oral MLN9708 in patients with differing malignancies (multiple myeloma, AL amyloidosis, nonhematologic cancers, and lymphoma), a total of 146 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 as they are all phase 1 trials. An overview of the most frequent (at least 10%) AEs occurring in the pooled safety population from single-agent oral MLN9708 Studies (C16003, C16004, C16007, and C16009) is shown in Table 1-2.

Table 1-2 Summary of Most Common (At Least 10% of Total) All Grade Treatment-Emergent Adverse Events (Oral MLN9708 Single-Agent [C16003/4/7/9] Safety Population)

Primary System Organ Class	**Preferred Term and Incidence N=146 n (%)**
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 102 (70)	Nausea 68 (47); Diarrhoea 55 (38); Vomiting 51 (35); Abdominal pain 21 (14); Constipation 21 (14)
General disorders and administration site conditions 98 (67)	Fatigue 71 (49); Pyrexia 31 (21); Oedema peripheral 15 (10)
Blood and lymphatic system disorders 77 (53)	Thrombocytopenia 60 (41); Anaemia 30 (21); Neutropenia 23 (16); Leukopenia 15 (10)
Nervous system disorders 63 (43)	Headache 20 (14); Dizziness 18 (12)
Metabolism and nutrition disorders 60 (41)	Decreased appetite 39 (27) Dehydration 21 (14)
Respiratory, thoracic and mediastinal disorders 60 (41)	Cough 22 (15); Dyspnoea 21 (14)
Skin and subcutaneous tissue disorders 60 (41)	Rash macular 17 (12)
Musculoskeletal and connective tissue disorders 56 (38)	Arthralgia 20 (14); Back pain 17 (12)
Infections and infestations 54 (37)	Upper respiratory tract infection 21 (14)

Source: MLN9708 Investigator's Brochure Edition 6

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator

In the 3 studies actively enrolling patients to investigate oral MLN9708 in combination with standard combination regimens in patients with newly diagnosed multiple myeloma, a total of 96 patients have been treated as of 30 April 2012. These patients have been treated with different doses of MLN9708 in combination with lenalidomide and dexamethasone in 2 trials (C16005 and C16008) and with melphalan and prednisone in 1 trial (C16006). The most frequent (at least 10%) adverse events occurring in the pooled safety population from Studies C16005, C16006, and C16008 is shown in Table 1-3. In combinations trials, related is defined as possibly related to any drug in the combination regimen, not just specifically related to MLN9708.

Table 1-3 Summary of Most Common (At Least 10% of Total) Treatment- Emergent Adverse Events (Oral MLN9708 Combination Agent [C16005/6/8] Safety Population)

Primary System Organ Class	**Preferred Term and Incidence N= 96 n (%)**
Subjects with at Least One Adverse Event 135 (92)	
Gastrointestinal disorders 70 (73)	Nausea 32 (33); Constipation 29 (30); Vomiting 25 (26) Diarrhoea 22 (23)
General disorders and administration site conditions 64 (67)	Fatigue 37 (39); Oedema peripheral 20 (21); Pyrexia 19 (20)
Skin and subcutaneous tissue disorders 57 (59)	Rash 13 (14)
Nervous system disorders 46 (48)	Neuropathy peripheral 13 (14); Dysgeusia 12 (13) Dizziness 11 (11)
Musculoskeletal and connective tissue disorders 45 (47)	Back pain 18 (19); Muscle spasms 10 (10)
Blood and lymphatic system disorders 42 (44)	Thrombocytopenia 28 (29); Anaemia 22 (23); Neutropenia 19 (20)
Infections and infestations 40 (42)	Upper respiratory tract infection 17 (18);
Metabolism and nutrition disorders 38 (40)	Decreased appetite 11 (11)
Respiratory, thoracic and mediastinal disorders 34 (35)	Dyspnoea 13 (14); Cough 11 (11)
Psychiatric disorders 23 (24)	Insomnia 15 (16)

Source: MLN9708 Investigator's Brochure Edition 6.

Treatment emergent is defined as any AE that occurs after administration of the first dose of any study drug through 30 days after the last dose of any study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline but worsens in intensity or is subsequently considered by the investigator to be drug-related.

Subject Incidence: A subject counts once for each preferred term. Percentages use the number of treated subjects as the denominator.

The clinical experience with MLN9708 also shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials. The antitumor activity has been seen with single-agent MLN9708, when combined with established therapies, and across the malignancies studied (advanced solid tumors [11], non-Hodgkin's disease, Hodgkin's disease [12], relapsed and/or refractory multiple myeloma [RRMM;[13,14]], relapsed or refractory systemic light chain amyloidosis [RRAL; [15]], and newly diagnosed multiple myeloma [NDMM;[16,17,18]]) to date.

Though additional data are needed to characterize the clinical benefit of this drug, the emerging data supports the ongoing development of MLN9708.

Of particular relevance to this study (C16011) is the clinical experience from Studies C16004 and C16007 in which single-agent MLN9708 is administered weekly in patients with RRMM or RRAL, respectively.

1.2.6 MLN9708 in Relapsed and/or Refractory Multiple Myeloma

Study C16004 is an open-label, dose-escalation, phase 1 study of MLN9708 administered weekly on Days 1, 8, and 15 of a 28-day cycle in adult patients with RRMM. Patients with MM enrolled in the dose-escalation component of the study have relapsed following at least 2 lines of therapy, which must have included bortezomib, thalidomide (or lenalidomide), and corticosteroids. The dose-escalation phase of the trial has completed. In this study, 2 of 3 patients experienced protocol-defined DLTs (Grade 3 rash and Grade 3 nausea, vomiting, and diarrhea) at a dose of 3.95 mg/m2. As per protocol, subsequent patients were treated at 1 dose level below (2.97mg/m2) where 1 of 6 patients experienced a DLT (Grade 3 nausea, vomiting, and diarrhea). The MTD of weekly oral MLN9708 was determined to be 2.97 mg/m2.

Once the MTD was established, cohorts of patients representing the heterogeneous patient population currently seen in clinical practice were enrolled in order to further evaluate the safety, tolerability, efficacy, PK, and pharmacodynamics of oral MLN9708. The MTD expansion cohorts enrolling are:

1. Relapsed and Refractory expansion cohort [refractory is defined as disease progression while on therapy or within 60 days after the last dose of therapy];

2. Carfilzomib expansion cohort

3. Proteasome Inhibitor-Naïve expansion cohort

4. Velcade-Relapsed expansion cohort

Final study results are not available for this ongoing trial, but preliminary data suggest MLN9708 has antitumor activity in heavily pretreated MM patients, with durable responses/disease control, and is generally well tolerated.[19,20]

As of the 30 April 2012 data cut, these patients are considered heavily pretreated as evidenced by a median number of 4 (range 1–13) prior lines of therapy, with 66% refractory to the last line of therapy. Patients have received a median of 2 cycles of therapy (range, 1- 11). Five patients have achieved objective response: 1 patient achieved a VGPR and 4 patients achieved a PR. Additionally, 15 patients achieved durable disease stabilization for up to 9.5 months. At data cut-off, 15 patients remain on treatment; discontinuation of treatment was primarily due to progressive disease (69%).

A summary of the safety profile of patients treated in Study C16004 is outlined in Table 1-4. Overall, 92% of patients experienced a TEAE of any grade and of any cause. Peripheral neuropathy was limited to Grade 1/ 2 in 6 patients, with 3 patients reporting baseline Grade 1 PN at study entry.

Table 1-4 Study C16004, Oral MLN9708, Single Agent, Given Weekly: Most Common TEAEs as of 30 April 12 (N= 52)

Most Common (> 20%) Any Grade and Irrespective of Cause	Thrombocytopenia (54%) Fatigue (48%) Nausea (44%), diarrhea (44%) Vomiting (37%) Decreased appetite (33%) Rash* (31%) Anemia (25%) Neutropenia (23%)
Drug-Related Grade ≥ 3 in > 5% of patients	Thrombocytopenia (38%) Diarrhea and neutropenia 17% (each), fatigue and lymphopenia 10% (each), nausea and decreased appetite 8% (each) and vomiting 6%

Source: MLN9708 Investigator's Brochure Edition 6
* Rash includes preferred terms of rash macular, rash, maculo-papular, rash morbilliform, rash pruritic, pruritus,, rash erythematous, exfoliative rash, and rash popular

Dose reductions required were due to AEs that included rash, neutropenia, thrombocytopenia, diarrhea, nausea, vomiting, dehydration, hypotension, increase in serum creatinine, abdominal pain, ileus, fatigue, and pneumonia. The AEs reported for the 5 patients who were required to discontinue treatment included Grade 2 MLN9708-related nausea/vomiting in 1 patient treated above the MTD, Grade 3 MLN9708-related diarrhea in a second patient, related Grade 3 thrombocytopenia, related Grade 2 dyspnea, and notrelated Grade 4 elevation in creatinine (1 patient each). There were no on-study deaths.

Study C16007 is evaluating single agent weekly , Day 1, 8, and 15 of a 28-day cycle, oral dosing in patients with RRAL after at least 1 prior therapy. The objectives of this study are to determine the safety, tolerability, and MTD, as well as to determine hematologic and organ response rates in this patient population. The starting dose level was selected from Study C16004 as previously described. In Study C16007 the dose was switched from the BSA-based dosing to the fixed dose, thereby the 4.0 mg fixed starting dose in Study C16007 corresponds to the 2.23 mg/m2 dose (one dose level below MTD) from Study C16004. This study is currently enrolling patients in the dose-expansion portion of the trial.

As of 30 April 2012, 14 patients have been treated in this study. At the first dose level of 4.0 mg, 1 of 6 patients experienced a protocol-defined DLT (that is, thrombocytopenia that lasted more than 2 weeks, which met the definition of a DLT due to the delay in starting Cycle 2). As per protocol, the dose was escalated to 5.5 mg for the next cohort of patients where 2 of 5 patients experienced a DLT (Grade 3 diarrhea, n=1; and Grade 2 dyspnea, Grade 2 acute rise in serum creatinine, and Grade 4 cardiac arrest, n=1). The latter patient did not appear to have cardiac AL amyloidosis by echocardiogram on study entry, but did have substantial renal involvement. After the occurrence of this DLT, diagnoses included cardiac involvement and CHF. The MTD of weekly oral MLN9708 was determined to be 4.0 mg. Following the establishment of the MTD, patients are currently being enrolled in to 1 of 2 cohorts: proteasome inhibitor naïve or proteasome inhibitor exposed.[21]

As of the 30 April 2012 data cut, the patients enrolled in the study are considered heavily pretreated, as evidenced by a median number of 3 prior lines of therapy (range 1–7), with 38%

and 46% of patients having been previously treated with bortezomib and lenalidomide, respectively. To be eligible for the study, patients must have amyloid involvement of the heart, kidney, or both; at the data cut the organ involvement distribution was 6, 4, and 4 patients, respectively. Patients have received a median of 2.5 cycles of therapy (range, 1-12). Eight patients remain on treatment. Early signs of activity have been reported. There were 11 patients who have received at least 1 cycle of therapy with completed response assessments (9 in the 4.0 mg [MTD] cohort and 2 in the 5.5 mg cohort). The overall hematologic response rate at MTD is 56% (5 patients achieved a hematologic response [4 VGPR and 1 PR]; 3 patients showed no change, and 1 patient had an early progression.

A summary of the safety profile of patients treated in Study C16007 is outlined in Table 1-5. Overall, 86% of patients experienced a TEAE of any grade and of any cause.

Table 1-5 Study C16007, Oral MLN9708, Single Agent Given Weekly Most Common TEAEs as of 30April 12 (N = 14)

Most Common (> 20%) Any Grade and Irrespective of Cause	Nausea (50%) Fatigue (36%) Thrombocytopenia (29%) Diarrhea (29%) Decreased Appetite (21%) Peripheral Edema (21%) Dyspnea (21%) Abdominal pain (21%)
Drug-Related Grade ≥ 3 in more than 3 Patients	Thrombocytopenia 5 patients, rash 3 patients, dehydration 2 patients, fatigue 2 patients

Source: MLN9708 Investigator's Brochure Edition 6

One patient discontinued study drug administration due to a TEAE (patient with DLT of acute rise in serum creatinine, dyspnea, and cardiac arrest treated at 5.5 mg, as noted above). No death has been reported.

The potential risks reported with MLN9708 use, pooled from all studies using the oral formulations, were anticipated based on preclinical data and previous experience with VELCADE and are noted in the MLN9708 IB, SMA, and ICF documents. Regardless of whether MLN9708 is administered on the once weekly or twice weekly dosing schedule, there is consistency among the type of TEAEs reported, despite some differences in the frequency and severity of the reported events. While the predominant potential toxicities may be severe in some cases, they are largely reversible, and can be managed by routine clinical monitoring and

standard medical interventions, which may include dose reductions and supportive care. Please refer to the MLN9708 IB and SMA for further information.

1.2.7 MLM9708 in Newly Diagnosed Multiple Myeloma (NDMM)

In Study C16005, MLN9708 is given weekly (Days 1, 8, and 15), in combination with lenalidomide (Days 1-21), and dexamethasone (Days 1, 8, 15, and 22) in a 28-day cycle. Enrollment to this study is closed.

Clinical data as of 30 April 2012 is available. The MTD in Study C16005 was determined to be 2.97 mg/m^2 given weekly in a 28-day cycle with LenDex. The DLTs were urticarial rash, dizziness, nausea, orthostatic hypotension, vomiting, diarrhoea, and syncope. The recommended phase 2 dose (RP2D) estimation was established following evaluation of the available data from the phase 1 portion of the trial which included, but was not limited to, analyses of efficacy results and adverse events (Grade 3/4 AEs, SAEs, all grades peripheral neuropathy, and treatment discontinuation). Given that the dose of MLN9708 at 2.97 mg/m^2 compromised the maximal dosing of lenalidomide and that the dose of 2.23 mg/m^2 is very tolerable and clinically active, Millennium designated 2.23 mg/m^2 as the RP2D after evaluation of the data and discussion with investigators. The RP2D of 2.23 mg/m^2 has been translated into a fixed dose of 4.0 mg based on the results from the population PK analysis. Enrollment in this study has been completed; final study results are not available, but preliminary data suggests oral MLN9708 given weekly plus lenalidomide and dexamethasone in a 28-day cycle appears well tolerated with manageable toxicity and encouraging antitumor activity.

In Study C16005, 15 of 15 (100%) patients in the dose escalation portion of the study experienced at least 1 TEAE irrespective of grade or causality. At the MTD across all dose expansion cohorts 49 of 53 patients (including 3 patients from the dose escalation cohort [92%]) reported at least 1 TEAE irrespective of grade or causality. In the MTD cohorts, fatigue was the most common AE reported (38%). Other common AEs reported include nausea (32%), constipation (30%), upper respiratory infection (23%), and peripheral oedema (21%). Skin toxicity, primarily erythematous rash, occurred in 62% of patients (of note, rash is an overlapping toxicity with MLN9708 and lenalidomide). Peripheral neuropathy was reported in 13% of patients; Grade 3 in 1 patient.

A summary of the overall safety profile of patients treated in Study C16005 is outlined in Table 1-6. Overall, 100% of 65 patients experienced at least one TEAE of any grade and of any cause.

Table 1-6 Study C16005: Oral MLN9708 Given Weekly in Combination With Lenalidomide and Dexamethasone, Most Common TEAEs as of 30 April 2012

Most Common (> 20%) Any Grade and Irrespective of	Fatigue (37%)

Cause	Nausea (34%)
	Constipation (31%)
	Vomiting (28%)
	Diarrhoea (26%)
	Thrombocytopenia (23%)
	Upper respiratory tract infection (22%)
	Anaemia and oedema peripheral (20% each)
Drug-Related[a] Grade ≥ 3 in ≥ 2 Patients	Nausea, vomiting (n=3 each)
	Thrombocytopenia, lymphopenia, rash pruritic (n=2 each)

Source: MLN9708 Investigator's Brochure Edition 6.

a Related means to ANY drug in the study drug combination.

The most common drug-related SAEs reported in Study C16005 as of 30 April 2012 include pneumonia, infection, diverticulitis, localised infection, gastrointestinal haemorrhage, respiratory syncytial virus (RSV) pneumonia faecaloma, pyrexia, pneumonia respiratory syncytial viral, non-cardiac chest pain, peripheral oedma, asthenia, hyponatraemia vomiting, diarrhoea, nausea, chest pain, dehydration, anemia, dizziness, peripheral sensory neuropathy, orthostatic hypotension, embolism, muscular weakness, acute renal failure, blood creatinine increased, maculopapular rash, atrial fibrillation, syncope, hypotension, and deep vein thrombosis, and back pain.

As of the clinical data cutoff, 4 patients have discontinued treatment due to TEAEs including gastrointestinal haemorrhage, angioedema, syncope, and RSV pneumonia.

One death was reported for a patient with RSV pneumonia; the event was deemed by the investigator to be related to treatment with MLN9708.

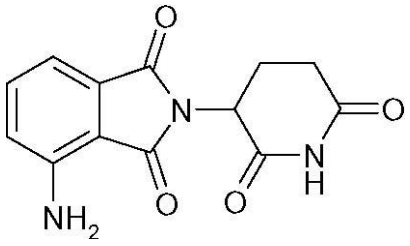
1.2.7.1 Clinical Trial Experience Using the Intravenous Formulation of MLN9708

See the IB for descriptions of the 2 ongoing studies investigating IV MLN9708 in advanced solid tumors and advanced lymphoma (Studies C16001 and C16002, respectively).

1.3 Pomalidomide

Pomalidomide is a thalidomide analogue indicated for patients with multiple myeloma who have received at least two prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy. Approval is based on response rate.

POMALYST is an immunomodulatory antineoplastic agent. The chemical name is (RS)-4-Amino-2-(2,6-dioxo-piperidin-3-yl)-isoindoline-1,3-dione and it has the following chemical structure:



POMALYST is available in 1 mg, 2 mg, 3 mg and 4 mg capsules for oral administration. Each capsule contains pomalidomide as the active ingredient and the following inactive ingredients: mannitol, pregelatinized starch and sodium stearyl fumarate. The 1 mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, white ink and black ink. The 2 mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide, FD&C red 3 and white ink. The 3 mg capsule shell contains gelatin, titanium dioxide, FD&C blue 2, yellow iron oxide and white ink. The 4 mg capsule shell contains gelatin, titanium dioxide, FD&C blue 1, FD&C blue 2 and white ink.

1.3.1 Mechanism of Action

Pomalidomide, an analogue of thalidomide, is an immunomodulatory agent with antineoplastic activity. In in vitro cellular assays, pomalidomide inhibited proliferation and induced apoptosis of hematopoietic tumor cells. Additionally, pomalidomide inhibited the proliferation of lenalidomide-resistant multiple myeloma cell lines and synergized with dexamethasone in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. Pomalidomide enhanced T cell- and natural killer (NK) cell-mediated immunity and inhibited production of pro-inflammatory cytokines (e.g., TNF-α and IL-6) by monocytes. Pomalidomide demonstrated anti-angiogenic activity in a mouse tumor model and in the in vitro umbilical cord model.

1.3.2 Pharmakokinetics

Absorption

Following administration of single oral doses of POMALYST, the Cmax for pomalidomide occurs at 2 and 3 hours post dose. The systemic exposure (AUC) of pomalidomide increases in

an approximately dose proportional manner. In patients with multiple myeloma who received POMALYST 4 mg daily alone or in combination with dexamethasone, pomalidomide steady-state drug exposure was characterized by AUC(T) of 400 ng.hr/ mL and maximum plasma concentration (Cmax) of 75 ng/mL. Following multiple doses, pomalidomide has an accumulation ratio of 27 to 31 %.

Distribution

Pomalidomide has a mean apparent volume of distribution (Vd/F) between 62 and 138 L at steady state. Pomalidomide is distributed in semen of healthy subjects at a concentration of approximately 67% of plasma level at 4 hours post-dose (~Tmax) after 4 days of once daily dosing at 2 mg. Human plasma protein binding ranges from 12% to 44% and is not concentration dependent.

Metabolism

Pomalidomide is primarily metabolized in the liver by CYP1A2 and CYP3A4. In vitro, CYP1A2 and CYP3A4 were identified as the primary enzymes involved in the CYP-mediated hydroxylation of pomalidomide, with additional minor contributions from CYP2C19 and CYP2D6.

Elimination

Pomalidomide is eliminated with a median plasma half-life of approximately 9.5 hours in healthy subjects and approximately 7.5 hours in patients with multiple myeloma. Pomalidomide has a mean total body clearance (CL/ F) of 7-10 L/ hr.

Following a single oral administration of [14C]-pomalidomide (2 mg) to healthy subjects, approximately 73% and 15% of the radioactive dose was eliminated in urine and feces, respectively, with approximately 2% and 8% of the radiolabeled dose eliminated unchanged as pomalidomide in urine and feces.

1.3.3 Non-clinical Toxicology

Carcinogenesis, Mutagenesis, Impairment of Fertility

Studies examining the carcinogenic potential of pomalidomide have not been conducted. One of twelve monkeys dosed with 1 mg/kg of pomalidomide (an exposure approximately 15-fold of

the exposure in patients at the recommended dose of 4 mg/per day) developed acute myeloid leukemia in a 9-month repeat-dose toxicology study.

Pomalidomide was not mutagenic or clastogenic in a battery of tests, including the bacteria reverse mutation assay (Ames test), the in vitro assay using human peripheral blood lymphocytes and the micronucleus test in orally treated rats administered doses up to 2000 mg/kg/day.

In a fertility and early embryonic development study in rats, drug-treated males were mated with untreated or treated females. Pomalidomide was administered to males and females at doses of 25 to 1000 mg/kg/day. When treated males were mated with treated females, there was an increase in post-implantation loss and a decrease in mean number of viable embryos at all dose levels. There were no other effects on reproductive functions or the number of pregnancies. The lowest dose tested in animals resulted in an exposure (AUC) approximately 100-fold of theexposure in patients at the recommended dose of 4 mg/day. When treated males on this study were mated with untreated females, all uterine parameters were comparable to the controls. Based on these results, the observed effects were attributed to the treatment of females.

Pomalidomide does not inhibit or induce CYP450 enzymes or any of the transporters in vitro.

1.3.4 Clinical Studies

Multiple Myeloma

The trial that led to the recent approval of pomalidimide was a Phase 2, multicenter, randomized open label study in patients with relapsed multiple myeloma who were refractory to their last myeloma therapy and had received lenalidomide and bortezomib. Patients were considered relapsed if they had achieved at least stable disease for at least one cycle of treatment to at least one prior regimen and then developed progressive disease. Patients were considered refractory if they experienced disease progression on or within 60 days of their last therapy. A total of 221 patients were randomized to receive pomalidomide alone or pomalidomide with Low dose Dex. In Trial 1, the safety and efficacy of pomalidomide 4 mg, once daily for 21 of 28 days, until disease progression, were evaluated alone and in combination with Low dose Dex (40 mg per day given only on Days 1, 8, 15 and 22 of each 28-day cycle for patients 75 years or younger, or 20mg per day given only on Days 1, 8, 15 and 22 of each 28-day cycle for patients greater than 75 years of age). Patients in the pomalidomide alone arm were allowed to add Low dose Dex upon disease progression.

Most common adverse reactions (≥30%) included fatigue and asthenia, neutropenia, anemia, constipation, nausea, diarrhea, dyspnea, upper- respiratory tract infections, back pain and pyrexia (6.1).

A recent phase III randomized trial comparing pomalidomide plus dexamethasone, to high-dose dexamethasone alone in patients with relapse and refractory MM, demonstrated higher response rates, PFS and OS in the pomalidomide arm. Ten percent (10%) of patients treated on the dexamethasone alone arm achieved an objective response and 31% of the patients on the combination arm with pomalidomide and low-dose dexamethasone achieved a response; odds ratio [OR] 4·22 [2·35 –7·58] p<0·0001 . [26] The treatment regimens most commonly used in Europe are very different from those used in the United States, as patient access to many of the novel agents is more limited in Europe. None of the patients enrolled/treated in that trial had been previously treated with carfilzomib or pomalidomide. For this trial, where MLN9708 will be added to pomalidomide and dexamethasone, patients with prior exposure to either of these agents would not be excluded. As many patients (>50%) are likely to have been previously treated with one or both of these agents we consider a response rate of 30% sufficient efficacy to justify further development.

1.4 Study Rationale

Pomalidomide is the newest immunomodulatory drug that is chemically a combination of thalidomide and lenalidomide. It has been studied in phase I-III trials for patients with relapsed myeloma. It has shown activity even in lenalidomide refractory patients and phase III trials have demonstrated superior overall and progression free survival (OS/PFS) compared to high dose dexamethasone. [22,23]

MLN9708 is a next generation small molecule 20-s proteasome inhibitor generated with the aim of improving the efficacy seen with bortezomib in MM but further improvement in drug administration. It has shown activity in the relapsed and relapsed/refractory MM setting including bortezomib refractory patients. [24] Therefore given the synergy seen with IMIDS and proteasome inhibitors as well as the activity of both compounds in relapsed MM, this becomes an attractive combination for study in the relapsed/relapsed refractory setting.

Dosing Justification

As mentioned above, the standard FDA approved dose of pomalidomide is 4mg days 1-21. Maximum response is seen when it is combined with dexamethasone. Because of an impetus in myeloma therapy to be relatively steroid sparing, the generally accepted dose of dexamethasone

is a " Low dose" weekly dosing of 40mg. Data generated from the MLN9708 plus lenalidomide and dexamethasone trial confirmed the tolerability of this new proteasome inhibitor with an IMID. The RP2D of MLN9708 is 4mg d1,8,15. However, the potential for overlapping hematologic toxicity especially in a more advanced disease population with pomalidomide (which tends to be more myelosuppressive than lenalidomide) in conjunction with MLN9708 led to the choice of an initial dose of 3mg for MLN9708. Because of the synergy between IMIDS and proteasome inhibitors we would still expect to see activity at this dose.

1.5 Potential Risks and Benefits

Please refer to the current MLN9708 Investigator's Brochure (IB) and the Package Insert for pomalidomide.

MLN9708 is a modified dipeptide boronic acid proteasome inhibitor similar to VELCADE, which has a known safety profile [VELCADE PI]. The most frequent AEs reported to date in the ongoing MLN9708 phase 1 studies were anticipated based on preclinical data and previous experience with VELCADE, and are noted in the IB, and the informed consent documents. However, it is possible that MLN9708 will have toxicities that were not previously observed in or predicted from such sources. Patients will be monitored closely for anticipated toxicities.

The toxicity profile of MLN9708 and pomalidomide in combination with dexamethasone is unknown and will be evaluated in this trial.

MLN9708 shows early signs of antitumor activity as evidenced by at least a 50% reduction in disease burden in some patients and prolonged disease stabilization in others across all ongoing trials [11,12,13,14,16,17,18].

This study will be conducted in compliance with the protocol, good clinical practice (GCP), applicable regulatory requirements, and International Conference on Harmonisation (ICH) guidelines.

2. STUDY OBJECTIVES

2.1 Study Objectives (Phase I)

2.1.1 Primary:

1. To determine the recommended phase II dose (RP2D) of MLN9708, when given in combination with pomalidomide and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma.

2.1.2 Secondary:

2. To evaluate the safety of MLN9708 at each dose level when given as part of a three drug combination by assessing the following:

- type, frequency, severity, attribution, time course and duration of adverse events

- clinical laboratory tests at various points in the study

2.2 Study Objectives (Phase II)

2.2.1 Primary:

1. To estimate the response rate and to evaluate the antitumor activity of the three drug combination: MLN9708 (at the RP2D), pomalidomide and dexamethasone, in patients with relapsed or relapsed/refractory multiple myeloma.

2.2.2 Secondary:

At the RP2D, for the three drug combination:

2. To characterize and evaluate toxicities, including type, frequency, severity, attribution, time course and duration.

3. To obtain estimates of response duration, depth of response, clinical benefit response, and survival (overall and progression-free).

3. STUDY ENDPOINTS

3.1 Primary Endpoints

Phase I:

The primary endpoint is toxicity. Toxicity will be graded according to the NCI-Common Terminology Criteria for Adverse Events version 4.03. A DLT will be defined as any of the following toxicities that are at least possibly related to either Pomalidomide or MLN9708 and occur during cycle 1:

- Grade 4 neutropenia
- Grade 3 neutropenia with fevers $\geq$ 38.5°C
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with bleeding

- Grade 3 or higher non-hematological toxicity will be considered dose limiting, with the following exceptions: diarrhea, fatigue, nausea or vomiting will only be considered dose limiting if, after 48 hours it has not recovered to <Grade 3 (despite maximal medical therapy), allergic reaction/hypersensitivity, or electrolyte/metabolic toxicity unable to be corrected to <Grade 1 or baseline within 48 hours will be considered dose limiting.
- Delay in starting cycle 2 on the scheduled day 1 for > 7 days due to treatment related toxicity
- Any dose modification or delay during cycle 1, except modifications/delays done in response to hypo- hyperthyroidism <=Grade 2, herpes zoster infection, all considered idiopathic or intrinsic to the underlying myeloma.

Phase II:

The primary activity endpoint is response rate (confirmed sCR/CR/VGPR or PR), based on the International Myeloma Working Group (IMWG) criteria, calculated as the number of responders divided by the number of evaluable patients. Confirmation of sCR/CR/VGPR or PR assessed by IMWG criteria.

Secondary activity endpoints for this study are as follows:

- Duration of response, defined as the time interval from the date of first documented response (sCR/CR/VGPR or PR) to documented disease relapse, progression or death whichever occurs first.

- Clinical benefit response, based on the International Myeloma Working Group (IMWG) criteria, calculated as the number of responders plus those with a minimal response (MR) or stable disease (SD) divided by the number of evaluable patients. Confirmation of sCR/CR/VGPR/PR/MR or SD assessed by IMWG criteria.

- Overall survival, defined as the time interval from date of first dose of study drug to date of death from any cause.

- Progression-free survival, defined as the time interval from date of first dose of study drug to first documented disease relapse, progression or death from any cause, whichever occurs first.

4. STUDY DESIGN

4.1 Overview of Study Design

4.1.1 Phase I:

The phase I portion of the study is based on a 3 + 3 dose escalation design, to evaluate toxicities associated with MLN9708 when given in combination with pomalidomide and dexamethasone. Two doses of MLN9708 (dose level -1 and dose level 1: 3mg; dose level 2: 4mg) will be tested in up to three possible dose levels. Based on previous combination trials of MLN9708, the 4mg dose of MLN9708 is expected to be well tolerated. Given that this is the first study to combine MLN9708, with dexamethasone and pomalidomide, patients will initially be treated at a 3mg dose. The maximum tolerated dose (MTD) will be established by evaluating dose limiting toxicity (DLT) during cycle 1. The recommended phase II dose (RP2D) of MLN9708 and pomalidomide will generally be the MTD, but it may be less than the MTD based on a review of available data/cumulative toxicities from phase I. Patients will be treated with oral MLN9708 on days 1, 8, and 15 of each 28 day cycle and with Dexamethasone on days 1, 8, 15 and 22 of each 28 day cycle. Pomalidomide will be given on days 1-21 of each 28 day cycle. The dose of MLN9708 and Pomalidomide administered will depend on the dose level assignment; the dose of dexamethasone will be fixed (Patients >75 years, at the time of trial registration, will receive a Dexamethasone starting dose of 20 mg on the same set schedule).

Phase II

Patients who enroll during the phase II portion of the trial will be treated at the same dose and schedule of MLN9708, pomalidomide and dexamethasone determined safe during the phase I study (the RP2D).

4.2 Number of Patients

The phase I study is expected to enroll and treat 9 patients; 3 patients at dose level 1, and another 6 treated at dose level 2 -assuming the 4mg dose of MLN9708 is well tolerated. The phase II portion of the trial is expected to enroll a minimum of 9 and a maximum of 25 patients. The six patients treated at the RP2D in the phase I portion of the study will count toward the 25 patients required; given this, we expect to enroll only 19 new patients on the phase II trial.

4.3 Duration of Study

Accrual, for both phases, is expected to be completed in 26 months; with approximately 2 patients enrolled each month. Patients will be treated in 28-day treatment cycles until disease relapse, progression or unacceptable toxicity, withdrawal of consent, or protocol specified parameters to stop treatment. Patients who discontinue study treatment for reasons other than disease relapse/progression will continue to have disease assessments per International Myeloma Working Group (IMWG) criteria until relapse or progression, initiation of new

anticancer treatment, or death whichever occurs first. Patients will be followed to collect further anticancer treatment and survival information until death, loss to follow-up, withdrawal of consent, study termination or up to 24 months post treatment.

5. STUDY POPULATION

5.1 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

1. Male or female patients 18 years or older.

2. Voluntary written informed consent must be given before performance of any study related procedure not part of standard medical care, with the understanding that consent may be withdrawn by the patient at any time without prejudice to future medical care.

3. Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting pomalidomide or MLN9708 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 or MLN9708 through 90 days after the last dose of study drug. 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 from the time of signing the informed consent form through 90 days after the last dose of study drug. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure.

4. All patients enrolled into this trial, must be registered in and must comply with all requirements of the POMALYST REMS™ program.

5. Patients must have a diagnosis of relapsed or relapsed and refractory Multiple Myeloma with a minimum of one prior regimen and a maximum of 5 prior regimens.

6. Patients must have had therapy with a proteasome inhibitor and lenalidomide and be refractory to lenalidomide according to the IMWG definition of refractory disease (progressive disease on or within 60 days of stopping lenalidomide).

7. Patients must have measurable disease defined as **one** of the following:

a. Serum M protein ≥ 0.5 g/dL

b. Urine M protein ≥ 200 mg/24 hours

c. Serum free light chain ≥ 10 mg/dL provided the FLC ratio is abnormal.

8. Eastern Cooperative Oncology Group (ECOG) performance status 0, 1, or 2.

9. Patients must meet the following clinical laboratory criteria:

- Absolute neutrophil count (ANC) ≥ 1,000/mm^3
- Platelet count ≥ 75,000/μL for patients in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count ≥ 50,000/μL for patients in whom ≥ 50% of bone marrow nucleated cells are plasma cells. Platelet transfusions are not allowed within 3 days of last platelet assessment to confirm eligibility.
- Total bilirubin ≤ 1.5 × the institutional upper limit of the normal range (IULN).
- Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × IULN.
- Calculated creatinine clearance ≥ 45mL/min (see Appendix 15.2).

5.2 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study:

1. Female patients who are pregnant or breastfeeding or have a positive serum pregnancy test during the screening period.
2. Failure to have fully recovered (ie, ≤ Grade 1 toxicity) from the reversible effects of prior chemotherapy.
3. Prior therapy with a combination regimen containing pomalidomide except the 2 drug combination of pomalidomide and dexamethasone.
4. Major surgery within 14 days before enrollment.
5. Radiotherapy within 14 days before enrollment. If the involved field is small, 7 days will be considered a sufficient interval between treatment and administration of the MLN9708.

6. Central nervous system involvement.

7. Infection requiring systemic antibiotic therapy or other serious infection within 14 days before study enrollment.

8. Evidence of current uncontrolled cardiovascular conditions, including uncontrolled hypertension, uncontrolled cardiac arrhythmias, symptomatic congestive heart failure, unstable angina, or myocardial infarction within the past 6 months.

9. Systemic treatment, within 14 days before the first dose of MLN9708, with strong inhibitors of CYP1A2 (fluvoxamine, enoxacin, ciprofloxacin), strong inhibitors of CYP3A (clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, posaconazole) or strong CYP3A inducers (rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, phenobarbital), or use of Ginkgo biloba or St. John's Wort.

10. Unable or unwilling to undergo antithrombotic prophylaxis.

11. Ongoing or active systemic infection, active hepatitis B or C virus infection, or known human immunodeficiency virus (HIV) positive.

12. Any serious medical or psychiatric illness that could, in the investigator's opinion, potentially interfere with the completion of treatment according to this protocol.

13. Known allergy to any of the study medications, their analogues, or excipients in the various formulations of any agent.

14. Known GI disease or GI procedure that could interfere with the oral absorption or tolerance of MLN9708 or pomalidomide including difficulty swallowing.

15. Diagnosed or treated for another malignancy within 2 years before study enrollment or previously diagnosed with another malignancy with evidence of residual disease. Patients with nonmelanoma skin cancer or carcinoma in situ of any type are not excluded if they have undergone complete resection.

16. Patient has > Grade 2 peripheral neuropathy on clinical examination during the screening period.

17. Participation in other clinical trials, including those with other investigational agents not included in this trial, within 21days of the start of this trial and throughout the duration of this trial (for all other standard therapies, no treatment within 14 days of the start of this trial).
18. Patients who are pomalidomide refractory, defined as patients who progress on or within 60 days of pomalidomide when given as a single agent or with dexamethasone.

6. PATIENT ENROLLMENT

Phase I Dose Escalation Portion – Prior to discussing protocol entry with the patient, contact the City of Hope Data Coordinating Center to ensure that a treatment slot on the protocol is available.

Phase I and II Patient Enrollment

The screening period for a particular patient commences when the patient signs the informed consent. Consent must be signed before any study-specific tests may be performed. After a patient has been screened and has successfully fulfilled all eligibility criteria, the site representative will email the inclusion/exclusion checklist and all other required source documentation to the City of Hope Data Coordinating Center. In order to ensure privacy/security, please ensure that you type #secure# in the subject line of all correspondence related to the trial/patient:

Lupe Duarte, CCRC
Multiple Myeloma Project Manager
Phone: 626-256-4673 x 63968
Fax: 626 301-8422
Email: dcc@coh.org

A unique patient number will be assigned at that time that will be used to identify the patient throughout the clinical study and must be used on all study documentation related to that patient. Patients will be assigned to a dose level at enrollment. Prior to accepting the registration, the COH DCC staff member will verify the following:

1. IRB approval at the registering institution
2. Patient eligibility
3. Existence of a signed consent form
4. Existence of a signed authorization for use and disclosure of protected health information (if applicable).

Treatment cannot begin prior to registration and must begin ≤ 7 days after registration. Pretreatment tests/procedures must be completed within the guidelines specified on the test schedule.

7. STUDY TREATMENT

7.1 Dose and Schedule

The phase I study will follow a standard 3 + 3 dose escalation design, to evaluate toxicities associated with MLN9708 when given in combination with pomalidomide and dexamethasone. Two doses of MLN9708 (3 mg and 4 mg) will be tested in up to three possible dose levels.

7.2 Dose Levels to be Tested

Schedule: Each cycle is 28 days			
Dose Level	**Pomalidomide**	**MLN9708**	**Dexamethasone***
-1	3mg daily on days 1-21	3 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22
1	4 mg daily on days 1 - 21	3 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22
2	4 mg daily on days 1 - 21	4 mg on days 1, 8 and 15	40 mg on days 1, 8, 15 and 22

*: Patients >75 years, at the time of trial registration, will receive a Dexamethasone dose of 20 mg on the same set schedule.

7.3 Dose Limiting Toxicity/Unacceptable Toxicity

Dose Limiting Toxicity (DLT) is defined as any of the following toxicities that are at least possibly related to either Pomalidomide or MLN9708 that occur during cycle 1. Toxicity will be graded according to the NCI-Common Terminology Criteria for Adverse Events, Version 4.03.

Note: The Phase II portion of the study will use the same definition to define unacceptable toxicity.

For the purposes of this study, DLT will be defined as:

- Grade 4 neutropenia
- Grade 3 neutropenia with fevers ≥ 38.5°C
- Grade 4 thrombocytopenia
- Grade 3 thrombocytopenia with bleeding
- Grade 3 or higher non-hematological toxicity will be considered dose limiting with the following exceptions: diarrhea, fatigue, nausea or vomiting will only be considered dose limiting if, after 48 hours it has not recovered to <Grade 3 (despite maximal medical therapy), allergic reaction/hypersensitivity, or electrolyte/metabolic toxicity unable to be corrected to <Grade 1 or baseline within 48 hours will be considered dose limiting.
- Delay in starting cycle 2 on the scheduled day 1 for > 7 days due to treatment related toxicity
- Any dose modification or delay of MLN9708 or Pomalidomide during cycle 1, except modifications/delays done in response to hypo- hyperthyroidism <=Grade 2, herpes zoster infection, all considered idiopathic or intrinsic to the underlying myeloma.

7.4 Dose Escalation/Expansion

DLT incidence will be based on toxicity events encountered during the first cycle of treatment with the combination of MLN9708, pomalidomide and dexamethasone.

Dose de-escalation, escalation or cohort expansion will only take place after 3 patients are fully assessed using the Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) version 4.03 following the completion of cycle 1.

Dose escalation will occur according to the following rules:

- If zero out of 3 evaluable patients has a DLT in cycle 1 then the next dose level of combination therapy will be tested.
- If 1 out of 3 evaluable patients has a DLT in cycle 1, three additional patients will be assessed at the same dose level of combination therapy.
- If 2 out of 3 patients have a DLT in cycle 1, dose escalation will cease and the next lower dose level of combination therapy will be expanded. Note: If 2 of 3 experience DLT on dose level -1, the trial will be stopped.
- If 1 out of 6 evaluable patients has a DLT in cycle 1, then dose escalation to the next dose level of combination therapy will continue.

- If 2 or more out of 6 patients have a DLT in cycle 1, dose escalation will cease and the next lower dose level of combination therapy will be expanded. Note: If 2 of 6 experience DLT on dose level -1 the trial will be stopped.

The highest dose level that produces ≤1/6 DLTs in cycle 1 will be the maximum tolerated dose (MTD).

Note: Patients may continue therapy unless there is unacceptable toxicity, disease progression or withdrawl of consent.

7.5 Recommended Phase II Dose (RP2D)

The MTD will be based on the assessment of DLT during cycle 1 (see section 7.4). The MTD will be defined as the highest dose at which ≤ 1/6 patients in a cohort experience DLT. The recommended phase II dose (RP2D) of MLN9708 and pomalidomide will generally be the MTD, but it may be less than the MTD based on a review of available data/cumulative toxicities from phase I.

7.6 Study Drug Administration

All protocol-specific criteria for administration of study drug must be met and documented before drug administration. Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified subinvestigator(s). Patients should be monitored for toxicity, as necessary, and doses of study drug should be modified as needed to accommodate patient tolerance to treatment; this may include symptomatic treatment, dose interruptions, and adjustments of dose.

7.6.1 MLN9708 Administration

Patients should be instructed to swallow MLN9708 capsules whole, with water, and not to break, chew, or open the capsules. MLN9708 should be taken on an empty stomach (no food or drink) at least 1 hour before or 2 hours after a meal. Each capsule should be swallowed separately with a sip of water. A total of approximately 8 ounces (240 mL) of water should be taken with the capsules.

Missed doses can be taken as soon as the patient remembers if the next scheduled dose is 72 hours or more away. A double dose should not be taken to make up for a missed dose. If the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

7.6.2 Pomalidomide Administration

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. Pomalidomide capsules may be taken with water.

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 at the next scheduled time point. Similarly, if the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose.

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

Pomalidomide (POMALYST®) will be provided to research patients 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 patients enrolled into this trial, and all research patients 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.

Special Handling Instructions

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

7.6.3 Dexamethasone Administration

Dexamethsone is commercially available and commercial supplies will be used for this study.

Oral dexamethasone will be given on an outpatient basis. Missed doses of dexamethasone will not be made up. Similarly, if the patient vomits after taking a dose, the patient should not repeat the dose but should resume dosing at the time of the next scheduled dose. Procedures for dose reductions and delays are summarized in Section 7.9.2.

7.6.4 Growth Factor Administration

For the Phase I portion of the study, growth factors, granulocyte colony stimulating factor [G-CSF], may be given prophylactically for at least two days on days 21 – 26 during or beyond cycle 2. For the Phase II portion of the study, G-CSF may be given prophylactically for at least two days on days 21-26 during or beyond cycle 1. It will be administered subcutaneously at a dose of 5ug/kg or per institutional standard practice dosing either daily or every other day for a minimum of two doses. If patients experience neutropenia or dosing delays, we would recommend consideration of growth factor in subsequent cycles.

7.7 Dose Modification Guidelines

Patients will be evaluated for adverse events at each visit with the NCI Common Toxicity Criteria, Version 4.03 used as a guide for the grading of severity.

As defined in section 7.3, during the phase I portion of the study, any toxicity related dose modification or delay of MLN9708 or Pomalidomide during cycle 1 except modifications/delays done in response to hypo- hyperthyroidism <=Grade 2, herpes zoster infection, all considered idiopathic or intrinsic to the underlying myeloma is a DLT. No dose escalations are permitted in any given patient once a dose level has been assigned. While patients experiencing DLT during Cycle 1 may continue on therapy, if toxicity can be managed according to the dose modification guidelines outlined below, the DLT event will contribute to the assessment of MTD for that given cohort. Patients will be considered evaluable for toxicity if they receive any study drug. Patients will be considered evaluable for dose limiting toxicity if they receive at least 75% of both Pomalidomide and MLN9708 and are followed for the full 28 days during cycle 1 or experience a DLT. For the phase II portion, as part of the primary analysis, patients will be considered evaluable for response if they are eligible, have baseline disease assessments, and receive any protocol treatment. As part of a secondary analysis, patients will be considered evaluable for response if they have baseline disease assessments, receive at least 75% of both Pomalidomide and MLN9708 during the first cycle of therapy and have had their disease re-evaluated.

Dose modifications may be performed in all subsequent cycles of treatment regardless of which phase of study the patient is enrolled on. If toxicities cannot be managed by dose modification or the patient cannot tolerate the lowest dose of study drug, the patient is to be discontinued from study treatment. However, patients that have achieved a plateau of response to study

therapy will continue to adhere to the schedule of assessments followed during the treatment phase of the study even though study drug has been discontinued.

7.8 Dose Reduction Steps

7.8.1 Dose Reduction Steps for Pomalidomide

Pomalidomide Dose Reduction Steps			
Starting Dose	**Daily on Days 1 – 21 every 28 days**		
4.0 mg	3.0 mg	2.0 mg	1.0 mg
3.0 mg	2.0 mg	1.0 mg	-
2.0 mg	1.0 mg	-	-
1.0 mg	-	-	-

7.8.2 Dose Reduction Steps for MLN9708

MLN9708 Dose Reduction Steps			
Starting Dose	**Daily on Days 1, 8 and 15 every 28 days**		
4.0 mg	3.0 mg	2.3 mg	1.5 mg
3.0 mg	2.3 mg	1.5 mg	-

7.8.3 Dose Reduction Steps for Dexamethasone

Dexamethasone Dose Reduction Steps**		
Starting Dose	**Days 1, 8, 15 and 22 every 28 days**	
40 mg	20 mg	12 mg
20 mg*	12 mg	6 mg
12 mg	-	-

*: Patients >75 years, at the time of trial registration, will receive a dexamethasone starting dose of 20 mg on the same set schedule.

**: After the patient has been on Dexamethasone over one year, the patient can discontinue Dexamethasone at their next scheduled visit.

- Dexamethasone may be permanently discontinued for toxicity at the discretion of the investigator but the patient can remain on study therapy with pomalidomide and MLN9708 if tolerated.

- After the patient has been on Dexamethasone over one year, the patient can discontinue Dexamethasone at their next scheduled visit.

7.9 Dose Modification Guidelines for Treatment Related Toxicity

For recommended comcomitant therapy to reduce the risk/severity of potential adverse events refer to Section 7.11. For recommendations on management of adverse events refer to section 7.12. In addition, the table below provides guidelines for dose modification based on toxicity. Dose modifications different from those recommended may be made in consultation with the Lead Principal Investigator based on investigators assessment of toxicity attribution and management of individual patients.

7.9.1 Dose Modification for MLN9708 and Pomalidmide During a Cycle of Therapy

Treatment modifications due to MLN9708 and Pomaliomide related AEs during a cycle of therapy are outlined below.

CTCAE Category	AGENTS	Toxicity During a Cycle
Hematologic Toxicity during a cycle of therapy		
≥ Grade 3 neutropenia associated with fever (temperature ≥ 38.5C) or Grade 4 neutropenia	**Pomalidomide**	Hold dose. Follow CBC weekly. Use of G-CSF is allowed and recommended. If neutropenia resolved to ≤ grade 2 within the cycle, resume pomalidomide and continue through the scheduled end of the cycle. If not resolved to ≤ grade 2, omit for remainder of cycle and reduce the dose of pomalidomide by one dose level at the start of the next cycle. Omitted doses are not made up. Granulocyte colony stimulating factor [G-CSF], may be used prophylactically on days 21 – 26. Section7.6.4

	MLN9708	Hold dose. Follow CBC weekly. If neutropenia resolves to ≤ grade 2 resume treatment on schedule day of cycle. However, if the Day 8 or 15 dose is held, that dose should be omitted and treatment should continue with next scheduled dose (i.e., if Day 8 is skipped, the next dosing day is Day 15) resume MLN9708 at same dose. If neutropenia dose not resolve to ≤ Grade 2 during the cycle and any 2 doses were held due to toxicity then reduce the MLN9708 dose by one level at the start of the next cycle. Granulocyte colony stimulating factor [G-CSF],) may be used prophylactically on days 21 – 26.
Platelet count < 25,000/mm^3 or G3 thrombocytopenia with bleeding	**Pomalidomide**	Hold dose. Follow CBC weekly. Use of platelet transfusions is allowed to proceed with dosing. If thrombocytopenia resolved to < grade 2 within the cycle, resume pomalidomide and continue through the scheduled end of the cycle. If not resolved to ≤ grade 2, omit for remainder of cycle and reduce the dose of pomalidomide by one dose level at the start of the next cycle. Omitted doses are not made up.
	MLN9708	Hold dose. Follow CBC weekly. If thrombocytopenia resolves to ≤ grade 2 resume treatment on schedule day of cycle. However, if the Day 8 or 15 dose is held, that dose should be omitted and treatment should continue with next scheduled dose (i.e., if Day 8 is skipped, the next dosing day is Day 15) resume MLN9708 at same dose. If thrombocytopenia dose not resolve to ≤ Grade 2 during the cycle and any 2 doses were held due to toxicity then reduce the MLN9708 dose by one level at the start of the next cycle.
For recurrent episodes of hematologic toxicity, MLN9708 and/ or pomalidomide may be dose reduced together or independently at the investigaotrs discretion to manage toxicity.		
Non-Hematologic toxicity during a cycle of therapy		
RASH **Grade 2 or 3**	**Pomalidomide**	Hold pomalidomide and MLN9708. Follow weekly. Implement supportive therapy (see section 7.11.2)

	MLN9708	If the toxicity resolves to ≤ grade 1, restart MLN9708 and pomalidomide and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of pomalidomide by one dose level at the start of the next cycle. Omitted doses are not made up. For subsequent occurances, alternate dose reductions with MLN9708 and pomalidomide.
Non-blistering rash Grade 4		Discontinue pomalidomide and MLN9708. Withdraw participant from the study.
Desquamating (blistering) rash-any Grade or Erythema multiforme ≥ Grade 3	**Pomalidomide/ MLN9708**	Discontinue treatment. Withdraw participant from study.
Hyperthyroidism or Hypothyroidism	**Pomalidomide**	Omit pomalidomide for remainder of cycle, evaluate etiology, and initiate appropriate therapy. Restart pomalidomide at investigator's discretion. For toxicity attributable to pomalidomide, reduce the dose by one dose level.
Neuropathy **Grade 2 peripheral neuropathy with pain or Grade 3**	**Pomalidomide MLN9708**	Hold MLN9708. Follow weekly. If the toxicity resolves to ≤ grade 1(or baseline), restart MLN9708 at next lower dose level and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of MLN9708 one dose level at the start of the next cycle. Omitted doses are not made up. For recurrent Grade 2 peripheral neuropathy with pain or grade 3 neuropathy, hold treatment. If the toxicity resolves to ≤ grade 1(or baseline), reduce pomalidomide and /or MLN9708 at investigators discretion.
Grade 4		Discontinue teatment. Withdraw participant from study.
Herpes Zoster reactivation any grade	**Pomalidomide MLN9708**	Hold MLN9708 and pomalidomide until lesions are dry. Initiate antiviral therapy (maintain dose level).
Venous	**Pomalidomide/**	Hold therapy and start full anticoagulation as

Thrombosis/Embolism ≥ Grade 3	**MLN9708**	appropriate; restart at investigator's discretion (maintain dose level).
Other Pomalidomide or MLN9708 related non-hematologic toxicity Grade ≥ 3 **Grade 4 related non-hematologic toxicity**	**Pomalidomide MLN9708**	Determine attribution of toxicity and hold both pomalidomide and MLN9708. Follow at least weekly. If toxicity resolves to ≤ grade 1 or baseline, resume therapy with one level dose reduction. Consider permanent discontinuation of therapy. Exceptions may be made following discussion with the Lead Principal Investigator for patients that are experiencing clinical benefit.

Once MLN9708 or pomalidomide is reduced for any toxicity, the dose may not be re-escalated.

7.9.2 Dexamethasone Dose Modification Guidelines*

Body System	Symptom	Recommended Action
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1–2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level.
Gastrointestinal	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level of current dose along with concurrent therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Gastrointestinal	Acute pancreatitis	Discontinue dexamethasone and do not resume
Cardiovascular	Edema >Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction.
Neurology	Confusion or Mood alteration > Grade 2 (interfering with	Hold dexamethasone until symptoms resolve. Restart with one dose level

	function +/- interfering with activities of daily living)	reduction. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living)	Decrease dexamethasone dose by one dose level. If weakness persists despite above measures, decrease dose by one dose level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral hypoglycemics as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

7.10 Criteria for Beginning or Delaying a Subsequent Treatment Cycle

For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm3.
- Platelet count must be ≥ 75,000/mm^3 or > =50,000/mm^3 for patients with baseline platelets ≥50,000/mm^3 but <75,000/mm^3.
- All other nonhematologic toxicity (except for alopecia) must have resolved to ≤ Grade 1 or to the patient's baseline condition

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, delay therapy and continue to re evaluate. The maximum delay before treatment should be discontinued will be 3 weeks or at the discretion of the Principal Investigator.

7.11 Concomitant Medications

7.11.1 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

Systemic treatment with any of the following metabolizing enzyme inhibitors is not permitted during this study. A drug/drug interaction (DDI) with a strong inhibitor would increase MLN2238 (metabolite of MLN9708) exposure.

- Strong inhibitors of CYP1A2: fluvoxamine, enoxacin, ciprofloxacin
- Strong inhibitors of CYP3A: clarithromycin, telithromycin, itraconazole, voriconazole, ketoconazole, nefazodone, and posaconazole

Systemic treatment with any of the following metabolizing enzyme inducers should be avoided unless there is no appropriate alternative medication for the patient to use. A DDI with a strong inducer would decrease MLN2238 (metabolite of MLN9708) exposure.

- Strong CYP3A inducers: rifampin, rifapentine, rifabutin, carbamazepine, phenytoin, and phenobarbital

Please refer to a complete listing of prohibited medications, strong CYP3A and CYP1A2 inhibitors that can be found via the following link: http://medicine.iupui.edu/clinpharm/ddis/main-table/.

The dietary supplements St John's wort and Ginkgo biloba are not permitted.

The following procedures are prohibited during the study:

- Any antineoplastic treatment with activity against MM except for drugs in this treatment regimen.
- Radiation therapy (the requirement for local radiation therapy generally indicates disease progression).
- Platelet transfusions to help patients meet eligibility criteria are not allowed within 3 days before study drug dosing.
- Adjuvant hormone therapy for breast or prostate cancer.

7.11.2 Permitted/Recommended Concomitant Medications and Procedures

The following medications and procedures are permitted during the study:

- Antiemetics, including 5-HT3 serotonin receptor antagonists, may be used at the discretion of the investigator and is strongly recommended.

- Loperamide or other antidiarrheal should be used for symptomatic diarrhea at discretion of the investigator. The dose and regimen will be according to institutional guidelines. Intravenous fluids should be given to prevent volume depletion.

- Erythropoietin will be allowed in this study. Their use should follow published guidelines and/or institutional practice.

- Patients should be transfused with red cells and platelets as clinically indicated and according to institutional guidelines.

- Concomitant treatment with bisphosphonates will be permitted, as appropriate.

- Patients who experience worsening neuropathy from baseline may be observed for recovery, and have dose reductions/delays as indicated in the protocol, and any supportive therapy or intervention may be initiated as appropriate at the discretion of the investigator.

- Supportive measures consistent with optimal patient care may be given throughout the study.

- Fluid deficits should be corrected before and throughout treatment.

7.11.3 Required/Recommended Concomitant Therapy

- Pomalidomide increases the risk of thromboembolism. Anti-coagulation prophylaxis is required after an assessment of each patient's underlying risk factors, unless there is an excess risk of bleeding.

- Antiviral therapy such as acyclovir is recommended for herpes prophylaxis.

- For the Phase I portion of the study, growth factors, granulocyte colony stimulating factor [G-CSF], may be given prophylactically for at least two days on days 21 – 26 during or beyond cycle 2. For the Phase II portion of the study, G-CSF may be given prophylactically for at least two days on days 21-26 during or beyond cycle 1. It will be administered subcutaneously at a dose of 5ug/kg or per institutional standard practice dosing either daily or every other day for a minimum of two doses. If patients experience neutropenia or dosing delays, we would recommend consideration of growth factor in subsequent cycles.

- Allopurinol is recommended for patients with high tumor burden due to the possibility of tumor lysis syndrome.

7.11.4 Pregnancy

It is not known what effects MLN9708 has on human pregnancy or development of the embryo or fetus. Pomalidomide can cause fetal harm when administered during pregnancy. Therefore, female patients participating in this study should avoid becoming pregnant, and male patients should avoid impregnating a female partner. Females of child bearing potential* and male patients should use effective methods of contraception through defined periods during and after study treatment as specified below.

A female of child bearing potential is any 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).

7.11.4.1 Females

Females of reproductive potential must commit either to abstain continuously from heterosexual sexual intercourse or to use two methods of reliable birth control simultaneously (one highly effective form of contraception – tubal ligation, IUD, hormonal (birth control pills, injections, hormonal patches, vaginal rings or implants) or partner's vasectomy and one additional effective contraceptive method – male latex or synthetic condom, diaphragm or cervical cap. Contraception must begin 4 weeks prior to initiating treatment, during therapy, during dose interruptions and continuing for 4 weeks following discontinuation of pomalidomide or 90 days following discontinuation of MLN9708. Reliable contraception is indicated even where there has been a history of infertility, unless due to hysterectomy. Females of reproductive potential should be referred to a qualified provider of contraceptive methods, if needed.

Females of reproductive potential must have 2 negative pregnancy tests before initiating therapy. The first test should be performed within 10-14 days, and the second test within 24 hours prior to prescribing pomalidmide and MLN9708. Once treatment has started and during dose interruptions, pregnancy testing for females of reproductive potential should occur weekly during the first 4 weeks of use, then pregnancy testing should be repeated every 4 weeks in females with regular menstrual cycles. If menstrual cycles are irregular, the pregnancy testing should occur every 2 weeks. Pregnancy testing and counseling should be performed if a patient misses her period or if there is any abnormality in her menstrual bleeding. Treatment with pomalidomide and MLN9708 must be discontinued during this evaluation. 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.

7.11.4.2 Males

Pomalidomide is present in the semen of males who take pomalidomide. The effects of MLN9708 are unknown. Therefore, males must always use a latex or synthetic condom during any sexual contact with females of reproductive potential while taking pomalidomide or MLN9708 and for up to 28 days after discontinuing pomalidomide or 90 days after discomtinuation of MLN9708, even if they have undergone a successful vasectomy. Male patients taking pomalidmide or MLN9708 must not donate sperm. 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.

7.12 Management of Clinical Events

Adverse drug reactions such as thrombocytopenia, diarrhea, fatigue, nausea, vomiting, and rash have been associated with MLN9708 treatment. Management guidelines regarding these events are outlined below. Further details of management of MLN9708 AEs are described the MLN9708 IB.

Prophylaxis Against Risk of Infection

If lymphopenia is noted, patients may be at an increased risk of infection. In particular, lymphopenia can be associated with reactivation of herpes zoster and herpes simplex viruses. Antiviral therapy such as acyclovir or valacyclovir may be initiated as clinically indicated. Other antivirals are also acceptable.

Nausea and/or Vomiting

Standard anti-emetics, including 5-HT3 antagonists, are recommended for emesis occurring upon treatment initiation; prophylactic anti-emetics may also be considered. Dexamethasone should not be administered as an anti-emetic. Fluid deficits should be corrected before initiation of study drug and during treatment.

Diarrhea

Diarrhea should be managed according to clinical practice, including the administration of antidiarrheals once infectious causes are excluded. Fluid intake should be maintained to avoid dehydration. Fluid deficits should be corrected before initiation of treatment and during treatment. Prophylactic antidiarrheals are not generally recommended.

Erythematous Rash With or Without Pruritus

As with VELCADE, rash with or without pruritus has been reported with MLN9708, primarily at the higher doses tested. The rash may range from some erythematous areas, macular and/or small papular bumps that may or may not be pruritic over a few areas of the body or more generalized, has been transient and has resolved either spontaneously or with standard symptomatic measures such as oral or topical steroids and/or antihistamines. Prophylactic measures should also be considered if a patient develops a rash (eg, using a thick, alcohol-free emollient cream on dry areas of the body). In the case of rash, the use of a topical or oral steroid (eg, prednisone $\leq$ 10 mg per day or equivalent) is permitted. A rare risk is Stevens-Johnson Syndrome, a severe, life-threatening or deadly rash with skin peeling and mouth sores, which should be managed symptomatically according to standard medical practice.

Thrombocytopenia

Thrombocytopenia has been reported to date primarily at the higher doses tested. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Thrombocytopenia may be severe but has been manageable with platelet transfusions according to standard clinical practice. Thrombocytopenia nadirs commonly recover without intervention by the beginning of the next scheduled cycle. MLN9708 administration should be modified as noted as per dose modification recommendations when thrombocytopenia occurs. A rare risk is thrombotic thrombocytopenic purpura (TTP), a rare blood disorder where blood clots form in small blood vessels throughout the body characterized by thrombocytopenia, petechiae, fever, or possibly more serious signs and symptoms. TTP should be managed symptomatically according to standard medical practice.

Neutropenia

Neutropenia has been reported with MLN9708 and pomalidomide. Blood counts should be monitored regularly as outlined in the protocol with additional testing obtained according to standard clinical practice. Neutropenia may be severe but has been manageable with G-CSF Neutropenic nadirs commonly recover without intervention by the beginning of the next scheduled cycle or with a short delay in treatment. MLN9708 administration should be modified when neutropenia occurs, as noted in the dose modification recommendations. Given that MLN9708 will be administered in combination with pomalidomide, with overlapping toxicity of neutropenia, G-CSF will be used prophylactically in this protocol.

Fluid Deficits

Dehydration should be avoided because MLN9708 may cause vomiting, diarrhea, and dehydration. Acute renal failure has been reported with MLN9708. Fluid deficits should be corrected before initiation of study drug and during treatment and as needed during therapy.

Nonsteroidal anti-inflammatory drugs (NSAIDs) induced prevalence of nephrotoxicity is relatively low; however, given the wide use of these agents many persons are at risk, including for example, patients with cardio-renal disease, dehydration, and the aging kidney. NSAIDs should be avoided with impaired renal function given reported NSAID-induced renal failure in patients with decreased renal function. Until further information is available, intake of NSAIDs while on this protocol should be avoided.

Hypotension

Symptomatic hypotension and orthostatic hypotension have been reported with MLN9708. Blood pressure should be closely monitored while the patient is on study treatment and fluid deficit should be corrected as needed, especially in the setting of concomitant symptoms such as nausea, vomiting, diarrhea, or anorexia. Patients taking medications and/or diuretics to manage their blood pressure (for either hypo- or hypertension) should be managed according to standard clinical practice, including considerations for dose adjustments of their concomitant medications during the course of the trial.

Posterior Reversible Encephalopathy Syndrome

One case of posterior reversible encephalopathy syndrome (PRES) has been reported with MLN9708. While this case ultimately resolved, PRES has also been reported rarely with another proteasome inhibitor, Velcade. PRES is characterized by headache, seizures and visual loss, as well as abrupt increase in blood pressure. Prompt diagnosis and initiation of antihypertensive and anticonvulsant therapy are important to prevent irreversible end-organ damage.

Anticoagulation Consideration

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

Consideration should be given to the requirement of aspirin (81 or 325 mg) or some other form of prophylaxis as deemed appropriate. Low molecular weight heparin may be utilized in patients that are intolerant to ASA. Coumadin should be used with caution and close monitoring of INR.

8. STUDY DRUG

8.1 Packaging and Labeling

8.1.1 MLN9708

The study drug MLN9708 capsules will be provided by Millennium. The study drug will be labeled and handled as open-label material, and packaging labels will fulfill all requirements specified by governing regulations.

MLN9708 capsules should be stored unopened at 2°C to 8°C (36°F-46°F). The capsules are individually packaged in cold form foil-foil blisters in a child-resistant package. The 0.5-, 2.3-, 3.0-, and 4.0 mg capsules are supplied as a 1 x 3 blister card in a child-resistant cardboard wallet.

8.1.2 Pomalidomide

Pomalidomide capsules will be provided by Celgene Corporation as 1.0, 2.0, 3.0 and 4.0 mg capsules for oral administration.

Pomalidomide (POMALYST®) will be provided to research patients 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 patients enrolled into this trial, and all research patients 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.

Pomalidomide investigational supplies are dispensed to the patients in individual bottles of capsules. Each bottle will identify the contents as study medication. In addition, the label will bear Celgene's name, quantity contained and the standard caution statement as follows: Caution: New drug - Limited by Federal law to investigational use. 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.

8.2 Storage, Handling, and Accountability

MLN9708 and pomalidomide are anticancer drugs and as with other potentially toxic compounds caution should be exercised when handling MLN9708 and pomalidomide capsules.

8.2.1 MLN9708

Upon receipt at the investigative site, MLN9708 should remain in the blister and carton provided until use or until drug is dispensed. The container should be stored at the investigative site refrigerated (36°F to 46°F, 2°C to 8°C). Ensure that the drug is used before the retest expiry date provided by Millennium. Expiry extensions will be communicated accordingly with updated documentation to support the extended shelf life.

In countries where local regulations permit, MLN9708 capsules dispensed to the patient for take-home dosing should remain in the blister packaging and refrigerated as noted above until the point of use. The investigative site is responsible for providing the medication to the patient in the correct daily dose configurations. Comprehensive instructions should be provided to the patient in order to ensure compliance with dosing procedures. Patients who are receiving take-home medication should be given only 1 cycle of medication at a time. Patients should be instructed to store the medication refrigerated (36°F to 46°F, 2°C to 8°C) for the duration of each cycle. Patients should be instructed to return their empty blister packs to the investigative site, rather than discarding them. Reconciliation will occur accordingly when the patient returns for their next cycle of take-home medication. Any extreme in temperature should be reported as an excursion and should be dealt with on a case-by-case basis.

Because MLN9708 is an investigational agent, it should be handled with due care. Patients should be instructed not to chew, break, or open capsules. In case of contact with broken capsules, raising dust should be avoided during the clean-up operation. The product may be harmful by inhalation, ingestion, or skin absorption. Gloves and protective clothing should be worn during cleanup and return of broken capsules and powder to minimize skin contact.

The area should be ventilated and the site washed with soap and water after material pick-up is complete. The material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (eg, from a broken capsule), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified. Patients are to be instructed on proper storage, accountability, and administration of MLN9708, including that MLN9708 is to be taken as intact capsules.

Investigational MLN9708 (expired or end of study) should be destroyed on site according to the institution's standard operating procedure. Be sure to document removal and destruction on drug accountability logs.

8.2.2 Pomalidomide

Care should be exercised in handling of pomalidomide. Pomalidomide capsules should not be opened or crushed. If powder from pomalidomide contacts the skin, wash the skin immediately and thoroughly with soap and water. If pomalidomide contacts the mucous membranes, flush thoroughly with water.

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

Storage
At the study site, all pomalidomide 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.

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

Only enough pomalidomide capsules for 1 cycle of therapy may be provided to the patient

each cycle.

9. STUDY COMPLIANCE

Study drug will be administered or dispensed only to eligible patients under the supervision of the investigator or identified sub-investigator(s). The appropriate study personnel will maintain records of study drug receipt and dispensing.

9.1 Treatment Assignment

Patients will be assigned at the time of enrollment (per section 6.0) to a given dose level during the phase I portion of the study or to the recommended phase II dose as determined during the phase I portion of the study.

9.2 Termination of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from the study at any time for any reason, without prejudice to their medical care. The investigator also has the right to withdraw patients from the study for any of the following reasons:

- Adverse event
- Lack of Protocol adherence
- Lost to follow-up
- Progressive disease
- Study termination

At the time of withdrawal, all study procedures outlined for the End of Treatment visit should be completed. The primary reason for patient's withdrawal from the study will be recorded in the source documents and CRF.

The Lead Principal Investigator or designee must be notified within 24 hours if a patient is withdrawn from the study by the Data Coordinating Center or designee.

If the reason for withdrawal is the occurrence of an AE, the Investigator will follow the patient until such events resolve, stabilize, and according to the Investigator's judgment, there is no need of further follow up.

10. STATISTICAL AND QUANTITATIVE ANALYSES

10.1 Statistical Methods

10.1.1 Determination of Sample Size

Phase I: The phase I study will follow a 3+3 design, to evaluate toxicities associated with MLN9708 when given in combination with pomalidomide and dexamethasone. Two doses of MLN9708 (dose level -1 and dose level 1: 3 mg; dose level 2: 4 mg) will be tested in up to three possible dose levels; there will be no dose reductions below the 3mg dose of MLN9708. In the phase I portion of this study, the total sample size will depend on the number of dose levels evaluated to determine the maximum tolerated dose (MTD). While the phase I study is expected to enroll and treat 9 patients (3 patients treated on dose level 1 and 6 additional patients treated at dose level 2 -assuming the 4mg dose is well tolerated), a maximum of 18 patients could be treated (6 patients per dose level). The highest dose level that produces ≤1/6 DLTs in cycle 1 will be the MTD. (See section 7.4 for dose expansion/escalation rules.) The recommended phase II dose (RP2D) of MLN9708 and pomalidomide will generally be the MTD, but it may be less than the MTD based on a review of available data/cumulative toxicities from phase I.

Phase II: For this trial, where MLN9708 will be added to pomalidomide and dexamethasone, patients with prior exposure to either of these agents would not be excluded, unlike the patients treated on the randomized phase III study of comparing pomalidomide plus dexamethasone, to high-dose dexamethasone alone. As many patients (>50%) are likely to have been previously treated with one or both of these agents we consider a response rate of 30% sufficient efficacy to justify further development.[26] In addition, the estimation of response in this refractory/high-risk population is of equal importance. Given this, the phase II portion of the trial, will use a Gehan two stage design (Gehan, 1961). The phase II trial is expected to enroll a minimum of 9 and a maximum of 25 patients. The six patients treated at the RP2D in the phase I portion of the study will count toward the 25 patients required. Given this, we expect to enroll only 19 new patients on the phase II trial. The sample size is based on the desire to estimate the response rate with at most 10% standard error, and early stopping if the combination is unexpectedly ineffective. The primary endpoint is confirmed tumor response (sCR/CR/VGPR or PR).

At stage 1, 9 patients will be entered on the study. If 0 responses are seen in the first 9 patients treated, the study will be terminated and the true regimen response will be declared ≤30%. If at least 1 patient responds, the trial will continue to the second stage. Because patients treated during the phase I portion of the trial at the dose selected for the phase II trial will be counted

(n=6), only 3 additional patients will be enrolled at stage 1. Under this design if the study regimen is >30% effective, there would be ~95.6% chance of at least one success. At stage 2, 16 additional patients will be entered. This accrual provides for estimation of the response rate with no more than 10% standard error.

10.1.2 Populations for Analysis

Phase I (Evaluable for Toxicity): Patients will be considered evaluable for toxicity if they receive any study drug. Patients will be considered evaluable for dose limiting toxicity if they receive at least 75% of both Pomalidomide and MLN9708 and are followed for the full 28 days during cycle 1 or experience a DLT. All patients who are not evaluable for dose limiting toxicity will be replaced.

Phase II (Evaluable for Toxicity): Patients will be considered evaluable for toxicity if they receive any study drug. Patients in Phase II will not be replaced based on toxicity.

Phase I and II (Evaluable for Response): For the phase II portion, as part of the primary analysis, patients will be considered evaluable for response if they are eligible, have baseline disease assessments, and receive any protocol treatment. As part of a secondary analysis, patients will be considered evaluable for response if they have baseline disease assessments, receive at least 75% of both Pomalidomide and MLN9708 during the first cycle of therapy and have had their disease re-evaluated. Patients will have their response classified according to the IMWG response criteria. All patients in phase II and those treated at the RP2D in phase I, who are not evaluable for response will be replaced.

10.1.3 Demographic and Baseline Characteristics

Patient demographic and baseline characteristics, including age, gender, medical history, and prior therapy, will be summarized using descriptive statistics. For continuous variables, descriptive statistics (number [n], mean, standard deviation, standard error, median (range) will be provided. For categorical variables, patient counts and percentages will be provided.

10.1.4 Efficacy Analysis

A primary activity endpoint is not defined for the Phase I study. The primary activity endpoint for the Phase II study is response rate. Response rates (overall, clinical benefit) and depth of response will be calculated as the percent of evaluable patients that have confirmed sCR/CR/VGPR or PR (overall) or sCR/CR/VGPR/PR/MR or SD (clinical benefit), exact 95% confidence intervals will be calculated for these estimates. Response rates will also be evaluated

based on number and type of prior therapy(ies). Response defined as per modified IMWG criteria. Time to response, duration of response, and survival (overall and progression-free) will be estimated using the product-limit method of Kaplan and Meier.

10.1.5 Safety Analysis and Stopping Rules for Excessive Toxicity

Toxicity information recorded will include the type, severity, and the probable association with the study regimen. Tables will be constructed to summarize the observed incidence by severity and type of toxicity.

The following table will be consulted as relevant toxicities are encountered. The early stopping rule for safety/toxicity will be assessed for each patient after cycle 1. The expected rate of unacceptable toxicity should not be ≥33%. Note: Unacceptable toxicity is defined in section 7.3 of the protocol. See the table below for detailed early stopping rules. These rules are in addition to the quarterly review of all toxicities submitted to the COH DSMC. Patients with ongoing toxicity (cycle 1 toxicity persisting beyond day +28) will be followed until resolution or stability. If more than the specified number of patients has significant treatment related toxicities, patient accrual will be halted and a full review of the data by the Data Safety Monitoring Committee (DSMC) will be mandated. Patient accrual will not resume until approved by the DSMC to do so.

# of patients treated at phase II dose	# of patients with unacceptable toxicity to halt enrollment[1]	Given the following toxicity rates, cumulative probability of early stopping:		
		15%	33%	45%
6	2	0.22	0.64	0.84
12	4	0.24	0.73	0.92
18	6	0.25	0.78	0.95
[1]: For each unacceptable toxicity, halt enrollment and evaluate if the cumulative # of patients reaches or exceeds the specified limits.				

We recognize that these stopping rules represent the overall stoping rules including the patient evaluated on a given dose during the Phase I portion. As such, these rules represent the stopping probabilities of a dose with the above toxicity rates, including stopping during the phase I dose finding portion. Once the MTD has been selected, and additional patients are accrued (presumably at the MTD), the probability of early stopping is less (e.g. 26% of chance of early stopping at 12 patients if the true probability of unacceptable toxicity is 33%, and a 44% chance

of early stopping at 18 patients in that scenario). This represents the probability of early stopping conditional on passing the criteria for MTD selection (0 or 1 out of 6).

11. DATA AND SAFETY MONITORING

11.1 Definition of Risk Level

This is a Risk Level 4 study, as defined in the "City of Hope Data and Safety Monitoring Plan", http://www.coh.org/dsmc/Pages/forms-and-procedures.aspx. City of Hope is sponsor of this IND.

11.2 Monitoring and Personnel Responsible for Monitoring

The Protocol Monitoring Team (PMT) consisting of the PI, Collaborating Investigator, CRC/protocol nurse, statistician and COH Data Coordinating Center staff is responsible for monitoring the data and safety of this study, including implementation of the stopping rules for safety and efficacy.

Beginning with the enrollment of the first patient, the PMT will meet weekly or bi-weekly via teleconference for patient and protocol management issues.

This study will utilize the Phase I tracking log to monitor data and safety for dose escalation, recording doses administered, and resultant adverse events**.** The tracking log will contain dose levels administered, DLT-defining adverse events, and documentation that the data from a dose level is complete before dose escalation. Those data and safety elements will be reported to the COH DSMC as applicable within the PMT report, which will be submitted quarterly from the anniversary date of activation, as noted in Table 1 below.

Table 1: City of Hope PMT Reporting Timelines for the DSMC

Risk Level	Phase	Standard Reporting Requirement
RL 1, RL2, and Compassionate Use Studies	No reports required	
3	I	Every 3 months from activation date, as indicated in MIDAS

3	Pilot, Feasibility, II-IV	Every 6 months from activation date, as indicated in MIDAS
4	Pilot, Feasibility, I-IV	Every 3 months from activation date, as indicated in MIDAS

During periods of active protocol enrollment, quarterly reports of all protocol activity will be submitted to the DSMC and will include:

1) The number of patients screened, enrolled and treated.
2) Cohort status updates.
3) List of AEs (including SAEs/UPs).
4) Protocol deviations.

Annual continuation reports will be made to the IRB, Cancer Protocol Review and Monitoring Committee (CPRMC) at COH and to the Food and Drug Administration (FDA). These reports will be made available to participating institutions (as requested).

11.3 Definitions

11.3.1 Pretreatment Event Definition

A pretreatment event is any untoward medical occurrence in a patient or subject who has signed informed consent to participate in a study but before administration of any study medication; it does not necessarily have to have a causal relationship with study participation. For serious pre-treatment events, the investigator must determine both the intensity of the event and the relationship of the event to the study procedures.

11.3.2 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has

increased in severity or frequency since the administration of study drug. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event.

An abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

11.3.3 Unexpected Adverse Event [21 CFR 312.32 (a)]

An AE is unexpected if it is not listed in the investigator's brochure and/or package insert; is not listed at the specificity or severity that has been observed; is not consistent with the risk information described in the protocol and/or consent; is not an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the AE.

11.3.4 Expected Adverse Event

Any event that does not meet the criteria for an unexpected event OR is an expected natural progression of any underlying disease, disorder, condition, or predisposed risk factor of the research participant experiencing the AE.

11.3.5 Serious Adverse Event (SAE) [21 CFR 312.32] is defined as any expected or unexpected AE that, at any dose, results in any of the following outcomes:

- Results in **death**.
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe);
- Requires inpatient **hospitalization or prolongation of an existing hospitalization** (except scheduled hospitalizations for non-acute, unrelated cause such as an elective surgery);

- Results in **persistent or significant disability or incapacity** (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect.**
- **Secondary malignancy**, or
- Any other **AE that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the outcomes listed above** (examples of such events include allergic bronchospasm requiring intensive treatment in the emergency room or at home, blood dyscrasisas of convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse).

11.3.6 Unanticipated problem – Any incident, experience or outcome that **meets all three** of the following criteria:

1. Unexpected (in term nature, severity, or frequency) given the following: a) the research procedures described in the protocol-related documents such as the IRB approved research protocol, informed consent document or Investigator Brochure (IB); and b) the characteristics of the subject population being studied; **AND**
2. Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcomes may have been caused by the drugs, devices or procedures involved in the research); **AND**
3. Suggests that the research places subjects or others at greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action

criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/mm^3 to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

AEs which are serious must be reported to Celgene and Millennium Pharmacovigilance (or designee) from the date the participant signs Informed Consent through 30 days after administration of the last dost of pomalidomide or MLN9708. Any SAE that occurs at any time after completion of MLN9708/pomalidmide treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Millennium/Celgene Pharmacovigilance (or designee). In addition, new primary malignancies that occur during the follow-up periods must be reported, regardless of causality to study regimen, for a minimum of three years after the last dose of the investigational product, starting from the first dose of study drug. All new cases of primary malignancy must be reported to Millennium/Celgene Pharmacovigilance (or designee).

Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or later than planned). All SAEs should 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). Each Investigator is also responsible for reviewing their institutional guidelines and reporting locally based on those guidelines (i.e., unanticipated problems).

Relationship to all study drugs for each SAE will be determined by the investigator or sub-investigator by responding yes or no to the question: Is there a reasonable possibility that the AE is associated with the study drug(s)?

11.2 Reporting of Unanticipated Problems and Adverse Events

Unanticipated Problems: Most unanticipated problems must be reported to the COH DSMC and IRB **within 5 calendar days** according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx. Any unanticipated problem that occurs during the study conduct will be reported to the DSMC and IRB by submitting

electronically in iRIS (http://iris.coh.org). Participating institutions will submit to the COH Data Coordinating Center.

Serious Adverse Events - **All SAEs occurring during this study, whether observed by the physician, nurse, or reported by the patient, will be reported according to definitions and guidelines at http://www.coh.org/hrpp/Pages/hrpp-policies.aspx and Table 2 below. Those SAEs that require expedited reporting will be submitted electronically in iRIS (http://iris.coh.org/).**

Adverse Events - Adverse events will be monitored by the PMT. Adverse events that do not meet the criteria of serious OR are not unanticipated problems will be reported only in the continuation reports and PMT reports (see Table 2 below).

Table 2: City of Hope Adverse Event and Unanticipated Problem Reporting Timelines for the DSMC and IRB

Required Reporting Timelines to DSMC for AE/SAEs
Investigator Initiated Studies

Required Reporting Timeframe to DSMC		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death while on active treatment or within 30 days of last day of treatment	
Possibly, Probably, Definitely	5 calendar days	
Unlikely, Unrelated		
	Death after 30 days of last active treatment/therapy	
Possibly, Probably, Definitely	5 calendar days	No reporting required
Unlikely, Unrelated	No reporting required	No reporting required
	Grades 3 and 4 AND meeting the definition of "serious"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	5 calendar days	10 calendar days
	Grades 1 and 2 AND resulting in "hospitalization"	
Possibly, Probably, Definitely	5 calendar days	10 calendar days
Unlikely, Unrelated	10 calendar days	10 calendar days

An event determined by the IRB of record to be an Unanticipated Problem (UP) will be communicated to the Investigator and COH DSMC through the COH IRB Operations Director. The DSMC will review the case and make a determination as to whether the

study will be suspended, terminated, amended, or allowed to continue without amendment.

Required Reporting Timeframe to IRB of Record		
Attribution	**UNEXPECTED**	**EXPECTED**
	Death	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grades 3 and 4 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual
	Grade 1 and 2 AND meeting the definition of a UP	
Possibly, Probably, Definitely	5 calendar days	Annual
Unlikely, Unrelated	Annual	Annual

The Sponsor-Investigator and the COH Data Coordinating Center must be notified by phone, fax or of the occurrence of any SAE or Unanticipated Problem within 24 hours of the investigator, designee, or site personnel's knowledge of the event. To report an SAE/UP, the site representative must complete the Notification of Unanticipated Problem/Serious Adverse Event/Pregnancy Form (attached as an Appendix 15.3) and MEDWATCH 3500A form , then fax or scan/email the forms (as noted below) using secure email (#secure# in subject line of email):

City of Hope Data Coordinating Center

Fax Number: 626 301-8422

COH DCC email: dcc@coh.org (always use #secure# in subject line)

Telephone reports must be followed by a written report within 24 hours. Follow-up reports must be submitted in a timely fasion as additional information becomes available.

The Investigator is responsible for notifying the Institutional Review Board (IRB) or Independent Ethics Committee (IEC) in accordance with local institutional regulations, of all SAEs. The Sponsor-Investigator, the City of Hope Data Coordinating Center and/or

Millennium/Celgene may request additional source documentation pertaining to the SAE. If a patient is permanently withdrwawn from the study because of a SAE, this information must be included in the initial or follow-up SAE report as well as the Study Discontinuation case report form.

The investigator is responsible for reporting serious adverse events that occur from the signing of the study specific consent through the duration of the post-therapy adverse event collection period to the City of Hope Data Coordinating Center (see section above for submission guidelines), as indicated when using MLN9708 and Pomalidomide within 24 hours of becoming aware of the SAE. Notification can be made via phone or telefacsimile using the MEDWATCH 3500A form. The Sponsor-Investigator, through the COH DCC, will report to Millennium and Celgene within 24 hours.

SAE and Pregnancy Reporting Contact Information - Millennium

Millennium Pharmacovigilance Designee, PPDI, PVG:

The COH DCC will fax the MEDWATCH 3500A form (Millennium Pregnancy Form attached as Appendix 15.4.4 when reporting pregnancy) within 24 hours to:

Cognizant

Contact Information:

Fax Number: 1-800-963-6290

Email: TakedaOncoCases@cognizant.com

SAE and Pregnancy Reporting Contact Information – Celgene

The Sponsor-Investigator through the COH DCC will inform Celgene in writing using the MEDWATCH 3500A of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (PO-MM-PI-0062) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to

Celgene should be attached to the SAE and retained with the patient records.

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park
300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax: (908) 673-9115/Email: drugsafety@celgene.com

ADDITIONAL REPORTING REQUIREMENTS

Serious Adverse Events meeting the requirements for expedited reporting to the FDA, as defined in 21 CFR 312.32, will be reported as an IND safety report using the MedWatch Form FDA 3500Afor Mandatory Reporting which can be found at:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm

The City of Hope Data Coordinating Center will work with participating institutions to obtain the required serious adverse event report forms including any follow up information.

The IND is held by COH, and the Sponsor-Investigator or designee, including the City of Hope Data Coordinating Center will be responsible for contacting the Office of IND Development and Regulatory Affairs (OIDRA) at COH to ensure prompt reporting of safety reports to the FDA. OIDRA will assist the PI and COH DCC with the preparation of the report and submit the report to the FDA in accordance with the following:

- any unexpected fatal or life threatening adverse experience associated with use of the drug must be reported to the FDA no later than 7 calendar days after initial receipt of the information [21 CFR 312.32(c)(2)];
- any adverse experience associated with use of the drug that is both serious and unexpected must be submitted no later than 15 calendar days after initial receipt of the information [21 CFR 312.32(c)(1)]
- any follow-up information to a study report shall be reported as soon as the relevant information becomes available. [21 CFR 312.32(d)(3)]

Sponsor-investigator or designee must also provide Millennium/Celgene Pharmacovigilance with a copy of all communications with applicable regulatory authorities related to the study or study drug(s), including, but not limited to, telephone conversation logs within 24 hours of such communication.

Adverse Events of Special Interest (AESIs) are a subset of AEs that are to be reported to Millennium on a quarterly basis by the sponsor-investigator. These adverse events will be captured using Medidata RAVE, the electronic data capture system used for data collection for this trial as part of routine data collection. A report will be generated and submitted to Millennium on a quarterly basis by the City of Hope Data Coordinating Center. Millennium will provide the current list of AESIs and updates to the list will be distributed to the sponsor-investigator as appropriate.

The highest grade of non-Serious Adverse Events of Special Interest (AESIs) observed in patients will be reported. AESIs are defined as:

1. Neuropathy
    - Neuropathy peripheral
    - Peripheral sensory neuropathy
    - Polyneuropathy
    - Paraesthesia
    - Hyperaesthesia
    - Burning sensation
    - Oral pain
    - Paraesthesia oral
    - Muscle spasms
    - Muscular weakness
2. Hematologic Toxicities
3. Rash
    - Rash

- Rash macular
- Rash maculo-papular
- Rash generalized
- Rash pruritic
- Pruritus
- Rash erythematous
- Erythema
- Rash popular
- Skin exfoliation
- Exfoliative rash

4. Respiratory Complaints
    - Pneumonia
    - Pneumonitis
5. Renal toxicity
    - Blood creatinine increased
    - Blood creatinine abnormal
    - Blood urea decreased
    - Renal failure acute
    - Renal failure
    - Renal impairment
6. Hypotension
    - Orthostatic hypotension
    - Presyncope
    - Syncope
7. New Primary Malignancy
    - For all myeloma studies, new primary malignancies must be reported for at least two years from the Clinical Trial patient's first dose of MLN9708.

Procedures for Reporting Drug Exposure During Pregnancy and Birth Events

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female patient occurring while the patient is on MLN9708 or pomalidomide, or within 90 days of the patient's last dose of therapy), are considered immediately reportable events. MLN9708 and pomalidomide are to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported. The investigator must notify the sponsor-investigator and the COH DCC immediately by phone and by completing and faxing the Notification of Unanticipated Problem/Serious Adverse Event/Pregnancy Form (attached as an Appendix 15.3). The sponsor-investigator through the COH DCC will be responsible for notifying Millennnium Pharmacovigilence(through Millennium Pregnancy Form attached as Appendix 15.4.4)//Celgene Drug Safety.

The female patient should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female patient until completion of the pregnancy, and must notify the sponsor-investigator and the COH DCC immediately phone and by completing by completing and faxing the Notification of Unanticipated Problem/Serious Adverse Event/Pregnancy Form (attached as an Appendix 15.3). The sponsor-investigator through the COH DCC will be responsible for notifying Millennnium Pharmacovigilence(through Millennium Pregnancy Form attached as Appendix 15.4.4)//Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.

If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE. The investigator must notify the sponsor-investigator and the COH DCC immediately phone and by completing by completing and faxing the Notification of Unanticipated Problem/Serious Adverse Event/Pregnancy Form (attached as an Appendix 15.3). The sponsor-investigator through the COH DCC will be responsible for

notifying Millennnium Pharmacovigilence(through Millennium Pregnancy Form attached as Appendix 15.4.4)//Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the in utero exposure to MLN9708 and pomalidomide should also be reported. The investigator must notify the sponsor-investigator and the COH DCC immediately phone and by completing by completing and faxing the Notification of Unanticipated Problem/Serious Adverse Event/Pregnancy Form (attached as an Appendix 15.3). The sponsor-investigator through the COH DCC will be responsible for notifying Millennnium Pharmacovigilence(through Millennium Pregnancy Form attached as Appendix 15.4.4)//Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event.

Male Patients

If a female partner of a male patient taking MLN9708 or pomalidomide becomes pregnant, the male patient should notify the Investigator immediately, and the pregnant female partner should be advised to call their healthcare provider immediately.

12. ADMINISTRATIVE REQUIREMENTS

12.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the study drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

12.2 Ethical Considerations

The study will be conducted in accordance with applicable regulatory requirement(s) and will adhere to GCP standards. The IRB will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will be conducted only at sites where IRB approval has been obtained. The protocol, Investigator's Brochure, informed consent form, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB by the investigator. Millennium/Celgene requests that informed consent documents be reviewed by Millennium/Celgene or designee prior to IRB submission.

This study must have the approval of a properly constituted IRB or IEC. Before the investigational drug is shipped to the Site Investigator, the Site Investigator or designee will provide the COH DCC with a copy of the IRB/IEC approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The COH DCC will be responsible for obtaining annual IRB/IEC reapproval throughout the duration of the study. Copies of the Investigator's annual report to the IRB/IEC and copies of the IRB/IEC continuance of approval must be submitted to the COH DCC.

The Site Investigator is also responsible for notifying their IRB/IEC of any significant adverse events that are serious, unanticipated and/or unexpected.

The COH DCC will provide study sites with any investigational new drug (IND) safety reports generated, changes to the Investigator's Brochure IB, and any safety updates. The Site Investigator is responsible for immediately notifying their IRB/IEC of any such updates.

The Lead Principal Investigator along with the COH DCC will initiate in writing any substantive changes to this protocol as a protocol amendment. The amendment will be submitted to the IRB/IEC, together with a revised informed consent, if applicable. Written documentation of IRB/IEC approval must be received before the amendment is implemented. Upon completion of the trial, the Site Investigator must provide the IRB/IEC with a summary of the trial's outcome.

12.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative before study participation. The method of obtaining and documenting the informed consent and the contents of the consent must comply with the ICH-GCP and all applicable regulatory requirements.

The City of Hope Data Coordinating Center will provide the Site Investigator with a sample consent form. Local and/or institutional requirements may require disclosure of additional information in the informed consent. Any changes to the consent form must be submitted to the COH DCC for approval, prior to submission to the IRB/IEC. The IRB/IEC will review the consenf form for approval. A copy of the approved form must be submitted to the COH DCC prior to initiation of the study.

Before implementing any study procedure, informed consent shall be documented by the use of a written consent form approved by the IRB/IEC and signed and dated by the patient or the patient's legally authorized representative at the time of consent. A copy of the signed informed consent will be given to the patient or patient's legally authorized representative. The original signed consent must be maintained by the Site Investigator and available for inspection by the COH DCC, its designated representatives, or regulatory authority at any time.

12.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. If requested, the investigator will grant monitor(s) and auditor(s) from City of Hope, Millennium/Celgene or its designees and regulatory authority (ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

The investigator/institution will permit direct access to source data and documents by the COH DCC staff, its designees, the FDA, and other applicable regulatory authorities. The access may consist of trial-related monitoring, including remote monitoring, audits, IRB/IEC reviews, and FDA/regulatory authority inspections.

Release of research results should preserve the privacy of medical information and must be carried out in accordance with Department of Health and Human Services Standards for Privacy of Individually Identifiable Health Information, 45 CFR 164.508.

12.5 Investigator Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Millennium/Celgene and written IRB approval/favorable opinion from City of Hope (as the sponsor) prior to implementation, except when the

modification is needed to eliminate an immediate hazard(s) to patients. The IRB may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB. The investigator will submit all protocol modifications to Millennium/Celgene and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

12.6 Study Documentation and Archives

12.6.1 Source Documents

Source documents are original documents, data, and records (e.g., medical records, data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. The Site Investigator or their designee will prepare and maintain adequate and accurate source documents. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source documents must be adequate to reconstruct all data transcribed onto the case report forms.

12.6.2 Case Report Form Completion

All data will be collecting using COH data collection forms via an electronic data capture system, Medidata RAVE. All case report forms must be completed by designated study personnel. The completed case report forms must be reviewed, signed and dated by the Site Investigator or designee in a timely fashion.

All data will be submitted as follows:

- **Eligibilty Checklist:** the participating institutions at the registering site will have completed and faxed this form at the time of registration.
- **On-Study/Baseline Forms:** completed on-study forms are due within two weeks of registration.
- **Treatment Forms (Cycle Forms):** completed forms are due within 2 weeks of completion of a cycle (unless needed sooner for DLT assessment during Phase I). The City of Hope Data Coordinating center will communicate with site staff if forms are needed sooner.

- **Adverse Event Collection:** completed adverse events are due within two weeks of a cycle (unless needed sooner for DLT assessment during Phase I). The City of Hope Data Cooridnating center will communicate with site staff if forms are needed sooner.

- **Response/Off Treatment/Off Study/Follow-Up:** forms will be completed each time a patient is evaluated for response, comes off treatment, new follow-up information is obtained or comes off study.

12.7 Archival of Records

According to 21 CFR 312.62I, the Site Investigators shall retain records required to be maintained under this part for a period of 2 years following the date a marketing application is approved for the drug for the indication for which it is being investigated. If no application is to be filed or if the application is not approved for such indication, the Site Investigator shall retain these records until 2 years after the investigation is discontinued and the FDA or applicable regulatory authorities are notified.

The Site Investigator must retain protocols, amendments, IRB/IEC approvals, copies of the Form FDA1572, signed and dated consent forms, medical records, case report forms, drug accountability records, all correspondence, and any other documents pertaining to the conduct of the study.

12.8 Study Monitoring and Data Collection

Following initiation of the study site, remote monitoring will be completed by the COH DCC. The Site Investigator will allocate sufficient time for the designated site staff to submit source documentation as required to complete remote monitoring.

The purpose of trial monitoring is to verify the following:

- The rights and well-being of human subjects are protected.
- The reported data are accurate , complete, and verificable from source documents.
- The conduct of the trial is in compliance with the currently approved protocol, amendment(s), ICH GCP, FDA CFR, and any other applicable regulatory requirements.

The COH DCC will submit a prepare a written report after each remote monitoring timepoint or trial related communication. Reports shall include a summary of what the monitor reviewed

remotely and significant findings, deviations and deficiencies, conclusions, actions taken or to be taken to ensure site compliance.

City of Hope's Data Coordinating Center, regulatory authorities, the IRB and/or Millennium/Celgene may request access to all source documents, data capture records, and other study documentation for on-site audit, inspection and remote monitoring. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

12.9 Investigator and Site Responsibility for Drug Accountability

Accountability for the study drug at all study sites is the responsibility of the principal investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records for each respective drug/company, MLN9708 for Millennium and pomalidomide for Celgene indicating the drug's delivery date to the site, inventory at the site, use by each patient, and amount returned to Millennium/Celgene or a designee or disposal of the drug (if applicable and if approved by Millennium/Celgene) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers. Accountability records will need to be submitted to the COH DCC as requested.

12.10 MLN9708 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below) and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

For Product Complaints, call MedComm Solutions at 877-674-3784 (877 MPI DRUG) (US and International)

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to Millennium.

12.11 Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator or Millennium/Celgene, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator or Millennium/Celgene by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient, incomplete and/or unevaluable data
- Determination of efficacy based on interim analysis
- Plans to modify, suspend or discontinue the development of the drug

12.12 Record Retention

The investigator will maintain all study records according to the ICH-GCP and applicable regulatory requirement(s).

13. USE OF INFORMATION

All information regarding MLN9708 supplied by Millennium and pomalidomide by Celgene to the investigator is privileged and confidential information. The investigator agrees to use this information to accomplish the study and will not use it for other purposes without consent from Millennium/Celgene. It is understood that there is an obligation to provide Millennium/Celgene with complete data obtained during the study. The information obtained from the clinical study will be used toward the development of MLN9708 and may be disclosed to regulatory authority(ies), other investigators, corporate partners, or consultants as required.

Upon completion of the clinical study and evaluation of results by Millennium/Celgene, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

14. REFERENCES

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15. APPENDICES

15.1 Eastern Cooperative Oncology Group (ECOG) Scale for Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

15.2 Cockcroft-Gault Equation

For males:

$$\text{Creatinine Clearance} = \frac{(140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{(140\text{–age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

For females:

$$\text{Creatinine Clearance} = \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{72 \times (\text{serum creatinine[mg/dL]})} \quad \text{OR} \quad \frac{0.85\ (140\text{-age[years]} \times \text{weight [kg]})}{0.81 \times (\text{serum creatinine[}\mu\text{mol/L]})}$$

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

15.3 NOTIFICATION OF UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT/PREGNANCY

City of Hope Data Coordinating Center
Department of Clinical Research Information Support

NOTIFICATION OF UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT/PREGNANCY
For Use by Participating Institutions Only

THIS FORM ALONG WITH A COPY OF THE MEDWATCH 3500A FORM MUST BE SUBMITTED TO THE DATA COORDINATING CENTER AT CITY OF HOPE WITHIN 24 HOURS OF KNOWLEDGE OF ONSET OF SERIOUS ADVERSE EVENT, UNANCTICIPATED PROBLEM OR KNOWLEDGE OF PREGNANCY (MEETING REPORTING CRITERIA DESCRIBED IN PROTOCOL). SCAN/EMAIL DOCUMENT TO DCC@COH.ORG (PLEASE USE #SECURE# IN SUBJECT LINE OF ANY CORRESPONDENCE)

COH IRB #12267 - Participating Site IRB # _____

Phase I/II trial of MLN9708 plus Pomalidomide and Dexamethasone for Relapsed or Relapsed Refractory Multiple Myeloma

Participating/Treating Institution: _____

Reporter: _____Phone #:_____

Email: _____

PATIENT INFORMATION Pt Study ID: _____

UNANTICIPATED PROBLEM/SERIOUS ADVERSE EVENT/PREGNANCY INFORMATION

Serious Adverse Event/Unanticipated Problem: _____

Grade: _____ Was this a dose limiting toxicity? _____

Attribution to MLN9708 (Unrelated, Unlikely, Possible, Probable, or Definite): _____

Attribution to Pomalidome (Unrelated, Unlikely, Possible, Probable, or Definite): _____

Start Date of SAE/UP: ____/____/____

REPORTING INFORMATION
Has the event been reported to the following?

Via Fax to Data Coordinating Center (COH) __ No __ Yes Date: __ __ / __ __ / __ __
Phone: 626-256-4673x63968/Email: dcc@coh.org (use #secure# in subject line)

Participating Site Institutional IRB? __ No __ Yes Date: __ __ / __ __ / __ __

SCAN/EMAIL THIS FORM AND THE MEDWATCH 3500A FORM OR PREGNANCY FORM TO DCC@COH.ORG (USE #SECURE# IN SUBJECT LINE)

15.3.1 Millennium Pregnancy Reporting Form

MILLENNIUM
THE TAKEDA ONCOLOGY COMPANY

Pregnancy Form

Report Type: ◯ Initial ◯ Follow-up | Date of Report: ___/___/_____ (DD MM Yr)

REPORTER INFORMATION: (Please forward if an alternative physician is more appropriate)

Reporter name: _____ Title: _____

Address: _____ Telephone No.: _____ Fax No. _____

City, State/Province: _____ Postal Code: _____ Country: _____

FATHER'S INFORMATION ❒ Father Unknown

Initials: _____ Date of Birth: ___/___/_____ (DD MM Yr) or Age: _____ years

Participating in an MPI clinical study? ❒ No ❒ Yes
If no, what company product was taken: _____
If yes, please provide: Study drug: _____ Protocol No: _____
Center No: _____ Patient No: _____

Medical / Familial / Social History
(i.e. Include chronic illnesses: specify, familial birth defects/genetic/chromosomal disorders; habitual exposure: specify, alcohol/tobacco; drug exposure: specify, substance abuse and medication use. Please include drug treatment prior to or around the time of conception and/or during pregnancy)

Race: _____
Occupation: _____
Number of children: _____

MOTHER'S INFORMATION:

Initials: _____ Date of Birth: ___/___/_____ (DD MM Yr) or Age: _____ years

Participating in an MPI clinical study? ❒ No ❒ Yes
If no, what company product was taken: _____
If yes, please provide: Study drug: _____ Protocol No: _____
Center No: _____ Patient No: _____

Race: _____
Occupation: _____

Medical / Familial / Social History
(i.e. Include alcohol/tobacco and substance abuse; complications of past pregnancy, labor/delivery, fetus/baby; illnesses during this pregnancy; assisted conception: specify; other disorders including familial birth defects/genetic/chromosomal disorders; method of diagnosis consanguinity, etc.)

Number of previous pregnancies: Full term ____ Pre-term ____
Outcomes of previous pregnancies:
(Please indicate number of occurrences)

- Spontaneous abortion: _____
- Therapeutic abortion: _____
- Elective abortion: _____
- Other: _____
- Normal live birth: _____
- Children born with defects: _____
- Stillbirth: _____
- Outcome unknown: _____

MOTHER'S DRUG EXPOSURE INFORMATION

Please include medical prescriptions, vaccinations, medical devices, OTC products, pregnancy supplements (such as folic acid, multivitamins)

Product Name	Dosage	Route administered to patient	Date of first use (DD/MM/Yr)	Date of end treatment (DD/MM/Yr)	Indication	Contraindicated to pregnancy
			(__/__/____)	(__/__/____)		○Yes ○No ○Unk
			(__/__/____)	(__/__/____)		○Yes ○No ○Unk
			(__/__/____)	(__/__/____)		○Yes ○No ○Unk
			(__/__/____)	(__/__/____)		○Yes ○No ○Unk

CURRENT PREGNANCY INFORMATION

Period at exposure: _____ weeks Trimester (1) (2) (3)
Date of last menstrual period: ___/___/____ DD MM Yr ❒ Unknown

Pregnancy Status

○ Pregnancy Ongoing
Estimated date of delivery: ___/___/____ DD MM Yr
○ Live Birth
○ Stillbirth
○ Early Termination
- ○ Spontaneous abortion*
- ○ Therapeutic abortion*
- ○ Elective abortion*
- ○ Other*:_____

If box is checked, please note reason in "Additional Details" section below

Fetal/Neonatal Status

❒ Normal
❒ Birth defect (structural/chromosomal disorder)*
❒ Other (non-structural, premature birth, intrauterine death/stillbirth)*

If box is checked, please note details in "Additional details" section below

Additional Details:

Is there evidence of a defect from a prenatal test? ❒Yes ❒No

If yes, indicate which test(s) showed evidence of birth defect:

❒Ultrasound ❒Amniocentesis ❒Maternal Serum-Alpha-Fetoprotein
❒Chorionic Villi Sampling ❒Human Chorionic Gonadotropin ❒Other:_____

Please specify details of defect(s), disorder(s), and/or other anomaly(ies): _____

What are the defect(s) attributed to:_____

Infant Information:

Gestational weeks at birth or at termination: _____weeks

Date of birth or termination: ___/___/_____ (DD MM Yr)

If multiple births (e.g. twins), indicate number: ____

(Please complete separate form for each child)

Birth Order (1, 2, 3, etc.) _____

Breast-fed: ❒Yes ❒ No ❒ Unk

Method of delivery: ❒ Normal vaginal ❒ Caesarean section

❒ Other: _____

Sex: ❒ Male ❒ Female ❒ Unk

Length: _____ ❒ cm ❒ in

Weight: _____ ❒ g ❒ lbs

Head circumference: _____ ❒ cm ❒ in

Apgar score (0-10) at 1 minute: ____ ❒ Unk

Apgar score (0-10) at 5 minute: ____ ❒ Unk

Resuscitation required: ❒ Yes ❒ No ❒ Unk

Admission to intensive care required:

❒ Yes ❒ No ❒ Unk

Additional Notes:

_____

_____

_____

Please attach RELEVANT LABORATORY TESTS AND PROCEDURES (e.g. results of ultrasounds, amniocentesis, chorionic villi sampling, or miscellaneous testing as applicable). In the case of an abnormal evolution or outcome, please send copies of results of all relevant laboratory testing and procedures, including pathology results of products of conception and or autopsy reports if applicable. Please submit any additional relevant information on a separate sheet.

Investigator signature: _____ Date: ___/___/_____ (DD MM Yr)

Investigator Name: _____

e-Pregnancy Form (27 November 2013)

15.4 International Myeloma Working Group Response Criteria[27]

Response[1]	*IMWG criteria*
sCR	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • ≥ 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
PR	• 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable,[3] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Stable Disease	• Not meeting criteria for CR, VGPR, PR or progressive disease
MR	• 25% but < 49% reduction of serum M protein *and* reduction in 24 hour urine M-

	protein by 50 to 89% which still exceeds 200 mg per 24 hr • In addition to the above criteria, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)
Progressive disease	Increase of ≥ 25% from lowest response value in any one of the following: • Serum M-component (the absolute increase must be ≥ 0.5 g/dL) and/or • Urine M-component (the absolute increase must be ≥ 200 mg/24h) and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

1. Adapted from Durie BGM, et al. Leukemia 2006; 20: 1467-1473;

All response categories (CR, sCR, VGPR, and PD) require two consecutive assessments made at anytime before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ I gm/dl are sufficient to define response if starting M-component is ≥ 5 g/dl.

IMWG clarification for coding PD: Clarified that Bone marrow criteria for PD are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that 25% increase refers to M protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.

Appendix 15.5: City of Hope Data Coordinating Center Plan

City of Hope
Data Coordinating Center

City of Hope has been designated to oversee this trial as the Data Coordinating Center.

This document will serve as guidance as to the responsibilities of the Data Coordinating Center, as well as those of the participating sites.

City of Hope Data Coordinating Center Responsibilities

There are multiple responsibilities associated with serving in the capacity of a data coordinating center. The City of Hope Data Coordinating Center within the Division of Clinical Research Information Support (CRIS) has adequate resources and expertise to carry out these responsibilities:

1. Assist with the design and development of the initial protocol, subsequent amendments and template informed consent documents for use at each participating institution (as applicable).
2. Selecting appropriately qualified participating sites/principal investigators (as applicable).
3. Ascertaining each protocol is reviewed and approved by the IRB at the participating site prior to enrollment of subjects at that site.
4. Ensuring, if the study is federally funded, that each collaborating institution holds an applicable OHRP-approved Federal Wide Assurance (FWA).
5. Collecting and maintaining critical documents for the Trial Master File from participating investigators, e.g. resume/CV, medical license, certification of completion of training (as applicable), laboratory certifications and laboratory norms, financial disclosure forms, etc. Maintaining the file throughout the course of the trial.
6. Distribution of Regulatory Document Binder template to participating sites. A standardized regulatory document template will be sent out to the sites that includes filing of all essential documents for the trial. A standard table of contents and tabbed dividers will be provided to the participating site prior to the protocol initiation meeting.
7. Storing and/or managing data and data and safety monitoring.
8. Protecting the confidentiality of data received from participating sites in accordance with HIPAA.
9. Ensuring informed consent is obtained and documented from each subject in compliance with US regulations.
10. Maintaining documentation of all participating site IRB approvals for the protocol (including all subsequent amendments). Ensuring that participating sites are using the correct version of the protocol and consent document.
11. Assuring that all relevant IRB correspondence (continuing review and amendments) and study status changes are communicated to all participating sites in a timely basis.
12. Providing study specific training to the research personnel at the participating site, both at trial initiation and throughout the course of the trial (re-training as needed). Training will include but not be limited to: protocol background, inclusion/exclusion, registration procedures, treatment schema, dose modification guidelines, AE/SAE/UP reporting guidelines, investigator/staff responsibilities, subsequent amendment changes, etc. The training will be documented and will be continuous throughout the course of the trial.
13. Developing and providing protocol specific case report forms for each participating site (paper and/or EDC). Training of staff on case report forms at study initiation. Continued training of participating site staff if any new changes occur to case report forms during length of study.
14. Centrally registering/randomizing subjects and tracking subject enrollment for all subjects.
15. Tracking, reporting and maintaining documentation of all serious adverse events and

unanticipated problems and dissemination of the information to participating sites for submission to their local committees (as applicable).

16. Providing periodic updates to study sponsor and participating sites on subject enrollment, general study progress, and relevant scientific advances either via email distribution or via teleconferences.
17. Preparation and coordination of teleconferences on an as needed basis (may be weekly, bi-weekly, monthly or quarterly).
18. Primary liaison for participating sites with continuous and frequent communication via email and/or teleconference to ensure protocol is running smoothly, questions have been answered and documenting any issues. Addressing issues with study sponsor immediately.
19. Documenting receipt, shipment and storage of study specimens, drugs and/or devices (if applicable).
20. Conducting continuous quality assurance checks of database, as well as protocol adherence on periodic basis (remote).
21. Monitoring, on a periodic basis, either onsite or remotely of the participating sites to assess research study progress and compliance with the IRB approved protocol.
22. Securing compliance at participating sites that are not adhering to the current version of the research protocol and/or good clinical research practices.
23. Terminating the involvement, if necessary, of non-compliant investigators and reporting such action to the IRB.

Responsibilities of the Participating Site Principal Investigators

1. Signs Form FDA 1572 to acknowledge responsibilities as defined by the regulations.
2. Provides the Data Coordinating Center and/or sponsor with required information that either attest to the absence of financial interests or arrangements as described in the Code of Federal Regulations (21. CFR 54.4) and reported on form FDA 3454 that is completed by the sponsor or provides the sponsor a complete and accurate disclosure of financial interests and arrangements as described in the regulations (21. CFR 54.4) and reported on form FDA 3455 that is completed by the sponsor.
3. Supervises members of the research team that are qualified by their education and training to accept these responsibilities for study related activities not directly performed by the PI.
4. Ensures the safety and welfare of study subjects by being knowledgeable about ongoing study protocols and investigator articles.
5. Participates as appropriate in the hiring and training of individuals recruited as members of the research team.
6. Ensures that specific sponsor requirements of the PI are fulfilled as requested.
7. Meets with the data coordinating center's and/or sponsors' representative as appropriate to discuss planned and ongoing studies. Participates in regularly scheduled teleconferences to discuss site specific information, including but not limited to: patient status, data collection, adverse event reporting, etc.
8. Ensures the participating site completes required data collection in a timely fashion and/or as spelled out in protocol.
9. Meets with auditors (sponsor, FDA, etc.) at the conclusion of their audits to review

findings (if applicable).

Each participating sites individual investigator must adhere to the following requirements in order to participate in the conduct of clinical trials with City of Hope:

- To review the Belmont report, Ethical principles and Guidelines for the Protection of Human Subjects of Research, the U.S. Department of Health and Human Services (DHHS) and FDA regulations for the protection of human subjects at 45 CFR 46, 21 CFR50, 56, 312 and 812; the COH Federal Wide Assurance; and, the COH institutional policies and procedures for the protection of human subjects, located at the COH IRB website through the COH Intranet (a copy will be distributed to participating sites).
- To understand and accept the responsibility to comply with the standards and requirements stipulated in the above documents and in the study protocol and to protect the rights and welfare of human subjects involved in research.
- To comply with all other applicable federal, international, state and local laws, regulations, and policies that may provide additional protection for human subjects participating in research.
- To abide by all determinations of the COH IRB and to accept the final authority and decisions of the COH IRB, including but not limited to directives to terminate participation in designated research activities.
- To complete any educational training required by the COH (including by the Data Coordinating Center) and/or the COH IRB prior to initiating research.
- To report promptly to the COH DCC any proposed changes in the research. These must be reviewed and approved by the COH IRB.
- To NOT initiate changes in the research without prior COH IRB review and approval, except where necessary to eliminate apparent immediate hazards to subjects.
- To report promptly to the COH PI any serious adverse events and/or unanticipated problems involving risks to subject or other as defined in the protocol and in accordance with COH policies and procedures.
- To obtain, document and maintain records of informed consent for each subject (when responsible for enrolling subjects) or each subject's legally authorized representative as required under DHHS and FDA regulations (or any other national procedural standards) as stipulated by the COH IRB.
- To acknowledge and agree to cooperate in the COH IRB's responsibility for initial and continuing reviews, record keeping and for internal and external research regulatory reporting requirements.
- To provide all information requested by the COH IRB in a timely fashion.
- To comply with all applicable FA regulations and fulfill all investigator responsibilities, including those described at 21 CFR 312 (IND regulations) and 812 (IDE regulations) when conducting research involving FDA regulated.
- To NOT enroll patients in research prior to review and approval by the COH IRB of the protocol and then subsequent review/approval at the participating site.
- To acknowledge that he/she is primarily responsible for safeguarding the rights and welfare of each research subject and that the subject's rights and welfare must take precedence over the goals and requirements of the research.
- To inform the COH/PI of important changes taken regarding membership status

of the participating site, investigators and other research staff personnel.

- To agree to communicate with the COH/PI in a timely manner.
- To agree that COH Data Coordinating Center staff will train current and/or new research personnel in protocol management and data collections.
- To agree to on-site and/or remote monitoring of all relevant data by COH Data Coordinating Center staff to assure compliance with protocol requirements and quality of the data. This will entail submission of all source documentation as requested by the COH DCC.
- To agree to remote review of source documentation as requested by the COH DCC staff.
- To participate in weekly teleconference calls (if applicable), to attend a quarterly group meeting (if applicable) and to attend an annual group meeting (if applicable), put together by the COH DCC.
- To submit all required data according to the protocol data submission schedule in a timely manner.
- To notify immediately the COH Data Coordinating Center upon notification of any external audit.

Responsibilities of the Participating Site Study Coordinator, Clinical Research Associate and/or Data Manager

1. Responsible for the sound conduct of the clinical trial, including but not limited to recruitment, screening, enrollment, treatment and follow-up of eligible subjects according to protocol requirements (e.g., subject follow-up, case report form completion in a timely fashion and reporting of adverse events, unanticipated problems).
2. Responsible for the maintenance of accurate and complete documentation including signed informed consent forms, source documentation, subject logs and study-related communications.
3. Responsible for the organizational management of all aspects of the trial including but not limited to overseeing timeliness in completing case report forms, reporting serious adverse events, managing caseload and managing study files.
4. Communicates all protocol-related issues/problems to the appropriate team members, including but not limited to questions regarding the conduct of the clinical trial, concern regarding possible Serious Adverse Events/Adverse Events/Unanticipated Problems (SAE/AE/UP) or subject compliance.
5. Develops organizational aids and checklists to facilitate patient recruitment and enrollment as well as the collection of complete and accurate study data.
6. Enrolls subjects in studies and manages their participation according to ethical, regulatory and protocol-specific requirements.
7. Tracks study enrollment.
8. Maintains study files for each study subject.
9. Maintains confidentiality of study subject's identity.
10. Participates in quality assurance activities (onsite and/or remote monitoring visits (including submission of de-identified source documents for remote monitoring), internal audits, sponsor audits, FDA audits.

Responsibilities of the Participating Site Regulatory Office and/or Designee

1. Responsible for protocol submission – initial protocol, informed consent and subsequent amendments.
2. Responsible for communication to the City of Hope Data Coordinating Center any questions related to the regulatory document submission process at their participating site.
3. Maintains the regulatory documentation and regulatory files for each applicable research project at the participating site.
4. Maintains the Regulatory Document Binder distributed by City of Hope's Data Coordinating Center locally. Ensures all documentation is up to date and filed in a timely fashion.
5. Submits institutional review board approvals for initial protocol submission as well as subsequent amendments to the City of Hope Data Coordinating Center.
6. If applicable, submits serious adverse events and/or unanticipated problems to their local regulatory committees, and sends appropriate copies to the Data Coordinating Center as spelled out in the protocol.

Required Documents to be Sent by Participating Site to the City of Hope Data Coordinating Center Prior to Site Activation

1. Participating site's Investigational Review Board (IRB) approval letter for initial protocol and consent form. All correspondence between the IRB and study site will be maintained at the study site in the regulatory binder.
2. Completed FDA1572 that includes all investigators who will participate in the clinical trial along with current signed and dated CV, copy of medical license for each investigator and Human Subjects Research and HIPAA training records and certifications.
    a. FDA1572 will be updated if changes/additions occur and a copy is to be sent to the Data Coordinating Center.
3. Financial Disclosure (FDA3455)
4. Delegation of Authority Form
    a. The delegation of authority form will be completed for all study personnel which will include the name, signature, and initials of all personnel signing Case Report Forms (CRFs), whether paper or in EDC.
5. Laboratory Certification
    a. The participating site will submit to the Data Coordinating Center all laboratory certifications from their institution as well as a copy of the normal ranges. A copy of the laboratory director's CV and medical license will also be submitted and kept on file.
6. Local IRB membership list
7. The Data Coordinating Center will complete a trial initiation checklist indicating all requirements for the study (including training of participating site) and the regulatory binder have been met prior to initiation/activation of the study at the participating site. A template for what is to be filed will be sent to each participating site. The site will maintain documents and send copies to the COH DCC.

Training:

COH Data Coordinating Center staff will be responsible for training research personnel at every participating site.

The COH Data Coordinating Center will also provide participating sites with a complete study roster that includes who to contact for any questions. This roster will be updated (as needed) throughout the course of the trial and distributed to sites.

Training will be conducted either on-site and/or at City of Hope or via teleconference. The following training will be completed at different time-points and/or as needed:

- Initial training of current research personnel during site initiation visit (via teleconference) on protocol management and data collection;
- Interim training on data collection on new case report forms as specified per protocol.
- Subsequent training of any new staff at participating sites.

Training components will include, but are not limited to protocol management, screening procedures, inclusion/exclusion criteria, randomization, study calendar, study procedures, investigational product, treatment plan, AE monitoring, dose modification, guidelines of SAE reporting, data submission schedule, eligibility checklist, informed consent process/documentation of informed consent (when applicable), and data collection training on all CRFs as required per protocol. This may include training on GCP guidelines to ensure compliance with all applicable rules and regulations. Training will also include review of all items needed in regulatory binder.

Data Collection Instruments:

1. Data for this trial will be collected using Medidata RAVE, City of Hope's electronic capture system.
2. Medidata RAVE is a web based, password protected system. It is fully compliant with global regulatory requirements, including 21CRF Part 11 compliant.
3. Participating staff will be required to complete an Account Activation Form (AAF) to obtain access to the Medidata RAVE system once IRB approval documentation is received.
4. Participating site staff will obtain log in information once they fax in the required AAF.
5. Once their AAF is received, the participating site staff will receive their individual login information.
6. The participating site staff (whether Principal Investigator or the staff collecting data at site) are required to take an eLearning Module within Medidata RAVE in order to obtain full access.
7. The participating site staff will receive training via teleconference by COH DCC staff to review eCRFs that are specific to this protocol. Continuous training will be offered to participating sites if any amendments affect changes to the eCRFs during the course of the trial.
8. The eCRFs within Medidata RAVE for this trial will have detailed instructions in the form of Help Text that provide instructions for completing each required field on each form.
9. Participating sites will be required to complete data collection within Medidata RAVE in a timely manner. Data will be expected to be completed within 2 weeks of each subject visit (or as per the study protocol – if needed sooner).
    a. The Data Coordinating Center will run monthly data expectation reports that will list any outstanding and overdue data.
    b. The Data Coordinating Center will send via email to the participating site a report monthly on any missing and/or overdue data forms. The participating site will be required to complete the missing and/or overdue data forms within 1 week of receipt of the report.
    c. If the data is not completed, the Data Coordinating Center will reach out to the participating site's Principal Investigator and site staff to ensure prompt completion of data.
    d. If any issues continue, the Data Coordinating Center will communicate with the sponsor with the hope to reach out to the participating sites in order to resolve any

issues.

10. Query reports will be generated on a monthly basis by the Data Coordinating Center.
    a. The Data Coordinating Center will send via email to the participating site a report monthly on any outstanding queries. The participating site will be required to complete the queries within 2 weeks of receipt of the report.
    b. If the queries have not been resolved in a timely manner, the Data Coordinating Center will reach out to the participating site's Principal Investigator and site staff to ensure prompt resolution of the queries and/or to discuss an extension on the due date.
    c. If the queries have not been completed in a timely manner, after discussion with the participating site's Principal Investigator and site staff, the Data Coordinating center will communicate with the sponsor with the hope of resolving any issues.

General Instructions for Completing Case Report Forms:

1. All data recorded on case report forms must be verifiable in the source documents maintained at the participating site. Source documents refer to all notes and reports contained in the subject's medical record.
2. When completing the initial eligibility checklist, participating sites are asked to print and use black ink.
3. The subject must not be identified by name on any study document. If a form such as a radiographic report or lab report is submitted, the subject's name must be obliterated and replaced with the subject's initials and registration number.
4. All dates must be verifiable by source documents.

Data Transmission:

1. Registration documents including eligibility checklist, demographics and corresponding source documentation will be sent to the Data Coordinating Center via fax or via City of Hope's Secure Mail system in order to ensure proper registration/randomization of each subject. As this information may contain identifiers (patient name, medical record number, date of birth, sex, race, ethnicity, zip code as required for internal registration), it is imperative that participating sites either fax this data OR use the Secure Mail route by typing #secure# in the email subject line. All participating sites will be sent out the City of Hope Secure Mail guide.
2. All subjects will be granted a protocol specific number (i.e., COH-001, CED-001) that will be assigned by the COH Data Coordinating Center.
3. Subsequent data collection then will take place via the web-based Medidata RAVE system. Participating sites will need to ensure they have the capability and access to a computer and the internet in order to complete data collection.
4. The Data Coordinating Center will at times need to contact the participating site to obtain information but will always refer to the protocol specific patient number.

Data Analysis:

Joycelynne M. Palmer, PhD, is responsible for data analysis. Details regarding the study design

and planned analyses can be found in section 10.0 of the protocol document.

Quality Assurance and Monitoring

1. The COH Data Coordinating staff will monitor each protocol conducted at participating sites to verify that the rights and well-being of human subjects are protected, the reported trial data are accurate, complete and verifiable from source documents, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s) with the GCP and with applicable regulatory requirements. The COH Data Coordinating Center will determine the appropriate extent and nature of the monitoring based on considerations such as study objective, purpose, design, complexity, blinding, size and endpoints of the trial. A trial may require onsite monitoring at the participating site or may be subject to remote monitoring. Remote monitoring will involve the participating site submitting de-identified source documentation to the COH Data Coordinating Center. Monitoring of that data will be done at COH by assuring the data captured onto CRFs is the same as the source documentation submitted.
2. Each IRB approved protocol will undergo monitoring evaluations by the COH Data Coordinating Center staff at varying time points as determined by the Division of Clinical Research Information Support. A trial may require onsite monitoring at the participating site or may be subject to remote monitoring. Remote monitoring will involve the participating site submitting de-identified source documentation to the COH Data Coordinating Center. Monitoring of that data will be done at COH by assuring the data captured onto CRFs is the same as the source documentation submitted.
3. In addition, COH research personnel from the Office of Clinical Research Auditing & Monitoring may audit protocol compliance at participating sites at intervals decided by the coordinating center and their office. Auditing is dependent upon the protocol's phase, accrual rate, IND status, and results of previous evaluations.
4. Participating sites will be informed of intended monitoring evaluations in a timely manner prior to the proposed visit and/or request for remote monitoring. When informed of an impending monitoring evaluation (either onsite or remotely) by COH staff, the participating site is required to prepare for the visit by including but not limited to: 1) providing adequate, private space for COH staff to conduct the evaluation, 2) having a contact person available for periodic questions, 3) providing the medical record or applicable documentation for each subject monitored on the day of the visit, 4) providing an organized collection of regulatory documents pertaining to the study, 5) flagging all source documents pertinent to data collections; and/or 6) de-identifying and submitting to the Data Coordinating Center all source documentation for subjects. Following any evaluation, an estimate of the next monitoring visit (whether onsite or remote) will be given to the participating site staff.
5. The DCC will compare the subject's records and other supporting documents with the data entered on the CRFs (paper or electronic).
6. The DCC will ensure:

    a. That the information recorded is complete and accurate.

b. That there are no omissions of specific data elements such as the administration to any subject of concomitant test articles or the development of an intercurrent illness.
c. Missing visits and examinations are noted in the records.
d. Subjects failing to complete the study and the reason for each failure are noted.
e. There is an original fully executed informed consent document in the subject record.
f. That study subjects initial (and subsequently thereafter, if applicable) met protocol mandated eligibility criteria for study participation.
g. That proper procedures were followed in obtaining informed consent from study subjects, as dictated by local regulatory guidelines (and may be subject to differences internationally).
h. That source data/documents and other trial records are accurate, complete, up-to-date and maintained.
i. That the participating site investigator provides all the required reports, notification, applications and submissions.
j. That these documents are accurate, completely, timely, legible and dated.

7. The Data Coordinating center will specifically verify that:

    a. The data required by the protocol are reported accurately on the CRF and are consistent with the source data/documents.
    b. Any dose and/or therapy modifications are well documented for each of the trial subjects.
    c. Adverse events, serious adverse events, concomitant medications and inter-current illnesses are reported in the CRFs in accordance with the protocol.
    d. That study procedures were performed in adherence to the protocol document and that deviations from written procedures were discovered and properly reported to the IRB.

8. The findings from the visit (whether on-site or remote) will be presented to the participating site in the form of a detailed, written report. This report will include a summary of what was reviewed and any findings concerning significant deficiencies and actions recommended for compliance. The report will be provided to appropriate participating site staff within 21 days of the evaluation completion. The participating site staff is required to provide a written response to the findings with the corrective plan of actions within 14 days upon receipt of the report (if corrective action is suggested).

Adverse Event/Serious Adverse Event/Unanticipated Problem Reporting

1. The Data Coordinating Center will be responsible for tracking, reporting and maintaining documentation of all serious adverse events and unanticipated problems and dissemination of the information to participating sites.
2. The Data Coordinating Center will be responsible for reporting of adverse event data to the study sponsor (as required).
3. The participating sites are responsible for reporting all adverse events as required in

Section 11.0 of the protocol, as well as to report per their local institutional guidelines.

4. The Data Coordinating Center will be responsible for distributing DSMC findings/updates/reviews to the participating sites for submission as per their local guidelines (if applicable).