A Phase I/II Study of Pomalidomide and Dexamethasone with Growth Factor Support in Patients with Relapsed/Refractory Multiple Myeloma

Protocol # 2013-0018
Version 3.0
October 11, 2013

Principal Investigator: Michael Wang, M.D.
The University of Texas MD Anderson Cancer Center

Amendment 2 June 23, 2017

Amendment 3 December 5, 2017

Amendment 4 October 3, 2018

Table of Contents

1 BACKGROUND

1.1 Multiple Myeloma

Multiple Myeloma (MM) is a clonal neoplastic proliferation of plasma cells affecting 19,900 US patients each year, according to Surveillance, Epidemiology, and End Results (SEER).[1] MM is characterized by anemia, bone destruction, monoclonal gammopathy, renal failure, hypercalcemia, and increased susceptibility to infections. The disease is systemic, and chemotherapy is indicated for management of symptomatic myeloma. Current treatments include combination chemotherapy with regimens using melphalan (Alkeran®), bortezomib (Velcade®), thalidomide (Thalomid®), and
lenalidomide (REVLIMID®) with and without corticosteroids. Younger patients are consolidated with high-dose therapy (ablative chemotherapy or radiation) with stem cell transplantation. Although improvements in progression-free survival (PFS) and overall survival have occurred in the past five years, even with the best available approved agents, 20–40% of patients fail to respond to the primary therapy, and almost all subjects are known to eventually relapse. The mean overall survival was 41 (median 24) months, as reported by SEER.[2]

1.2 Pomalidomide Pre-Clinical Background

Pomalidomide, a thalidomide analogue, is an immunomodulatory agent that displays similar anti-angiogenic activity, but far greater anti-proliferative and immunomodulatory activity compared to the parent drug. Pomalidomide has been shown to inhibit the production of pro-inflammatory cytokines, inhibit TNF-a production, augment the activity of natural killer (NK) cells and stimulate antibody-dependent cytotoxic T-cell activity (ADCC). [3, 4]

Immunomodulatory agents exert their anti-myeloma effects through effects on the host immune system, modulation of the tumor microenvironment, and direct anti-proliferative and pro-apoptotic influences. Despite their profound activity against multiple myeloma, the majority of patients ultimately relapse due to the evolution of drug-resistant plasma cell clones. Recent studies have suggested that one mechanism of resistance is the activation of the Wnt/β-catenin pathway, which may reduce plasma cell sensitivity to immunomodulatory agents through adhesion-mediated drug resistance exerted by CD44.[5] Another recent study identified Cereblon as a key target required for the activity of lenalidomide or pomalidomide, and showed that suppression or deletion of Cereblon mediated resistance to these drugs.[6] These findings together support our central pre-clinical hypothesis, which proposes that gene expression profiling of patient-derived plasma cells at baseline

prior to initiation of pomalidomide and dexamethasone to identify Wnt/β-catenin activity and Cereblon expression will correlate with patient outcomes on therapy. Specifically, patients with high levels of Cereblon expression and low levels of Wnt/β-catenin activity will respond well to

POM/dex, while patients with low levels of Cereblon expression and high levels of Wnt/β-catenin activity will respond poorly to therapy.

1.3 Pomalidomide Clinical Background

At tolerated doses (MTD = 2 mg QD and 5 mg QOD), pomalidomide has been shown to be active in subjects with relapsed or refractory multiple myeloma (MM) (study CC-4047-00-001). [7,8] In 45 subjects who received doses of pomalidomide ranging, by cohort, up to 10 mg daily, the most commonly occurring dose-limiting toxicity (DLT) was reversible neutropenia. As with other immunomodulatory drugs (IMiDs) administered to subjects receiving concomitant systemic steroids, deep vein thrombosis (DVT) was seen (in 1 subject each in this study and in Celgene's subsequent named patient supply rollover program).[7]

Preliminary efficacy and safety data from an ongoing phase II study, led by Martha Lacy, et al, at Mayo Clinic, were published.[9] Sixty patients with relapsed or refractory multiple myeloma were enrolled. Pomalidomide (CC-4047) was given orally at a dose of 2 mg daily on days 1-28 of a 28-day cycle and dexamethasone was given orally at a dose of 40 mg daily on days 1, 8, 15, 22 of each cycle. Patient also received aspirin 325 mg once daily for thromboprophylaxis. The study endpoints were the response rate in patients taking pomalidomide plus dexamethasone including patients with lenalidomide resistant refractory multiple myeloma, and safety of pomalidomide plus dexamethasone. Responses were recorded using the criteria of the International Myeloma Working Group. Thirty eight patients achieved objective response (63%) including CR in 3 patients (5%), VGPR in 17 patients (28%), and PR in 18 patients (30%). The CR + VGPR rate was 33%. Grade 3 or 4 hematologic toxicity occurred in 23 patients (38%) and consisted of anemia in three patients (5%), thrombocytopenia in two patients (3%) and neutropenia in 21 (35%). Among those that developed grade 3/4 neutropenia, all first experienced the neutropenia in cycle 1-3; no new patients experienced grade 3/4 neutropenia in cycle 4 or later. The most common non-hematological grade 3/4 toxicities were fatigue (17%) and pneumonia (8%). Other grade 3/4 non-hematological toxicities that occurred in less than 5% included diarrhea, constipation, hyperglycemia, and neuropathy. One patient (1.6%) had a thromboembolic event of deep vein thrombosis.

Lacy et al. have also demonstrated promising clinical activity of pomalidomide in myeloma patients with persistent disease following lenalidomide treatment. The overall response rate was ≥ PR was 32% in a cohort of 34 patients.[10]

CC-4047-MM-002 is a Celgene sponsored phase 1b/2 multi-center, randomized, open-label, dose escalation study that is evaluating the safety and efficacy of oral pomalidomide alone and in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma. Eligible patients must have received at least 2 prior regimens and all patients must have received prior treatment that includes lenalidomide and bortezomib. This study consists of a phase 1 single agent pomalidomide (maximum tolerated dose [MTD]) segment and phase 2 randomized (pomalidomide plus low-dose dexamethasone versus pomalidomide alone) segment. The MTD was 4 mg 21/28 days (there were 4 drug-related DLTs [grade 4 neutropenia] at 5 mg). Neutropenia and anemia were the most common grade 3/4 toxicities; there was a dose-dependent increase in grade 4 neutropenia. Based on the preliminary safety and response data, 4 mg 21/28 days is the dose for the phase 2 segment. A total of 221 subjects were enrolled into the Phase 2 segment between November 2009 and September 2010. Preliminary efficacy results for the first 28 evaluable subjects in Phase 1 and 120 subjects enrolled in the Phase 2 segment as of 30 Apr 2010 showed a response rate (≥ PR) of 25%. The most common Grade 3/4 hematologic toxicity was neutropenia (53% in Phase 1, 42% in Phase 2), and the most common Grade 3/4 non-hematologic toxicity was infection (30% in Phase
1 and 31% in Phase 2).[11]

A subsequent phase II trial was conducted at the Mayo Clinic to compare the two different dosing regimens in MM subjects who were refractory to both lenalidomide and bortezomib. Pomalidomide was given orally 2 mg/day or 4 mg/day, on Days 1 to 28 of a 28-day cycle, with dexamethasone 40 mg daily on Days 1, 8, 15 and 22. A total of 70 subjects were enrolled (35 in the 2 mg cohort and 35 in the 4 mg cohort). The most common Grade 3/4 hematologic toxicity was neutropenia, and the most common non-hematologic toxicity was fatigue. The overall response rate (≥ PR) was 25% and 29% for the 2 mg and 4 mg cohorts, respectively.[12]

The results of studies conducted thus far indicate that pomalidomide has activity in patients with

relapsed and/or refractory MM, including patients who are refractory to lenalidomide and bortezomib. Confirmed response rates range between 30% and 60% at pomalidomide doses of

between 2 and 4 mg/day. Notably, pomalidomide produces responses in subjects who are refractory to lenalidomide, another IMiDs® compound, aligning with the non-clinical results observed in lenalidomide-resistant cells.[13] The most common hematological toxicity experienced by these subjects is neutropenia (non-febrile), which can be managed by dose reductions or interruptions. The most common non-hematological toxicities are fatigue and pneumonia.

1.3.1 Zarxio (G-CSF) Background

Colony-stimulating factors are glycoproteins which act on hematopoietic cells by binding to specific cell surface receptors and stimulating proliferation, differentiation commitment, and some end-cell functional activation. Endogenous G-CSF is a lineage specific colony-stimulating factor which is produced by monocytes, fibroblasts, and endothelial cells. G-CSF regulates the production of neutrophils within the bone marrow and affects neutrophil progenitor proliferation, differentiation, and selected end-cell functional activation (including enhanced phagocytic ability, priming of the cellular metabolism associated with respiratory burst, antibody dependent killing, and the increased expression of some functions associated with cell surface antigens.

Zarxio® (filgrastim–sndz) is a 175 amino acid protein manufactured by recombinant DNA technology. Zarxio® is produced by Escherichia coli (E coli) bacteria into which has been inserted the human granulocyte colony-stimulating factor gene. Zarxio® has a molecular weight of 18,800 daltons. The protein has an amino acid sequence that is identical to the natural sequence predicted from human DNA sequence analysis, except for the addition of an N-terminal methionine necessary for expression in E coli

Refer to the package Insert for full prescribing information.

2 Study Rationale

Pomalidomide is a distinct immunomodulatory agent that has demonstrated direct anti-myeloma effects in lenalidomide-refractory patients in vivo, and antiproliferative activity in vitro.[15,16] Pomalidomide has a different clinical efficacy and safety profile, with a maximum tolerated dose (MTD) of 4 mg daily when given for 21 days of a 28-day cycle in a phase I/II study in relapsed/refractory multiple myeloma (MM).[17,18] Dose-limiting toxicities of pomalidomide have been predominantly hematologic in nature, with myelosuppression and neutropenia being especially prevalent. Those patients who received higher pomalidomide doses, however, did have a trend towards an improved response rate and response quality. Our central clinical hypothesis therefore proposes that it will be possible to improve the tolerability and efficacy of pomalidomide with dexamethasone by administering it to patients at higher doses in conjunction with granulocyte colony stimulating factor support.

3 Study Objectives

3.1 Primary Objective

Phase I: To determine the maximum tolerated dose (MTD) of pomalidomide and dexamethasone when given with growth factor support in patients with relapsed and refractory multiple myeloma.

Phase II: To evaluate the safety of pomalidomide and dexamethasone at the MTD.

3.2 Secondary Objectives

To obtain preliminary estimates of the anti-myeloma activity of higher doses of pomalidomide given with low dose dexamethasone and growth factor support in patients with relapsed and refractory multiple myeloma.

Activity will be defined by the overall response rate (ORR); (partial response (PR) or better) and clinical benefit response (CBR) rate (minor response (MR) or better), as well as by the response durability (duration of response (DOR), progression-free survival (PFS), and time to progression (TTP).

To further evaluate the safety of pomalidomide and dexamethasone at the maximum tolerated dose (MTD).

3.3 Exploratory Objectives

To examine the influence of Cereblon expression and activation of the Wnt/β-catenin pathway on the activity of high dose pomalidomide with low dose dexamethasone.

4 Entry Criteria

4.1 Inclusion Criteria

Subjects must meet all of the following inclusion criteria to be eligible to enroll in this study.

Disease Related:

1. Relapsed and/or refractory multiple myeloma with measurable disease, as defined by one or both of the following (assessed within 14 days prior to initiation of therapy):
    a. Serum M-protein≥ 0.5 g/d;
    b. Urine Bence-Jones protein ≥ 200 mg/24 hours.
2. Patients with light chain only myeloma are eligible. The involved free light chain level ≥ 100 mg/L with abnormal serum free light chain ratio.
3. Patients must have prior treatment with ≥ 2 cycles of lenalidomide and ≥ 2 cycles of bortezomib (either in separate regimens or as part of the same regimen) (primary refractory of subjects refractory to the most recent regimen are eligible)
4. The patient has received ≤ 5 lines of prior therapy. (See Appendix E for definition of lines of therapy).

Demographic:

1. Age >/= 18 years
2. Eastern Cooperative Oncology Group performance status 0–2

Laboratory:

1. Adequate hepatic function, with serum ALT < 3.5 times the upper limit of normal and serum direct bilirubin < 2 mg/dL (34 Omol/L) within 7 days of time of consent.
2. Absolute neutrophil count (ANC) ≥ 1.0 × 109/L within 7 days of time of consent, without G-CSF.
3. Hemoglobin > 9 g/dL (80 g/L) within 7 days of time of consent(subjects may be receiving red blood cell transfusions in accordance with institutional guidelines)

4. Platelet count > 100×10^9/L.

5. Creatinine clearance > 50 mL/minute within 7 days of time of consent, either measured or calculated using a standard formula (e.g., Cockcroft and Gault)
6. Written informed consent in accordance with federal, local, and institutional guidelines
7. All study participants must be registered into the mandatory POMALYST REMS^{TM} program, and be willing and able to comply with the requirements of the POMALYST REMS^{TM} program.
8. Females of childbearing potential (FCBP)† must have a negative serum or urine pregnancy test with a sensitivity of at least 25 mIU/mL within 10 – 14 days and again within 24 hours prior to starting Cycle 1 of pomalidomide and must either commit to continued abstinence from heterosexual intercourse or begin TWO acceptable methods of birth control, one highly effective method and one additional effective method AT THE SAME TIME, at least 28 days before she starts taking pomalidomide. FCBP must also agree to ongoing pregnancy testing and follow pregnancy testing requirements as outlined in the POMALYST REMS^{TM} program. Men must agree to use a latex condom during sexual contact with a FCBP even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix: F, G and H.

4.2 Exclusion Criteria

Disease-related

1. Hypersensitivity to previous lenalidomide or thalidomide.
2. History of serious allergic reactions to pegfilgrastim or filgrastim-sndz.
3. Chemotherapy (approved or investigational) within 3 weeks prior to signing consent
4. Antibody therapy within 6 weeks prior to signing consent
5. Radiotherapy to ≥ 3 sites at the same time within 1 week prior to signing consent
6. Immunotherapy within 28 days prior to signing consent

Concurrent Conditions

1. Pregnant or breast feeding females

2. Major surgery within 21 days prior to signing consent
3. Acute active infection requiring treatment (systemic antibiotics, antivirals, or antifungals) within 14 days prior to signing consent
4. Known human immunodeficiency virus infection
5. Known Active hepatitis B or C infection
6. Unstable angina or myocardial infarction within 4 months prior to registration, NYHA Class III or IV heart failure, uncontrolled angina, history of severe coronary artery disease, severe uncontrolled ventricular arrhythmias, sick sinus syndrome, or electrocardiographic evidence of acute ischemia or Grade 3 conduction system abnormalities unless subject has a pacemaker
7. Uncontrolled hypertension or uncontrolled diabetes within 14 days prior to signing consent
8. Non-hematologic malignancy within the past 3 years with the exception of a) adequately treated basal cell carcinoma, squamous cell skin cancer, or thyroid cancer; b) carcinoma in situ of the cervix or breast; c) prostate cancer of Gleason Grade 6 or less with stable prostate- specific antigen levels; or d) cancer considered cured by surgical resection or unlikely to impact survival during the duration of the study, such as localized transitional cell carcinoma of the bladder or benign tumors of the adrenal or pancreas
9. Significant neuropathy (Grades 3–4, or Grade 2 with pain) within 14 days prior to signing consent
10. Subjects with known or likely systemic amyloidosis
11. Ongoing graft-vs.-host disease
12. Any other clinically significant medical disease or condition that, in the Investigator's opinion, may interfere with protocol adherence or a subject's ability to give informed consent

5 Study Design and Treatment Schedule

5.1 Study Design

This is a Phase I/II investigator-initiated, single center, open-label study of high dose pomalidomide and dexamethasone with growth factor support for subjects with relapsed and or refractory multiple myeloma. Phase I will be a standard 3 + 3 design to determine the MTD. Phase II will accrue additional patients at the MTD. Both Phase I and Phase II will have 6 cycles of induction therapy followed by a maintenance schedule.

The maximum sample size is 55 patients including 42 patients in phase 1 and 13 additional patients at MTD in Phase II. The primary objective of the phase I trial is to determine the MTD for this new combination. The primary objective of Phase II is to further assess the toxicity profile at MTD. The secondary objectives will be to obtain preliminary information on response rate and duration of response.

5.2 Treatment Schedule

Pomalidomide will be administered orally at escalating doses ranging from 4 mg to 10 mg (during Phase I), while dexamethasone will be given at a fixed dose of 40 mg orally once weekly. Patients will receive pomalidomide daily on Days 1-21 of each 28-day cycle for up to 6 cycles during a 6-month “induction phase,” after which the pomalidomide dose will be 2 mg in the “maintenance phase.” Treatment will be continued until there is evidence of disease progression, or development of an unacceptable toxicity, or the patient withdraws consent for further treatment. Any patients who progress during their maintenance dosing of pomalidomide will be eligible to have their previous pomalidomide dose resumed in an attempt to regain control of their disease.

Granulocyte colony stimulating factor (G-CSF) will be administered at 5 microgram/kilogram for five days during days 22-28 of each cycle of induction therapy. CBC differential with platelets will be checked on Day 25 or Day 26. If the ANC is greater than or equal to 7300/ul, G-CSF will be held. The 7-day period without pomalidomide dosing could be extended for another 14 days to allow neutrophils to recover sufficiently to start the next cycle of therapy. G-CSF may be continued during this period as well at the discretion of the treating physician and/or study principal investigator. Colony stimulating factor support will not be administered during the maintenance phase dosing of pomalidomide and dexamethasone.

The patient will be seen by study physician before the next cycle may begin. There will be a +/- 3 day window for study visits, and procedures except for screening and baseline visit.

Patients will also be asked to report any adverse events they experience during the course of the study.

Subjects will receive the treatment in 28-day cycles until disease progression or unacceptable toxicity (whichever occurs first). Subjects will be followed for 30 additional days after completion or early discontinuation of treatment for safety follow-up. Long-term follow-up for disease status and survival will continue until the subject has withdrawn consent for further participation, is lost to follow-up, has died, or a decision is made to close the study.

5.2.1 OUTSIDE PHYSICIAN PARTICIPATION DURING TREATMENT

MD Anderson physician communication with the outside physician is required prior to the patient returning to the local physician. This will be documented in the patient record. A letter to the local physician outlining the patient's participation in a clinical trial will request local physician agreement to supervise the patient's care. Protocol required evaluations outside MD Anderson will be documented by telephone, fax or e-mail. Fax and/or e-mail will be dated and signed by the MD Anderson physician, indicating that they have reviewed it. Changes in drug dose and/or schedule must be discussed with and approved by the MD Anderson physician investigator, or their representative prior to initiation, and will be documented in the patient record. A copy of the informed consent, protocol abstract, treatment schema and evaluation during treatment will be provided to the local physician. Documentation to be provided by the local physician will include drug administration records, progress notes, reports of protocol required laboratory and diagnostic studies and documentation of any hospitalizations. The home physician will be requested to report to the MD Anderson physician investigator all life threatening events within 24 hours of documented occurrence. Patients will return to MD Anderson every month for evaluation.

5.3 Phase I Dose Levels

Phase I Induction (Cycles 1 – 6)

Cohort	Pomalidomide Daily days 1 - 21	Dexamethasone On days 1, 8. 15. 22	G-CSF* Days 22- 28
0	4 mg	40 mg	5mcg/kg
1	5mg	40 mg	5mcg/kg
2	6 mg	40 mg	5mcg/kg
3	7mg	40 mg	5mcg/kg

4	8 mg	40 mg	5mcg/kg
5	9 mg	40mg	5mcg/kg
6	10 mg	40 mg	5mcg/kg

***To be given during induction cycles 1- 6 only**

5.4 PHASE I AND II MAINTENANCE

Pomalidomide will be administered at 2 mg/day on days 1 – 21 of each 28 day maintenance cycles (Cycle 7+). Dexamethasone will continue at 40 mg on days 1, 8, 15 and 22 or the last tolerated dose/schedule following cycle 6. Patients unable to tolerate 2 mg may be dose reduced to 1 mg during the maintenance phase of the study.

5.5 Maximum Tolerated Dose Definition

The maximum tolerated dose is defined as the highest dose that causes dose limiting toxicity in less than 2 patients treated out of a 6 patient cohort, during the first cycle of combination treatment.

NOTE: No more than 6 evaluable patients may be enrolled per dose level.

5.6 Dose Limiting Toxicity Definition

Dose limiting toxicity (DLT) will be assessed during the first course of each cohort (28 days), and refers to a medically significant event which meets one of the following criteria using the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.03:

- Grade 4 neutropenia (absolute neutrophil count (ANC) < 500/mm3) lasting more than 14 consecutive days or Grade 3 neutropenia of any duration with fever and/or infection, where fever is defined as an oral Temperature ≥ 38.5°C on 2 consecutive evaluations.
- Grade 4 thrombocytopenia (platelets < 25,000/mm3) lasting more than 14 consecutive Days or Grade 3 thrombocytopenia with clinically significant bleeding or a platelet count < 10,000/mm3 at any time.
- Grade 3 or greater nausea and/or emesis despite the use of optimal anti-emetic prophylaxis. Optimal anti-emetic prophylaxis is defined as an anti-emetic regimen that employs a 5-HT3 antagonist given in standard doses and according to standard schedules.
- Grade 3 or greater diarrhea that occurs despite maximal supportive therapy
- Any other Grade 3 or greater non-hematologic toxicity with the following exceptions:

  - Grade 3 arthralgia/myalgia
  - Brief (< 1 week) Grade 3 fatigue
- A delay of more than 2 weeks in the initiation of Cycle 2 of treatment because of a lack of adequate recovery of therapy related hematological or non-hematologic toxicities.

5.7 Phase I Dose Escalation Process

The first cohort of three subjects enrolled into Phase I of the study will receive dose level 0. A full safety evaluation will be conducted when these subjects have completed one cycle (28 days) of combination therapy. Patients must complete a minimum of 1 cycle of treatment (28 days) with the minimum safety evaluation or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions. Dose escalation decisions will be based on a synthesis of all relevant data available from each dose level. However, additional data from all other ongoing dose levels may also be included in the dose escalation decision.

Dose escalation for subsequent patients will proceed as follows:

Prior to advancing/changing dose levels a cohort summary must be completed and submitted to the Clinical Research Monitor (IND Office).

If no Dose Limiting Toxicity (DLT) is reported in the first three subjects at a dose level, that dose level will be considered safe and three subjects will be enrolled at the next dose level.

If 1/3 subjects in a cohort at a dose level has a DLT, the dose level will be expanded to obtain six evaluable subjects.

If there are < 2 subjects with a DLT among the expanded cohort of six evaluable subjects a cohort of three subjects will be enrolled in the next higher dose level.

If there are 2 or more subjects with a DLT among the expanded cohort of six evaluable subjects, that dose level will not be considered safe, no further dose escalation will take place, and the MTD will have been exceeded. The previous dose level at which ≤ one of 6 patients experienced DLT will be declared the MTD.

Once MTD is determined, an additional 13 patients will be enrolled at the MTD as an expansion cohort to further evaluate the safety profile. The patient enrollment will be stopped at any time when more than 33% of DLT are observed at the MTD.

5.8 Subject Replacement

If less than 6 subjects have been treated in the next lower dose level (the possible MTD level), additional subjects will be entered into this dose level until there are 6 subjects treated. If ≤1 of

these 6 subjects encountered DLT, then this dose level will be declared to be the MTD. If 2 or more of the 6 subjects

encounter DLT, then the MTD has been exceeded. The 6 patients treated at MTD will be the first 6 patients of the extension COHORT.

Subjects, who discontinue study drug prior to the completion of their first 28-day study assessments for a reason other than an adverse event, will be replaced in order to have an adequate number of subjects for determination of the MTD.

6 Study Drug Supply

6.1 Pomalidomide

6.1.1 Pomalidomide Description

Pomalidomide, a thalidomide analogue, is an immunomodulatory agent that displays anti-angiogenic activity.

6.1.2 Formulation

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

6.1.3 Supply

Celgene will supply pomalidomide as 1.0 mg, 2.0 mg, 3.0 mg and 4.0 mg capsules for oral administration.

6.1.4 Storage

At the study site, all investigational study drugs will be stored in a locked, safe area to prevent unauthorized access.
The study drug should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

6.1.5 Special Handling Instructions

Pomalidomide should not be handled or administered by females of child-bearing potential unless wearing gloves.

6.1.6 Drug Dispensing Requirements

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

Pomalidomide will be dispensed through a qualified healthcare professional (including but not limited to, nurses, pharmacists and physicians). These healthcare professionals will be trained in

requirements specific to counseling of subjects. Once trained these healthcare staff will counsel

subjects prior to medication being dispensed to ensure that the subject has complied with all requirements including use of birth control and pregnancy testing (FCBP) and that the subject understands the risks associated with pomalidomide. This step will be documented with a completed Education and Counseling Guidance Document (Appendix G), and no drug will be dispensed until this step occurs. Counseling includes verification with the patient that required pregnancy testing was performed and results were negative. A Pomalidomide Information Sheet (Appendix H) will be supplied with each medication dispense.
Only enough pomalidomide capsules for 1 cycle of therapy will be supplied to the patient each cycle. This is in accordance with the POMALYST REMS™ program.

6.1.7 Accountability

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

Drug accountability records must be readily available for inspection by representatives of Celgene and by regulatory authorities.

Empty and partially used bottles should be accounted for and destroyed at the study site in accordance with the internal standard operating procedures or as instructed by Celgene. Drug destruction records must be readily available for inspection by representatives of Celgene and by regulatory authorities.

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented in the source documents.
Only sites that cannot destroy unused drug on-site will be required to return their unused supply of investigational product.

6.2 Dexamethasone

6.2.1 Dexamethasone description

Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder. It is stable in air. It is practically insoluble in water.

6.2.2 Formulation

Dexamethasone is available in tablets for oral administration. It is designated chemically as 9-fluoro-11β, 17, 21-trihydroxy-16α-methylpregna-1, 4-diene, 3, 20-dione.

6.2.3 Supply

Commercial supplies will be obtained for this study.

6.2.4 Storage

Stored at controlled room temperature 20 to 25ºC (68 to 77ºF).

6.2.5 Accountability

Sites will be required to record and document patient compliance regarding dexamethasone dosing.

6.3 Zarxio (G-CSF)

6.3.1 Description

Zarxio® is a sterile, clear, colorless, preservative-free liquid for parenteral administration containing filgrastim-sndz at a specific activity of 1.0 ± 0.6 x 108 U/mg (as measured by a cell mitogenesis assay). The product is available in single-use vials and prefilled syringes. The single-use vials contain either 300 mcg or 480 mcg filgrastim-sndz at a fill volume of 1.0 mL or 1.6 mL, respectively. The single-use prefilled syringes contain either 300 mcg or 480 mcg filgrastim-sndz at a fill volume of 0.5 mL or 0.8 mL, respectively. See Package Insert for full details.

6.3.2 Supply

Commercial supplies of Zarxio will be used in this study.

6.3.3 Storage

6.3.4

Zarxio® should be stored in the refrigerator at 2° to 8°C (36° to 46°F). Avoid shaking. Prior to injection, Zarxio® may be allowed to reach room temperature for a maximum of 24 hours. Any vial or prefilled syringe left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulates or discoloration are observed, the container should not be used. See Package Insert for full details

7 Study Drug Administration

7.1 Pomalidomide Administration

- Pomalidomide will be taken PO once daily on Days 1-21 of each 28-day cycle and should be taken at approximately the same time each day. Only enough pomalidomide capsules for 1 cycle of therapy may be provided to the patient each cycle. And only after the patient has been counseled regarding the Pomalidomide Pregnancy Prevention Plan (see Appendix E, F, G)

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

- If a dose of pomalidomide is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up, rather it should be taken at the next scheduled time point

- 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.

- No intra-subject dose escalation of pomalidomide will be permitted during the induction cycles 1 – 6. However, any patients who progress during their maintenance dosing of pomalidomide at 2 mg will be eligible to have their previous pomalidomide dose taken during the induction phase resumed in an attempt to regain control of their disease.

- Pomalidomide will be provided to research subjects for the duration of their participation in this trial at no charge to them or their insurance providers

7.2 Dexamethasone Administration

- Dexamethasone oral tablets will be administered weekly on Days 1, 8, 15, and 22 of each 28 day cycle.

7.3 Zarxio (G-CSF) Administration

- Zarxio (G-CSF) will be administered by subcutaneous injection at 5 mg/kg for 5 days during days 22 – 28 of each induction cycle (cycles 1 – 6). Additional days of therapy prior to initiation of the next cycle are permitted to allow for recovery of neutrophils.
- The patient package insert provides complete information and instructions for patients and care givers in the administration of Zarxio (G-CSF)

8 Dose Modifications and Initiation of a New Cycle of Therapy

8.1 Dose Modifications

Subjects will be evaluated for AEs at each visit with the NCI Common Toxicity Criteria, Version 4.03 (see Appendix C) used as a guide for the grading of severity. This section contains dose reduction steps and Section 7.2 for instructions on dose modifications.

During the dose escalation phase, no dose modifications are permitted during Cycle One unless a DLT has been experienced. No dose escalations are permitted in any given patient once a dose level has been assigned. However any patients who progress during their maintenance dosing of pomalidomide at 2 mg will be eligible to have their previous pomalidomide dose taken during the induction phase resumed in an attempt to regain control of their disease. Patients experiencing DLT during Cycle One may continue on therapy if the toxicity can be managed according to the dose modification guidelines outlined below. However, the DLT event will contribute to the assessment of MTD for that given cohort. Patients experiencing DLT at the 4 mg dose during Cycles 1-6 of the Induction phase can begin maintenance dosing at 2mg. If they then experience further DLT, they can follow the dose modification guidelines outlined for maintenance cycles below. If the toxicities cannot be managed by dose modification, the subject has to be withdrawn from the trial. Dose modifications may be performed in Cycle One of Phase II and for all subsequent cycles. If the toxicities cannot be managed by dose modification, the subject has to be withdrawn from the trial.

8.1.1 Pomalidomide Dose Reduction Steps

Pomalidomide dose Reduction Steps for cycles 1 - 6						
Starting Dose	**Step –1**	**Step –2**	**Step –3**	**Step -4**	**Step -5**	**Step -6**
10 mg	9 mg	8 mg	7 mg	6 mg	5 mg	4mg
9mg	8mg	7mg	6mg	5mg	4mg	-
8mg	7mg	6mg	5mg	4mg	-	-
7mg	6mg	5mg	4mg	-	-	-
6mg	5mg	4mg	-	-	-	-
5mg	4mg	-	-	-	-	-
4 mg	-	-	-	-	-	-

Pomalidomide dose Reduction Steps for maintenance cycles		
Starting dose	**Step -1**	**Step - 2**
2 mg	**1 mg**	**-**

8.1.2 Dexamethasone Dose Reduction Steps

Dexamethasone Dose reduction steps**		
Starting dose	**Step- 1**	**Step- 2**
40 mg D 1, 8, 15, 22	20 mg D 1, 8, 15, 22	20 mg D 1 and 15

**Alternate doses of dexamethasone may be used at the investigators discretion including discontinuation.

8.2 Dose Modification Guidelines

Dose reductions are not permitted during Cycle 1 unless the patient experiences a DLT. The patient may continue on protocol therapy if the toxicity resolves and the patient can be managed by a dose reduction. However, the occurrence of the DLT will be counted toward the assessment of the MTD.

For patients who are unable to tolerate the protocol-specified dosing schedule in cycle 2 and beyond, dose adjustments are permitted according to rules described in this section. Dose modifications different from those stated in the protocol should only be made in consultation with the Principal Investigator.

Administration of the study drugs will be discontinued in the event of a treatment-related toxicity that persists despite appropriate dose reductions or any other toxicity that, in the opinion of the Investigator, warrants discontinuation.

Toxicity will be assessed using the NIH-NCI Common Terminology Criteria for Adverse Events, version 4.03.

All interruption or changes to study drug administration must be recoded.

8.2.1 Dose Modification for Pomalidomide

Worst Toxicity **CTCAE Grade* unless otherwise specified (Value)**	**Dose Modification Guidelines** **at any time DURING A CYCLE of therapy**
HEMATOLOGICAL TOXICITIES	

Thrombocytopenia	Grade 4 (< 25 x 10^9/L)	Temporarily discontinue pomalidomide If resolved to ≤ grade 3 within the cycle

		restart pomalidomide at same dose level and complete the cycle. If evidence of bleeding, or for second or subsequent occurrence, which resolves to ≤ grade 3 within the cycle, reduce pomalidomide by one dose level and complete the cycle. If not resolved to ≤ grade 3 within the cycle, start new cycle with one level dose reduction of pomalidomide when the criteria for a new cycle are met. Platelets may be supported by the use of transfusions as per institutional guidelines
Neutropenia (ANC)	Grade 4 (ANC < 0.5 x 10^9/L)	Temporarily discontinue pomalidomide. Administer G-CSF according to protocol guidelines If resolved to ≤ grade 3 within the cycle restart pomalidomide at same dose level and complete the cycle. For second or subsequent occurrence, which resolves to ≤ grade 3 within the cycle, reduce pomalidomide by one dose level and complete the cycle. If not resolved to ≤ grade 3 within the cycle, start new cycle with one level dose reduction of pomalidomide and when the criteria for a new cycle are met.
	Febrile neutropenia (ANC < 1.0 x 10^9/L, fever ≥ 38.5°C)	Temporarily discontinue pomalidomide. If resolved to ≤ grade 2 within the cycle restart pomalidomide at same dose level and complete the cycle. For second or subsequent occurrence, which resolves to ≤ grade 2 within the cycle, reduce pomalidomide by one dose level and complete the cycle. If not resolved to ≤ grade 2 within the cycle, start new cycle with one level dose reduction of pomalidomide.

NON-HEMATOLOGICAL TOXICITIES		
Tumor Lysis Syndrome	(≥ 3 of the following: ≥ 50% increase in Cr, uric acid, or phosphate ≥ 30% increase in K; ≥ 20% increase in calcium; or ≥ 2 fold increase in LDH)	Hold pomalidomide until all symptoms have resolved. Take precautionary measures and resume at full dose or one level reduction at the investigators discretion.
Vomiting/Nausea/diarrhea* **	Grade 1 & 2 not requiring treatment or controlled using standard treatment	Maintain dose level
	Grade 3 or 4 or Grade 3 that cannot be controlled despite the use of standard treatment	Temporarily discontinue pomalidomide until resolved to ≤ grade 1, or baseline, then resume at one level dose reduction.
Peripheral Neuropathy	Grade 2 with pain or ≥ grade 3	If persists for more than 2 week hold pomalidomide until resolved to ≤ grade 1 or grade 2 without pain. Restart at one level dose reduction
	Grade 4	Discontinue pomalidomide
Skin Reaction	Grade ≥ 3 or progressive skin reaction	Discontinue pomalidomide
	Toxic epidermal necrolysis or Stevens-Johnson Syndrome	Discontinue pomalidomide
Infection	Grade 3 or 4	Hold therapy until systemic treatment is complete. May resume at same dose level.
Any other drug related toxicity	≥ grade 3	Hold pomalidomide until resolved to ≤Grade 1. Resume at one level dose reduction
All dose modifications should be based on the worst preceding toxicity.		
* Common Terminology Criteria for Adverse Events (CTCAE Version 4.03)		
*** See also concomitant medication Section 9		

8.2.2 Dose Modifications of Dexamethasone

Treatment Guidelines for Toxicity Related to Dexamethasone

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 function +/- interfering with activities of daily living)	Hold dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite above measures, discontinue dexamethasone 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.

8.2.3 Dose Modifications For Zarxio (G-CSF)

Continuation of Zarxiobeyond day 28 (up to 14 days) is permitted to allow adequate recovery of neutrophils prior to initiation of the next cycle. Zarxio will not be routinely administered during the maintenance phase. However, it can be used if needed to maintain ANC greater than 1,000/µL.

8.3 Initiation of a New Cycle of Therapy

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

- The ANC is $\geq$ 1,000/μL
- Platelet count > 75,000
- Any other treatment related adverse event that may have occurred has resolved to $\leq$ grade 2 or as indicated in section 7.2.

If these conditions are not met on Day 1 of a new cycle, the subject will be evaluated weekly and a new cycle of therapy will not be initiated until the toxicity has resolved as described above.

If pomalidomide dosing was halted during the previous cycle and was restarted with a one-level dose reduction without requiring an interruption for the remainder of the cycle, then that reduced dose level will be initiated on Day 1 of the new cycle. If pomalidomide dosing was omitted for the remainder of the previous cycle or if the new cycle is delayed due to toxicity newly encountered on the scheduled Day 1, then the new cycle will be started with a one-level dose reduction.

If a patient requires a dose delay of > 21 days due to drug related toxicity, from the intended day of the next scheduled dose, then the patient must be discontinued from the study. If however the patient was clearly benefiting from therapy, the patient may be able to continue treatment with a dose reduction at the Investigator discretion and in consultation with the Principal Investigator, after resolution of the adverse event.

9 Concomitant Therapy

All medications (prescription and non-prescription), treatments and therapies taken from the first day of study drug through the end of the study, must be recorded on the source documents and PDMS.

9.1 Required Concomitant Therapy

- Anti-coagulant therapy:
    - 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 dexamethasone and other drugs known to cause thrombosis.
    - All patients with a platelet count > 50,000/mm3 are required to use 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.

- Anti-Infection Prophylactics
    - If the absolute neutrophil count is less than 1000/mm3, prophylactic antibiotics will be used. These include ciprofloxin at 500 mg orally twice daily, Diflucan 100 mg orally daily and Valtrex 500 mg orally daily.

- Required Pregnancy Prevention Precautions:
    - 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. FCBP must also agree to ongoing pregnancy testing. Men must agree to use a latex condom during sexual contact with a female of childbearing potential even if they have had a successful vasectomy. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. See Appendix E, F and G for Celgene's Pregnancy Prevention Counseling Program.
- The use of filgrastim-sndz (G-CSF) is required to prevent and or support neutropenia given the high dose of pomalidomide used in this trial during cycles 1 – 6.

9.2 Permitted Concomitant Medications

- Subjects should receive full supportive care, including transfusions of blood and blood

products, antibiotics, and antiemetics, anti-diarrheals, analgesics, etc. and prophylactic

treatment for potential hypersensitivity reactions and tumor lysis syndrome when appropriate.

- Bisphosphonate therapy IV or PO as indicated in accordance with institutional guidelines.

9.3 Contraindicated Concomitant Medication

- Concurrent therapy with an approved or investigative anticancer therapeutic with activity against multiple myeloma is not allowed.
- Corticosteroids for non-malignant conditions (e.g., asthma, inflammatory bowel disease) equivalent to a dexamethasone dose ≥ 4 mg/day or prednisone ≥ 20 mg/day are not
  permitted.
- Other investigative agents should not be used during the study.

10 Correlative Studies

Gene expression profiling will be performed on primary plasma cells obtained at baseline to interrogate the overall expression profile, and specifically to identify the level of Cereblon expression and Wnt/β-catenin activity.

Plasma cells will be collected from patients at baseline when they are undergoing their initial evaluation to determine eligibility for this clinical trial.

CD138 + and CD 138-myeloma tissue samples will be collected according to standard procedures in our Myeloma Tissue Bank at M. D. Anderson Cancer Center.

11 Discontinuation From Treatment

Treatment with study drug is to be discontinued when any of the following occur:

1. Disease Progression: Patients will be taken off active treatment if they have progressive disease (PD) or clinically significant deterioration at any time during the study. However, any patients who progress during their maintenance dosing of pomalidomide at 2 mg will be eligible to have their previous pomalidomide dose resumed in an attempt to regain control of their disease.

2. Personal Reasons: Patients may choose to withdraw from the study at any time.

3. Adverse Event(s) (AEs) that, in the judgment of the investigator, may cause severe or permanent harm or which rule out continuation of study drug.

4. Clinical Judgment of the Investigator: A patient may be withdrawn from the study, if in the opinion of the investigator, it is not in the patient's best interest to continue.

5. Requiring other anti-neoplastic therapies.

6. Major violation of the study protocol (i.e., unable to adhere to study schedule).

7. Withdrawal of consent.

8. Lost to follow-up.

9. Death.

10. Confirmed pregnancy.

The date of discontinuation and reason(s) for patient discontinuation from the study will be recorded in the chart and PDMS. All evaluations which are required at the final study visit will be conducted within 30 days of the last study drug treatment for each patient who discontinues treatment. Subjects that discontinue treatment prior to the end of cycle 1 will be followed for adverse events for 30 days either by clinic visit or telephone contact.

12 Visit Schedule and Assessment

12.1 Study Procedures

The Investigator is responsible for keeping a record of all subjects who sign an Informed Consent Form and are screened for entry into the study. Physical examinations, adverse event queries, vital signs, and clinical laboratory evaluations and other evaluations/tests required at screening and during study are listed on the Schedule of Assessments (Appendix A). Investigators will follow patients very closely with their local oncologist, if appropriate, for interim monitoring of lab values and adverse events between cycles. The Investigator/treating physician must review labs done outside MDACC, determine clinical significance, and sign/date lab results. All treatment decisions must be made by Investigator/collaborating physician.

Schedule end of study evaluation within 30 days of last study treatment or within 30 days of study discontinuation, regardless of the reason. Follow Up contact with subjects should occur at a minimum of every 3 months for 1 year, then every 6 months thereafter. Survival is not an objective of the study, but it will be recorded as a secondary endpoint.

An unscheduled visit can occur at any time during the study. Source must be maintained for these unscheduled visits. The date for the visit and any data generated must be recorded on PDMS. Source documents for these unscheduled visits must also be maintained.

A schedule of the assessments can be found in Appendix A, Schedule of Study Assessments.

12.2 Efficacy Assessment

Subjects will be evaluated for disease progression and response according to the IMWG response criteria in Appendix D. Disease status categories include sCR, CR, VGPR, PR and SD. In addition, the number of patents achieving the response category of MR will also be evaluated and reported.

12.3 Safety Assessments

Safety assessments will consist of monitoring and recording all adverse events and serious adverse events.

Adverse events will be assessed according to the Common Toxicity Criteria for Adverse Events (CTCAE) version 4.03. CTCAE v4.03 can be accessed on the NIH/NCI website at: (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev4.pdf)

12.4 Follow-Up Assessments

The date of discontinuation and reason(s) for patient discontinuation from the study will be recorded in the chart. All evaluations which are required at the final study visit must be conducted for each patient who discontinues treatment. There will be no end of study tests needed for patients who do not complete cycle 1.

Subjects will be followed every 3 months for 1 year, then every 6 months thereafter, for information on progression of disease, and overall survival. For purposes of survival follow-up, when known, the exact date of death will be recorded.

The patient will be followed until disease progression is documented or study drug is discontinued for another reason. All patients who discontinue study for any reason will continue to be followed for survival and post-study treatment.

13 Adverse Events

13.1 Adverse Events Definitions

An adverse event (AE) is any untoward medical occurrence in a study subject administered an investigational product and that does not necessarily have a causal relationship with this treatment.

An AE therefore can be any unfavorable and unintended sign (including laboratory finding), symptom or disease temporally associated with participation in an investigational study, whether or not considered drug-related. In addition to new events, any increase in the severity or frequency of a pre-existing condition that occurs after the subject signs a consent form for participation is considered an AE. This includes any side effect, injury, toxicity, or sensitivity reaction.

An unexpected AE is any adverse drug event, the specificity or severity of which is not consistent with the current IB or prescribing information for a marketed compound. Also, reports which add significant information on specificity or severity of a known, already documented AE constitute unexpected AEs. For example, an event more specific or more severe than described in the IB would be considered “unexpected”.

Whenever possible, the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 should be used to describe the event and for assessing the severity of AEs (see Appendix C). Any events representing a change in the CTCAE Grade need to be reported on the AE case report form. This includes any abnormal laboratory values that the investigator considers clinically significant.

Adverse events and all protocol specific data will be entered into PDMS/CORe. PDMS/CORE will be used as the electronic case report form for this protocol.

For AEs not adequately addressed in the CTCAE, the severity table below may be used:

Severity	Description
GRADE 1 – Mild	Transient or mild discomfort; no limitation in activity; no medical intervention/therapy required.
GRADE 2 – Moderate	Mild to moderate limitation in activity—some assistance may be needed; no or minimal medical intervention/therapy required.
GRADE 3 – Severe	Marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalizations possible.
GRADE 4 – Life-threatening	Extreme limitation in activity, significant assistance required; life-threatening (immediate risk of death); significant medical intervention/therapy required, hospitalization or hospice care probable.
GRADE 5 – Fatal	Death

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

Any condition, laboratory abnormality, or physical finding with an onset date prior to the subject signing consent for study participation is considered to be pre-existing in nature and part of the subject's medical history.

13.2 Adverse Event Causality Assessment

The Investigator or physician designee is responsible for verifying and providing source documentation for all adverse events and assigning the attribution for each event for all subjects enrolled on the trial.

Using the following criteria, the relationship of the AE to the study drug should be assessed as follows:

- Yes: The event is suspected to be related if:
  - there is a clinically plausible time sequence between onset of the AE and administration of study treatment; and/or
  - there is a biologically plausible mechanism for the study treatment to cause or contribute to the AE; and/or
  - the event responds to withdrawal of the study medication (de-challenge) and/or recurs with re-challenge (when clinically feasible); and/or
  - the AE cannot be reasonably attributed to concurrent/underlying illness, other drugs, or procedures
- No:

- the AE is more likely to be explained by the subject's clinical state, underlying disease, concomitant medication, study or non-study procedure; and/or
- the time of occurrence of the AE is not reasonably related to administration of study treatment; and/or
- the event is unlikely to be related to the investigational product(s)

13.3 Adverse Events of Special Interest

Given the high dose of pomalidomide that may be administered, monitoring of safety beyond cycle 1 will be implemented. Grade 4 and 5 adverse events will be monitored for the emergence of a previously unrecognized treatment-related adverse event or event that exceeds the expected rate. In particular the rate of observed pneumonitis and neutropenia, including febrile neutropenia will be observed. Investigator will communicate with participants' local oncologists regarding adverse events as needed.

13.4 Serious Adverse Event Definition

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.

- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.

- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.

- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 30 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.

- Additionally, any serious adverse events that occur after the 30 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

13.5 Reporting To FDA

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

- **It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.**

13.5.1 Investigator Communication With Celgene

Serious adverse events (SAE) are defined above. The Investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile with 24

hours/1 business day.. These notifications should be performed in parallel to the Regulatory

Agency submissions but in no case any later than 1 business day from the submission date. This must be documented on a MD Anderson Internal SAE form. This form must be completed and supplied to Celgene in English.

The initial report must be as complete as possible, at a minimum including the serious adverse event term (s), patient identifier, date of awareness of the event; an assessment of the causal relationship between the event and the investigational product(s), and name of the reporter (investigator). 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 MD Anderson Internal SAE form, and submitted to Celgene in the same timelines as outlined above. The Celgene protocol number and the institutional protocol number should be included on all 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.

All other SAE's will be sent to Celgene on a biannual basis in the form of a line listing in English. The line listing must include the following information; patient initials, date of birth, sex, SAE onset date, SAE stop date, event name (term), outcome, date of first dose of study drug(s), date of last dose of study drug(s) prior to the event, action taken with study drug(s) the Investigator's assessment of causality (relationship to pomalidomide), and the Investigator's assessment of expectedness to pomalidomide. The sponsor reserves the right to review the CRFs or source documents in response to any inquires by regulatory agencies that the sponsor may receive.

Celgene Drug Safety Contact Information:
Celgene Corporation
Drug Safety
86 Morris Avenue
Summit, N.J. 07901

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

13.6 Pregnancy Reporting Requirements

Pregnancies and suspected pregnancies (including a positive test regardless of age or disease state) of a female subject occurring while the subject is on IP, or within 4 weeks, are considered immediately reportable events. IP is to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form.

*The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.*The Investigator will follow the pregnant

female until completion of the pregnancy, and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form.. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form..

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects may be related to the in utero exposure to pomalidomide should also be reported to Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.
In the event of a live "normal" birth, Celgene Drug Safety should be advised as soon as the information is available.

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

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

13.7 IND Annual Reports

If the FDA has granted and IND number, it is a requirement of 21 CFR 312.33 that an annual report is provided to the FDA within 60-days of the IND anniversary date. 21 CFR 312.33 provides the data elements that are to be submitted in the report. The Annual Report should be filed with MD Anderson's IND office, who will then forward to FDA. An additional copy should be placed in the study's Regulatory Binder and a copy must be sent to Celgene as a supporter of this study as follows.

13.8 Adverse Event Updates and IND Safety Reports

Celgene shall notify the Investigator via an IND Safety Report of the following information:
Any AE associated with the use of study drug in this study or in other studies that is both serious and unexpected, any changes on the investigational brochure or any other safety information that changes the risk/benefit profile of pomalidomide during the conduct of the study.

Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

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

The Investigator must keep copies of all AE information, including correspondence with Celgene and the IRB/EC, on file.

14 Statistics Analysis

14.1 Study Design

This is a Phase I/II study is to determine the maximum tolerated dose (MTD) of pomalidomide, and dexamethasone when administered in combination with G-CSF in treating patients with relapsed multiple myeloma. The standard "3+3" design is applied with 7 pre-defined dose levels based on the previous experience.

Cohort	Pomalidomide Daily days 1 - 21	Dexamethasone On days 1, 8. 15. 22	G-CSF* Days 22- 28
0	4mg	40 mg	5mcg/kg
1	5mg	40 mg	5mcg/kg
2	6 mg	40 mg	5mcg/kg
3	7mg	40 mg	5mcg/kg
4	8 mg	40 mg	5mcg/kg
5	9 mg	40mg	5mcg/kg
6	10 mg	40 mg	5mcg/kg

*G-CSF is used during cycles 1 – 6.

In Phase II patient will be treated at the MTD determined in Phase I. Both Phase I and Phase II will I include 6 cycles of induction therapy followed by maintenance therapy until disease progression or inacceptable toxicity.

14.2 Analysis Endpoints

The safety and disease response endpoints that will be evaluated are listed below, followed by descriptions of the derivations of selected endpoints.

14.2.1 Primary Endpoint Analysis

1. The MTD of pomalidomide and dexamethasone when both agents are administered with G- CSF support. The MTD will be defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT.

2. The recommended Phase II dose of pomalidomide and dexamethasone, when both agents are administered together with G-CSF.

14.2.2 Secondary Endpoint

Best overall response will be assessed after 4 cycles of therapy. Overall response will be defined using the International Myeloma Working Group Uniform Response Criteria (IMWG-URC), with the addition of MR according to the European Group for Blood and Marrow Transplant (EBMT) criteria (Appendix D). Overall response will include sCR, CR, VGPR, and PR. The duration of objective response and PFS also will be evaluated.

14.3 Sample Size Considerations

14.3.1 Phase I

The primary objective of phase I part is to determine the maximum tolerated dose (MTD) of pomalidomide, and dexamethasone with G-CSF support in patients with relapsed and or refractory multiple myeloma. The standard "3+3" design is applied with 7 pre-defined dose levels.

Applying the 3+3 design, the first cohort of 3 patients will be treated at dose level 0 and evaluated for DLT at the end of first cycle (28 days). The algorithm is as follows: (1) If 0 out of 3 patients experiences dose-limiting toxicity (DLT), the next cohort of 3 patients will be treated at the next higher dose level. (2) If 1 out of 3 patients develop a DLT, an additional 3 patients will be treated at the same dose level. If no more DLTs develop at this dose, i.e. 1 out of a total of 6 patients develops a DLT, the dose escalation continues for the next cohort of 3 patients. (3) At any given dose, if greater than 1 out 3 patients or 1 out of 6 patients experience DLT, the dose level exceeds the MTD and 3 more patients will be treated at the next lower dose if there are less than 6 patients already treated at that dose. Following the above scheme, MTD is defined as the highest dose level in which 6 patients have been treated with less than 2 instances of DLT. Given 7 predefined dose levels, it is anticipated that up to 42 patients are required for the phase I dose determination.

14.3.2 Phase II

Estimates of the anti-myeloma activity of high dose pomalidomide given with low dose dexamethasone and growth factor support in patients with relapsed and refractory multiple myeloma. Activity will be defined by the overall response rate (ORR); (partial response (PR) or better) and clinical benefit response (CBR) rate (minor response (MR) or better), as well as by the

response durability (duration of response (DOR), progression-free survival (PFS), and time to progression

(TTP). The maximum number of patients that will be recruited for Phase II is 19. The 6 patients who are treated at the MTD in the phase I part will be included. The response rate with pomalidomide and dexamethasone would be expected to be 25%, and we would find this high dose regimen interesting if it increased that response rate to 45%.

14.4 Safety Analysis Plans

Safety and tolerability will be assessed by clinical review of all relevant parameters including AEs, DLTs, laboratory values, and vital signs. Toxicity type and severity will be summarized by frequency tables. Patients must complete a minimum of 1 cycle of treatment (28 days) with the minimum safety evaluation or have had a DLT within the first cycle of treatment to be considered evaluable for dose escalation decisions. Dose escalation decisions will be based on a synthesis of all relevant data available from each dose level. However, additional data from all other ongoing dose levels may also be included in the dose escalation decision.

15 Response Criteria

Subjects will be evaluated for disease progression and response according to the IMWG response criteria in Appendix D. Disease status categories include sCR, CR, VGPR, PR and SD. In addition, the number of patents achieving the response category of MR will also be evaluated and reported. The efficacy endpoints including response rate and response duration will be explored for the expansion patient cohort. The 6 patients who are treated at the MTD in the dose-finding part will be included.

16 Protocol Amendments and Deviations

16.1 Protocol Amendments

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

16.2 Protocol Deviations

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

16.3 Investigator Responsibilities

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

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

The Investigator, or a designated member of the Investigator's staff, must be available at some time during monitoring visits to review data and resolve any queries and to allow direct access to the subject's record (e.g., medical records, office charts, hospital charts, and study related charts) for source data verification.

17 Regulatory Considerations

17.1 Institutional Review Board/Ethics Committee approval

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

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

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

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

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

Before the investigational drug is shipped to the Investigator, the Investigator or designee will provide Celgene with a copy of the IRB or Ethics Committee approval letter stating that the study protocol and any subsequent amendments and informed consent form have been reviewed and approved.

The Investigator or designee will be responsible for obtaining annual IRB or Ethics Committee re-approval throughout the duration of the study. Copies of the Investigator's annual report to the IRB or Ethics Committee and copies of the IRB or Ethics Committee continuance of approval must be provided to Celgene.

The Investigator is also responsible for notifying their IRB or Ethics Committee of any significant adverse events that are serious and/or unexpected.

17.2 Informed Consent

The Investigator must obtain informed consent of a subject or his/her designee prior to any

study related procedures as per GCPs as set forth in the CFR and ICH guidelines.

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

17.3 Subject Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy. In compliance with United States federal regulations, Celgene requires the Investigator to permit Celgene representatives and, when necessary, representatives of the FDA or other regulatory authorities to review and/or copy any medical records relevant to the study in accordance with local laws.

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

17.4 Study Records Requirements

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

17.5 Premature Study Discontinuation

17.5.1 Single Center

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

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

17.5.2 Study as A Whole

Celgene and MD Anderson, the IND sponsor, reserve the right to terminate this clinical study at any time for reasonable medical or administrative reasons.

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

18 References

1. Ries LAG MD, Krapcho M, Mariotto A, Miller BA, Feuer EJ, et al (eds). SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2004/, based on November 2006 SEER data submission, posted to the SEER website,. 2007.
2. Jawed I LC, Tward JD, Macdonald OK, Martincic D, Vudarla N, Fairbanks RK,, al. e. Survival outcomes for multiple myeloma over three decades: a surveillance,epidemiology, and end results (SEER) analysis. J Clin Oncol. 2007 ASCO Annual Meeting Proceedings Part I. Vol 25, No. 18S (June 20 Supplement),. 2007:8019.
3. Corral LG, Haslett PA, Muller GW, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-alpha. J Immunol 1999; 163(1): 380-6.
4. Muller GW, Chen R, Huang SY, et al. Aminosubstituted thalidomide analogs: potent inhibitors of TNF-alpha production. Bioorganic and Medicinal Chemistry Letters, 1999; 9: 1625–1630.
5. Chad C. Bjorklund, Wencai Ma, Zhi-Qiang Wang, R. Eric Davis, Deborah J. Kuhn, Steven M. Kornblau, Michael Wang, Jatin J. Shah, and Robert Z. Orlowski. Evidence of a Role for Activation of Wnt/β-Catenin Signaling in the Resistance of Plasma Cells to Lenalidomide. J. Biol. Chem. 2011 286: 11009-11020. First Published on December 28, 2010, doi:10.1074/jbc.M110.180208
6. Yuan Xiao Zhu, Esteban Braggio, Chang-Xin Shi, Laura A. Bruins, Jessica E. Schmidt, Scott Van Wier1, Xiu-Bao Chang, Chad C. Bjorklund, Rafael Fonseca, P. Leif Bergsagel, Robert Z. Orlowski, and A. Keith Stewart. Cereblon expression is required for the antimyeloma activity of lenalidomide and pomalidomide. Blood November 3, 2011 vol. 118 no. 18 4771-4779.
7. Schey SA, Fields P, Bartlett JB, et al. Phase I study of an immunomodulatory thalidomide analog, POMALIDOMIDE, in relapsed or refractory multiple myeloma. J Clin Oncol 2004; 22:3269-3276.
8. Streetly MJ, Gyertson K, Daniel Y, Zeldis JB, Kazmi M, Schey SA. Alternate day pomalidomide retains anti-myeloma effect with reduced AEs and evidence of in vivo immunomodulation. Br J Haematol 2008; 141(1): 41-51
9. Lacy MQ, Hayman S, Gertz M, Dispenzieri A et al. Pomalidomide (CC4047) Plus Low-Dose Dexamethasone as Therapy for Relapsed Multiple Myeloma. J Clin Oncol 2009; 27:5008-5014.
10. Lacy MQ, Hayman SR, Gertz MA et al. Pomalidomide (CC4047) plus low dose dexamethasone (Pom/dex) is active and well tolerated in lenalidomide refractory multiple myeloma (MM). Leukemia. 2010a 24, 1934–1939.
11 Richardson PG, Siegel D, Baz R, et al. A Phase 1/2 multicenter, randomized, open label dose escalation study to determine the maximum tolerated dose (MTD), safety, and efficacy of pomalidomide alone or in combination with low-dose dexamethasone in patients with relapsed and refractory multiple myeloma who have received prior treatment that includes lenalidomide and bortezomib. 2011 IMW Annual Meeting Abstract # O-12.
12. Lacy MQ, Mandrekar S, Abraham M et al. Pomalidomide plus low-dose dexamethasone in myeloma refractory to both bortezomib and lenalidomide: Comparison of two dosing strategies in dual-refractory disease [abstract]. Proceedings of the 52nd Annual Meeting of the American Society of Hematology (ASH) 2010b; December 4-7; Orlando, FL; USA: Abstract #863
13. Adams M, Schafer P, and Bartlett JB. The anti-proliferative effect of lenalidomide on MM cells in vitro is ameliorated by prior exposure to pomalidomide, an agent with activity against lenalidomide resistant MM cells. ASH Annual Meeting Abstracts 2009 114: 4926
14. Amgen Package Insert for Neupogen.

15. Hideshima T, Chauhan D, Shima Y, et al. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood. 2000;96:2943-2950.
16. Mitsiades N, Mitsiades CS, Poulaki V, et al. Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. Blood. 2002;99:4525-4530.
17. Schey SA, Fields P, Bartlett JB, et al. Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. J Clin Oncol. 2004;22:3269-3276.
18. Streetly MJ, Gyertson K, Daniel Y, Zeldis JB, Kazmi M, Schey SA. Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of in vivo immunomodulation. Br J Haematol. 2008;141:41-51.
19. Durie et al. International uniform response criteria for multiple myeloma. Leukemia 2006;20:1467-
20. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, Blade J, Richardson P, Orlowski R, Siegel D, Jagannath S, Facon T, Avet-Loiseau H, Lonial S, Palumbo A, Zonder J, Ludwig H, Vesole D, Sezer O, Munshi NC, San Miguel J; Consensus recommendations for the uniform reporting of clinical trials: report of the of the International Myeloma Workshop Consensus Panel 1. Blood. 2011 May 5;117(18):4691-4695. Epub 2011 Feb 3.

APPENDIX A. SCHEDULE OF STUDY ASSESSMENTS

Assessment	Screening	Cycles 1 - 6				Maintenance	End of Treatment[16]	LTFU
	(within 14 days of registration except where indicated)	Day 1	Day 8	Day 15	Day 22	Day 1		
Medical/RX history[1]	X							
Physical exam[2]	X	X[14]				X[2]	X	
Height, weight	X	X					X	
Vital signs and ECOG[4]	X	X	X	X	X	X	X	
Neurologic assessment[5]	X	X				X	X	
Hematology[6]	X	X[14]	X	X	X	**X**	X	
Full serum chemistries[7]	X	X					X	
Thyroid Function	X						X	
ECG	X						X	
PT/PTT	X						X	
Abbreviated serum chemistries[8]			X	X	X	X[8]		
Pregnancy test and counseling[9]	X	X[9]	X	X	X	X	X	
Disease assessment:[10, 11, 12, 15]								
SPEP/UPEP/immunofixation	X	X[14]				X	X	
Serum Free Light Chain	X	X[14]				X	X	
Bone marrow, FISH[11]	X					X		
Plasmacytoma[15]	X					X	X	
Quantitative immunoglobulins	X	X[14]				X	X	
β_2 microglobulin	X							
Skeletal survey[12]	X						X[12]	
Gene expression profiling	X[18]							
Pomalidomide administration[13]		Days 1 - 21				X		
Dexamethasone administration[13]		Days 1, 8, 15 and 22				X		
G-CSF administration[13]					Day 22 - 28			
Adverse events		X						

Disease status and survival								X[17]

1. Medical history: prior treatments for multiple myeloma, significant medical conditions, neuropathy history
2. Physical examination: Complete physical exam at baseline including evaluation of plasmacytoma if applicable. Following cycle 1, complete symptom directed Physical exam on day 1 of each cycle.
3. Height, weight. Height only required at screening.
4. Vital signs: systolic and diastolic blood pressure, respiration, pulse, oral temperature. ECOG performance status.
5. Neurologic exam: Physician performed neuro exam during the first 6 cycles of treatment and physician/mid-level provider performed neuro-exam starting with cycle 7 during the maintenance phase of study: exam is to detect peripheral neuropathy, note grade and/or changes in preexisting neuropathy
6. Hematology: hemoglobin, hematocrit, WBC with complete manual differential (neutrophils [segmented and bands], lymphocytes, monocytes, eosinophils, basophils), RBCs, platelet count (for screening, historical panel may be used if within 14 days prior to registration) Obtain and review within 24 hours of Day 1 and on days 8 and 15 and 22 of cycles 1 - 6 or as clinically indicated. Following cycle 6, CBC on day 1 of each subsequent cycle.
7. Full blood chemistry panel: BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium, albumin, total protein, magnesium, total bilirubin, alkaline phosphatase, ALT, AST, LDH (for screening, historical panel may be used if within 14 days prior to registration) at screening, day 1 of each induction cycle and end of study
8. Abbreviated blood chemistry panel: BUN, creatinine, glucose, uric acid, bicarbonate, calcium, chloride, phosphorus, potassium, sodium. An abbreviated chemistry may be done on day 1 of maintenance cycles or as clinically indicated at the investigators discretion.
9. A female of childbearing potential (FCBP) is a sexually mature female who: 1) has not undergone a hysterectomy (the surgical removal of the uterus) or bilateral oophorectomy (the surgical removal of both ovaries) or 2) has not been naturally postmenopausal (not having menstrual cycles due to cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (i.e., has had menses at any time during the preceding 24 consecutive months).Pregnancy test within 7 days of cycle 1 day 1 and each subsequent day 1. FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation. See Appendix F,G and H for details on counselling and birth control requirements
10. B2Microglobulin (at screening only), SPEP and UPEP with M protein quantification by immunofixation, quantitative immunoglobulin assay, free light chain to be performed at screening, the end of cycle 2 and every other cycle. Response confirmations should occur at the next cycle followed by every other cycle with repeated evaluations as per the IMWG response criteria Appendix D.
11. Bone marrow sample: quantify % myeloma cell involvement, cytogenetics and FISH (baseline sample can be within 30 days prior to registration). FISH will be performed only at screening. Repeat bone marrow to confirm response as required by IMWG Uniform response criteria Appendix D.
12. Skeletal survey: lateral radiograph of the skull, anteroposterior and lateral views of the spine, and anteroposterior views of the pelvis, ribs, femora, and humeri (screening may be within 12 weeks prior to registration); will be repeated in the event of suspected PD
13. Pomalidomide given on days 1 – 21 of each 28 day cycle at the assigned dose (Phase I) or at the MTD (Phase II) during the induction cycles 1 - 6. Following cycle 6, the dose will be reduced to the maintenance level of 2 mg. Dexamethasone is given on days 1,8,15 and 22. Zarxio is given for 5 days during days 22 - 28 of cycles 1 – 6. (See Section 7)
14. For Day 1 of Cycle 1, screening results/assessments may be used if within 24 hours of Cycle 1 Day 1
15. Plasmacytoma – by CT, PET/CT or MRI as appropriate at screening and end of study. If present at baseline, the plasmacytoma should be monitored throughout the study using the same technique.

16. All End of Study Assessments must be performed prior to initiation of any other treatment.
17. Progressions free survival, overall survival and health status assessment every 3 months for 1 year, then every 6 months thereafter.
18. Gene expression profiling will be performed on primary plasma cells obtained at baseline to interrogate the overall expression profile, and specifically to identify the level of Cereblon expression and Wnt/β-catenin activity. Plasma cells will be collected from patients at baseline when they are undergoing their initial evaluation to determine eligibility for this clinical trial.

APPENDIX B ECOG PERFORMANCE STATUS

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

APPENDIX C NCI CTCAE VERSION 4.03

Common Terminology Criteria for Adverse Events (CTCAE) of the National Cancer Institute (NCI) v4.03

Publish Date: (v4.03: June 14, 2010) http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

APPENDIX D MULTIPLE MYELOMA RESPONSE CRITERIA

International Myeloma Working Group Uniform Response Criteria for Multiple Myeloma

Response	*IMWG criteria* [19,20]
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
Molecular CR	Stringent CR plus • negative ASO-PCR (sensitivity 10-5)
Immunophenotypic CR	Stringent CR plus • Absence of phenotypic aberrant PC (clonal) in bone marrow with a minimum of one million of total BM cells analyzed by multiparametric flow cytometry (with ≥4 colors)
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
Minor response in patients with relapsed and refractory myeloma adapted	≥ 25% but < 49% reduction of serum M protein and reduction in 24 hour urine M protein by 50 – 89%, which still exceeds 200 mg/24hrs. In addition to above; if present at baseline, 25-49% reduction in the

from the EMBT criteria	size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response)
Stable Disease	• Not meeting criteria for CR, VGPR, PR or progressive disease
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/24 h) 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

All relapse categories (CR, sCR, VGPR, and PD) require two consecutive assessments made at any time before the institution of any new therapy; CR's, 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.

Criteria for coding CR and VGPR in patient in whom the only measurable disease is by serum FLC: CR in such patients requires a normal FLC ration of 0.26-1.65 in addition to the listed CR criteria. VGPR in such patients requires in addition a > 90% decrease in the difference between involved and uninvolved FLC levels.

**Bone marrow criteria for Progressive Disease are to be used only in patients without measurable disease by M protein and by FLC levels. A 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 E: LINES OF THERAPY DEFINITION

According to the IMWG Consensus panel 1 on uniform reporting criteria in clinical trials[20], a line of therapy consists of at least 1 or more cycles of a planned treatment regimen. This may consist of single-agent or combination therapy or a sequence of treatments administered in a planned manner.

For example, a planned induction, followed by ASCT followed by maintenance is considered one line of therapy. A new line of therapy starts when a planned course is modified as a result of progression, relapse or toxicity or when a planned period of observation is interrupted by the need for additional treatment of the disease.

Modification of drug doses or resuming therapy after holding will not be considered a new line of therapy provided that there was no evidence of progression of disease as defined in the "Response Criteria" section of this document.

APPENDIX F: POMALIDOMIDE RISKS OF FETAL EXPOSURE, PREGNANCY TESTING GUIDELINES AND ACCEPTABLE BIRTH CONTROL METHODS

Risks Associated with Pregnancy

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

Criteria for females of childbearing potential (FCBP)

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

Counselling

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

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

The investigator must ensure that females of childbearing potential:

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

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

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

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

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

Contraception

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

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

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

Because of the increased risk of venous thromboembolism in patients with multiple myeloma taking pomalidomide and dexamethasone, combined oral contraceptive pills are not recommended. If a patient is currently using combined oral contraception the patient should switch to another one of the effective methods listed above. The risk of venous thromboembolism

continues for 4−6 weeks after discontinuing combined oral contraception. The efficacy of contraceptive steroids may be reduced during co-treatment with dexamethasone.

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

Pregnancy testing

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

Before starting study drug

Female Patients:

FCBP must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study drug. The first pregnancy test must be performed within 10-14 days prior to the start of study drug and the second pregnancy test must be performed within 24 hours prior to the start of study drug. The patient may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative.

Male Patients:

Must practice complete abstinence or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 28 days following study drug discontinuation, even if he has undergone a successful vasectomy.

During study participation and for 28 days following study drug discontinuation

Female Patients:

- FCBP with regular or no menstrual cycles must agree to have pregnancy tests weekly for the first 28 days of study participation and then every 28 days while on study, at study discontinuation, and at day 28 following study drug discontinuation. If menstrual cycles are irregular, the pregnancy testing must occur weekly for the first 28 days and then every 14 days while on study, at study discontinuation, and at days 14 and 28 following study drug discontinuation.
- At each visit, the Investigator must confirm with the FCBP that she is continuing to use two reliable methods of birth control.
- Counselling about pregnancy precautions and the potential risks of fetal exposure must be conducted at a minimum of every 28 days.
- If pregnancy or a positive pregnancy test does occur in a study patient, study drug must be immediately discontinued.

- Pregnancy testing and counselling must be performed if a patient misses her period or if her pregnancy test or her menstrual bleeding is abnormal. Study drug treatment must be discontinued during this evaluation.
- Females must agree to abstain from breastfeeding during study participation and for at least 28 days after study drug discontinuation.

Male Patients:

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

Additional precautions

- Patients should be instructed never to give this medicinal product to another person and to return any unused capsules to the study doctor at the end of treatment.
- Patients should not donate blood during therapy and for at least 28 days following discontinuation of study drug.
- Male patients should not donate semen or sperm during therapy or for at least 28 days following discontinuation of study drug.
- Only enough pomalidomide for one cycle of therapy may be dispensed with each cycle of therapy.

APPENDIX G: POMALIDOMIDE EDUCATION AND COUNSELING GUIDANCE DOCUMENT

To be completed prior to each dispensing of study drug.

Protocol Number: _____

Patient Name (Print):_____DOB:_____/_____/_____(mm/dd/yyyy)

(Check the appropriate box to indicate risk category)

Female:

If female, check one:

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

NOT FCBP

Male:

Do Not Dispense study drug if:

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

FCBP:

1. I verified that the required pregnancy tests performed are negative.
2. I counselled FCBP regarding the following:
    - Potential risk of fetal exposure to pomalidomide: If pomalidomide is taken during pregnancy, it may cause birth defects or death to any unborn baby. Females are advised to avoid pregnancy while taking pomalidomide. The teratogenic potential of pomalidomide in humans cannot be ruled out. FCBP must agree not to become pregnant while taking pomalidomide.

- Using TWO reliable methods of birth control at the same time or complete abstinence from heterosexual contact [at least 28 days prior to therapy, during therapy, during dose interruption and 28 days after discontinuation of study drug].
- That even if she has amenorrhea she must comply with advice on contraception
- Use of one highly effective method and one additional method of birth control AT THE SAME TIME. The following are examples of highly effective and additional effective methods of contraception:
  - Highly effective methods:
    - Intrauterine device (IUD)
    - Hormonal (birth control pills, injections, implants)
    - Tubal ligation
    - Partner's vasectomy
  - Additional effective methods:
    - Male condom
    - Diaphragm
    - Cervical Cap
- Pregnancy tests before and during treatment, even if the patient agrees not to have reproductive heterosexual contact. Two pregnancy tests will be performed prior to receiving study drug, one within 10-14 days and the second within 24 hours of the start of study drug.
- Frequency of pregnancy tests to be done:
  - Every week during the first 28 days of this study and a pregnancy test every 28 days during the patient's participation in this study if menstrual cycles are regular or every 14 days if cycles are irregular.
  - If the patient missed a period or has unusual menstrual bleeding.
  - When the patient is discontinued from the study and at day 28 after study drug discontinuation if menstrual cycles are regular. If menstrual cycles are irregular, pregnancy tests will be done at discontinuation from the study and at days 14 and 28 after study drug discontinuation.
- Stop taking study drug immediately in the event of becoming pregnant and to call their study doctor as soon as possible.
- NEVER share study drug with anyone else.
- Do not donate blood while taking study drug and for 28 days after stopping study drug.
- Do not breastfeed a baby while participating in this study and for at least 28 days after study drug discontinuation.

- Do not break, chew, or open study drug capsules.
- Return unused study drug to the study doctor.

3. Provide Pomalidomide Information Sheet to the patient.

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

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

MALE:

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

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

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

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

APPENDIX H: POMALIDOMIDE INFORMATION SHEET

FOR PATIENTS ENROLLED IN CLINICAL RESEARCH STUDIES

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

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

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

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

contraception.

If you are a female not of childbearing potential:

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

If you are a male:

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

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

2. Restrictions in sharing study drug and donating blood:

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

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