

Official Title of Study:

A Phase 2, Multicenter, Multi-cohort, Open-label Study of Pomalidomide in Combination with Low-dose Dexamethasone or Pomalidomide in Combination with Low-dose Dexamethasone and Daratumumab in Subjects with Relapsed or Refractory Multiple Myeloma following Lenalidomide Based Therapy in the First or Second Line Setting

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**A PHASE 2, MULTICENTER, MULTI-COHORT, OPEN-LABEL STUDY OF POMALIDOMIDE IN COMBINATION WITH LOW-DOSE DEXAMETHASONE OR POMALIDOMIDE IN COMBINATION WITH LOW-DOSE DEXAMETHASONE AND DARATUMUMAB IN SUBJECTS WITH RELAPSED OR REFRACTORY MULTIPLE MYELOMA FOLLOWING LENALIDOMIDE-BASED THERAPY IN THE FIRST OR SECOND LINE SETTING**

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<b>SPONSOR NAME / ADDRESS:</b>	Celgene Corporation 86 Morris Avenue Summit, NJ 07901
<b>IN-COUNTRY CARETAKER NAME / ADDRESS:</b>	Celgene K.K. JP Tower, 2-7-2 Marunouchi Chiyoda-ku Tokyo 100-7010 JAPAN

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<b>Contact Information:</b>	
<b>Name:</b>	[REDACTED]
<b>Title:</b>	[REDACTED]
<b>Address:</b>	Celgene Corporation, 86 Morris Avenue, Summit, NJ 07901
<b>Phone:</b>	[REDACTED]
<b>E-mail:</b>	[REDACTED]

**Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.**

<b>Back-up 24-Hour Global Emergency Contact Call Center: +1-877-501-7738</b>
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**dd mmm yyyy**

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<b>Institution Name:</b> _____	
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## PROTOCOL SUMMARY

### Study Title

A phase 2, multicenter, multi-cohort, open-label study of pomalidomide in combination with low-dose dexamethasone or pomalidomide in combination with low-dose dexamethasone and daratumumab in subjects with relapsed or refractory multiple myeloma following lenalidomide-based therapy in the first or second line setting.

### Indication

Relapsed or refractory multiple myeloma (MM) after treatment with lenalidomide (LEN)-based therapy in the first or second line setting.

### Objectives

#### *Primary Objective*

The primary objective of the study is to evaluate the efficacy of the combination of pomalidomide and low-dose dexamethasone (POM + LD-dex) or pomalidomide in combination with daratumumab and low-dose dexamethasone (POM+DARA+ LD-dex) in subjects relapsing after or refractory to LEN-based therapy in the first or second line setting.

#### *Secondary Objective*

The secondary objective of the study is to evaluate the safety of the combinations of POM + LD-dex or POM+DARA+LD-dex in subjects with relapsed or refractory multiple myeloma following lenalidomide-based therapy in the first or second line setting.

#### *Exploratory Objective*

The exploratory objectives of the study are to investigate pharmacodynamic effects of POM+LD-dex or POM+DARA+LD-dex combination therapy, and potential biomarkers predictive of response or resistance to the therapy in relation to the clinical endpoints from all enrolled subjects who provide informed consent for participation in the exploratory biomarker portion of the trial.

### Study Endpoints

#### *Primary Endpoint*

- Overall response rate (ORR)

#### *Secondary Endpoints*

- Progression-free survival (PFS)
- Overall survival (OS)
- Duration of response (DoR)
- Time to response (TTR)
- Time to progression (TTP)

- Adverse event (AE) assessment (type, frequency, seriousness, severity, relationship to POM and/or DARA and/or LD-dex and outcomes), including second primary malignancies (SPM)

### ***Exploratory Endpoints***

- Molecular, immune and cellular markers that might predict response or resistance to POM+ LD-dex or POM+DARA+LD-dex combination therapy
- Pharmacodynamic and mechanistic biomarkers of pomalidomide-daratumumab-dexamethasone combination therapy
- Quality of life (for subjects enrolled in Cohort B only) as measured by the descriptive system of the EQ-5D

### **Study Design**

This is a multicenter, multi-cohort, open-label, phase 2 study of POM + LD-dex or POM+DARA+LD-dex in subjects relapsing after or refractory to LEN-based therapy in the first or second line setting.

This study consists of the following consecutive phases: Screening, Treatment, and Follow-up. Study visits and evaluations will be performed as outlined in [Table 1](#) (Table of Events).

### ***Screening Phase***

Study subjects will sign an informed consent document (ICD) prior to undergoing any study-related procedures. Subjects will undergo screening for protocol eligibility within 28 days prior to Cycle 1 Day 1, as outlined in [Table 1](#).

Subjects who meet all eligibility criteria will receive the study treatment and will be maintained on the pregnancy prevention program for the duration of the study, including the 28-day follow-up period.

The inclusion procedure will be confirmed by a validated interactive voice/web response system (IVRS/IWRS) and electronic case report form (eCRF).

### ***Treatment Phase***

Each subject will receive the following study treatment until progressive disease (PD), unacceptable toxicity, death, withdrawal of active participation in the study or withdrawal of consent, or lost to follow-up, or as long as they benefit from therapy, according to the opinion of the responsible study investigator and approved by the sponsor:

- Cohort A (POM+ LD-dex):
  - POM administered orally at the starting dose of 4 mg/day on Days 1-21 of a 28-day cycle,
  - LD-dex administered orally at the starting dose of 40 mg/day (for subjects ≤ 75 years old) or 20 mg/day (for subjects > 75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle.

- Cohort B and Cohort C (POM+DARA+LD-dex):
  - POM administered orally at the starting dose of 4 mg/day on Days 1-21 of a 28-day cycle,
  - LD-dex administered orally at the starting dose of 40 mg/day (for subjects ≤ 75 years old) or 20 mg/day (for subjects > 75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle,
  - DARA administered intravenously (IV) at a starting dose of 16 mg/kg at following schedule:
    - Days 1, 8, 15, and 22 of a 28-day cycle for Cycle 1 and Cycle 2
    - Days 1 and 15 for Cycle 3 through Cycle 6
    - Day 1 for Cycle 7 and each cycle thereafter until disease progression

Subjects qualified to enroll in Cohort A will have had 2 prior lines of therapy with the most recent line of therapy containing lenalidomide. Subjects qualified to enroll in Cohort B and Cohort C will have had 1 or 2 prior lines of therapy with the most recent line of therapy containing lenalidomide.

Bone marrow aspirate, blood samples, and normal tissue (saliva samples) will be collected for exploratory biomarker analysis from subjects who give additional consent in Cohort A and are mandatory for subjects in Cohort B at participating sites. The collection of samples will occur as outlined in [Table 1](#). Normal tissue will be collected at screening only by non-invasive methods. Samples will be processed at sites as per lab manual. Bone marrow aspirate will be collected and are mandatory for subjects in Cohort C.

### ***Follow-up Phase***

All study subjects will enter the follow-up phase within 28 days of last dose of study medication. During follow-up, the following information will be collected from all subjects 4 times per year (every 3 months) for up to 5 years after the last subject is enrolled in each respective cohort: survival, SPM, subsequent anti-myeloma treatments (type of treatment, start and stop dates, best response whenever possible and date of progression).

### **Study Population**

The study is anticipated to enroll approximately 188 subjects with relapsed MM or refractory MM who fulfill the eligibility criteria. At the time of this amendment, enrollment to Cohort A and B already completed with 56 and 112 subjects respectively. Cohort C will enroll approximately 20 subjects.

### **Length of Study**

This study will remain open to enrollment until the target subject enrollment of approximately 188 subjects has been reached. Subjects will be followed for up to 5 years after the last subject is enrolled in each respective cohort.

Subjects continue treatment until documented progression, unacceptable toxicity, death, withdrawal of active participation in the study or withdrawal of consent, or lost to follow-up, or they no longer benefit from the treatment, or they or the treating physician withdraw them from

treatment. Once discontinued from the study treatment, subjects will be followed for OS and occurrence of SPM 4 times per year (every 3 months) for up to 5 years after the last subject is enrolled in each respective cohort (unless the follow-up is shorter due to withdrawal of consent, loss to follow-up, or death).

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

### **Study Treatments**

All subjects will be treated with open label POM + LD-dex or POM+DARA+LD-dex. Dexamethasone is commercially available and will be provided by the investigator via prescription to subjects who are registered into this study. For Cohort C, dexamethasone will be supplied as 2 mg or 4 mg tablets for oral administration as Investigational Product by Celgene Corporation.

Pomalidomide will be supplied as Investigational Product by Celgene Corporation as 1 mg, 2 mg, 3 mg, and 4 mg capsules for oral administration. Study drug will be packaged in bottles containing a 21-day supply of POM.

Daratumumab will be supplied as Investigational Product by Celgene Corporation in single-use vials in single-count cartons. Daratumumab is a colorless to pale yellow, preservative-free solution and will be supplied in vials containing 400 mg/20 mL vial or 100 mg/5 mL vial for intravenous administration. The dosing schedule is as follows:

- POM is administered orally at the starting dose of 4 mg/day on Days 1-21 of a 28-day cycle,
- LD-dex is administered orally at the starting dose of 40 mg/day ( $\leq 75$  years old) or 20 mg/day ( $> 75$  years old) on Days 1, 8, 15, and 22 of a 28-day cycle.
- DARA administered intravenously at a starting dose of 16 mg/kg at following schedule:
  - Days 1, 8, 15, and 22 of a 28-day cycle for Cycle 1 and Cycle 2
  - Days 1 and 15 for Cycle 3 through Cycle 6
  - Day 1 for Cycle 7 and each cycle thereafter until disease progression

Guidelines for dose modifications for POM, DARA, and LD-dex are further described in Section 8.2.

### ***Allowed Medications and Treatments***

Low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant will be given to all subjects. Antithrombotic prophylaxis will be recorded in the eCRF form at each visit.

Prior to study entry and during the treatment phase, subjects with myeloma-associated bone disease may receive bisphosphonate therapy, as well as other agents that may be used for

myeloma-associated bone disease, such as denosumab and teriparatide, unless such therapy is contraindicated.

Hematopoietic growth factors, platelet and/or red blood cell transfusions are allowed throughout the study, including the screening period, at the discretion of the investigator.

Pre-medications for infusion related reactions (IRR) associated with DARA infusion including corticosteroids, antipyretics, leukotriene receptor antagonist, and antihistamines as outlined in Section 9.2 (Required Concomitant Medications and Procedures)

Radiation therapy to a pathological fracture site or to treat bone pain is permitted. Such subjects are allowed to remain on study treatment.

### ***Prohibited Medications and Treatments***

Concomitant use of other anti-myeloma therapy while the subject is taking study drug is prohibited. Subsequent treatment for MM should not be initiated until PD is documented or until subject does not tolerate study treatment.

Chronic use of steroids other than the study drug (dex) or any other immunosuppressive therapies are prohibited in this study without approval from the Medical Monitor.

Drugs known to prolong the QT corrected (QTc) interval should be avoided unless deemed medically necessary. See [Appendix G](#) for a comprehensive list of drugs which are known to prolong the QTc.

### ***Treatment Discontinuation***

Subjects will continue study treatment until the documentation of confirmed PD, intolerable toxicity, death, withdrawal of active participation/consent in the study, or loss to follow-up, or as long as they benefit from therapy according to the opinion of the responsible study investigator and discussed with the sponsor.

Subjects are not permitted to start any other anti-myeloma therapy before progression is confirmed or subject cannot tolerate study treatment. A treatment discontinuation visit will be required for all subjects who discontinue treatment.

- If POM is permanently discontinued, then the subject must be permanently discontinued from all study treatments.
- For Patients in Cohort B and Cohort C, if DARA is withheld or permanently discontinued, then POM, and LD-Dex dosing may be continued.
- If LD-dex dosing is withheld or permanently discontinued, then POM and DARA (for patients in Cohort B and Cohort C) dosing may be continued.

See dose administration guidance in Section 8.3.

### **Overview of Efficacy Assessments**

Tumor response, will be based on investigator's assessment using local imaging review (if applicable) and central laboratory results according to modified International Myeloma Working Group (mIMWG) criteria (per [Appendix B](#)).

For subjects with daratumumab interference on serum immunofixation (IFE), the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test will be used to distinguish a positive SPEP/IFE due to the presence of daratumumab versus the presence of underlying (endogenous) monoclonal protein. Subjects that meet all other International Myeloma Working Group (IMWG) criteria for complete response (CR), and whose positive IFE is confirmed to be daratumumab, will be considered complete responders.

For subjects with light chain multiple myeloma, both serum and urine immunofixation test and serum free light chain assay will be performed routinely. As daratumumab is a monoclonal IgG antibody, additional serum samples may be utilized to monitor for potential daratumumab interference with the IFE.

Time to response, DoR, TTP, and PFS will be calculated based on the investigator's response assessment. Subjects also will be followed for OS. All time-to-event endpoints will be estimated from the time of study enrollment, except DoR which will be estimated at the time from response.

- Myeloma paraprotein
- Serum immunoglobulins
- Serum Free Light Chain
- Serum beta-2 Microglobulin
- Bone marrow aspiration/biopsy
- Radiographic assessments of lytic bone lesions
- Extramedullary plasmacytoma (EMP) assessments
- Radiographic assessments of lytic bone lesions (skeletal survey)
- Eastern Cooperative Oncology Group (ECOG) performance status
- Quality of Life (QoL) as measured by the descriptive system of the EQ-5D questionnaire (subjects enrolled in Cohort B only)

### **Overview of Safety Assessments**

- Pregnancy testing / counseling.
- Clinical laboratory evaluations (hematology, serum chemistry, urinalysis).

With the exception of pregnancy tests, all laboratory measures for safety and efficacy assessments will be performed centrally.

An abnormal laboratory value is considered to be an AE if the abnormality results in discontinuation from the study; requires treatment, modification/interruption of investigational product (IP) dose, or any other therapeutic intervention; or is judged to be of significant clinical importance by the investigator.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event (SAE).

- Venous thromboembolism (VTE) monitoring

- Electrocardiogram (ECG) (only for subjects enrolled in Cohort A)
- Concomitant medications and procedures
- Adverse events of all grades will be recorded on the eCRF throughout the study from signing of the ICD until 28 days after discontinuation from the study treatment, including AE type, frequency, seriousness, severity, relationship to study drug, and outcome.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (version 4.03, June 2010). Summaries will be provided by system organ class, and preferred term.

- Second primary malignancies will be monitored as events of interest and should be included as part of the assessment of AEs throughout the course of the study. Investigators must report any SPM as an SAE regardless of causal relationship to IP (POM, DARA, or LD-dex), occurring at any time from the time of signing the ICD until the end of follow-up.

For all subjects who develop SPM, sites will be required to submit all diagnostic reports (eg, pathology, cytogenetics, flow cytometry results) from the MM diagnostic confirmation samples submitted at screening and all reports for the tumor samples from the SPM diagnosis. For SPMs diagnosed at another institution, (outside of the investigational site) sites will be required to make every effort to obtain these reports for SPM confirmation.

### Overview of Exploratory Biomarker Assessments

Subjects who give informed consent for participation in the biomarker assessments in Cohort A, all subjects in Cohort B will provide normal tissue, whole blood, and bone marrow aspirate and all subjects in Cohort C will provide bone marrow aspirate at defined time-points or events. The samples will be taken at clinical sites able to collect and process the mandated samples. Only noninvasive approaches to collect normal tissue for comparative analysis with tumor specimens will be used.

- **Bone marrow aspirate:** Bone marrow aspirates and cellular fractions isolated from them will be used for nucleic acid (eg, gene expression profiling and DNA sequencing), protein, and other biochemical analyses. These studies will focus on genomes, candidate genes, proteins, and signaling pathways identified by earlier work and will characterize aberrations associated with high-risk MM and changes induced by pomalidomide or pomalidomide/daratumumab based therapy. Serially collected samples may be used to study changes associated with clonal evolution and for measuring depth of responses to therapy. The analytical techniques involved will include methods such as cell sorting, immunohistochemistry, flow cytometry, Western blotting techniques, array-based and Quantitative polymerase chain reaction (QPCR) gene expression profiling, DNA sequencing and allele copy number measurements. The CD 138 + and CD 138- cells isolated from bone marrow mononuclear cells will be used for DNA, gene expression, and protein analysis.

Analyses of DNA for subsets of genes and specific dysregulated pathways associated with pomalidomide/dexamethasone or pomalidomide/daratumumab/dexamethasone activity or genetic aberrations associated with high-risk multiple myeloma will be evaluated for mutations, aberrations, or changes in copy number (ie, allelic loss or gain). Gene expression analyses will be conducted from baseline as well as subsequent samples for comparison of pomalidomide/dexamethasone or pomalidomide/daratumumab/dexamethasone treatment effect on the expression of genes, such as cereblon. Similarly, for proteins, targets (such as Cereblon, IRF 4, cMyc, etc) and other factors important for pomalidomide/daratumumab/dexamethasone synergistic activity will be measured by several techniques such as immunohistochemistry, western analysis or flow cytometry respectively. In some subjects, clonal evolution of MM cells or minimal residual disease (MRD) may be measured using bone marrow aspirates collected at diagnosis to study depth of response to pomalidomide, daratumumab and LD-dex and the sensitivity of different subclones of the MM disease to treatment by using sensitive next generation sequencing-based approaches.

- **Whole Blood:** Flow cytometry analyses will be conducted on whole blood collected from subjects treated with pomalidomide/dexamethasone/ daratumumab combination therapy. Clonality analyses, MRD, presence of soluble protein biomarkers, mutational analysis, and immune function tests will be performed on PBMC and/or plasma and/or serum.
- **Normal tissue at study entry:** To accurately identify genetic and biochemical changes associated specifically with the tumor and with responses to pomalidomide/dexamethasone or pomalidomide/daratumumab/dexamethasone treatment it is necessary to have non-tumor samples as comparators. Noninvasive procedures will be used to collect normal tissues which may include the collection of saliva.

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## 1. INTRODUCTION

Multiple myeloma (MM) is a rare and incurable progressive neoplastic disease that accounts for 10% of all hematological malignancies. It was estimated in 2017 that 30,280 new cases and 12,590 deaths from the disease occurred in the United States (Siegel, 2017; The Cancer Society, 2017). It was estimated in 2016 that 8,700 new cases and 4,200 deaths from the disease occurred in Japan (Cancer Statistics in Japan, 2016).

Multiple myeloma (MM) is typically sensitive to a variety of cytotoxic drugs. Although responses are typically durable, relapse is an expected part of the disease course and MM is not considered curable with current approaches. Treatment of MM has been rapidly evolving with the introduction of new classes and new generation of drugs: immunomodulating drugs (IMiDs), proteasome inhibitors (PIs), monoclonal antibodies, and histone deacetylase (HDAC) inhibitors. In addition, there is increasing understanding of the tumor biology, creating the rationale of new combination therapies (Anderson, 2011; Hideshima, 2002; NCCN, 2018). In recent years, innovative therapies such as proteasome inhibitors and immunomodulators have improved the prognosis for previously treated MM subjects (Kumar, 2008). However, the disease follows a relapsing course in the majority of patients, regardless of treatment regimen or initial response to treatment. Multiple myeloma remains incurable using conventional treatments, with a median survival duration of approximately 5 years (Richardson, 2007a). Therefore, there is a need for more effective therapeutic options for the treatment of relapsed or refractory multiple myeloma.

The primary purpose of protocol amendment #3 is the addition of Cohort C will enroll approximately 20 patients to provide efficacy and safety data for Japanese patients. Lenalidomide is being utilized frequently as doublet- or triplet-based induction therapy and/or maintenance therapy for newly diagnosed and early relapse patients. Multiple myeloma remains an incurable disease and when patients relapse or become refractory to lenalidomide there is a limited number of treatment options. This represents a growing unmet need and pomalidomide has been exclusively studied in the lenalidomide exposed patient population and has shown statistically significant improvement in PFS (progression free survival). There is growing data for the combination therapy of pomalidomide and low-dose dexamethasone in combination with daratumumab. The number of Japanese patients enrolled in previous studies are small. The additional Cohort C will address the need for clinical data for the previously lenalidomide exposed Japanese patient.

### 1.1. Treatment Options for Relapsed or Refractory Multiple Myeloma

The treatment options approved for use in relapsed and/or refractory MM currently include:

**Lenalidomide plus dexamethasone:** Lenalidomide in combination with dex is approved in the US, Canada, European Union (EU), Japan and many other countries around the world for the treatment of patients with MM (Benboubker, 2014; Dimopoulos, 2007; Weber, 2007).

**Bortezomib:** Bortezomib monotherapy is approved in the US, Canada, European Union, Japan and many other countries around the world for the treatment of patients with MM (Richardson, 2005).

**Pegylated liposomal doxorubicin plus bortezomib:** Pegylated liposomal doxorubicin in combination with BTZ is approved in the US for the treatment of patients with MM who have not previously received BTZ and have received at least one prior therapy (Orlowski, 2007).

**Carfilzomib:** Carfilzomib is a proteasome inhibitor that is indicated in the US, Canada, Japan and many other countries around the world in combination with dexamethasone or with lenalidomide plus dexamethasone for the treatment of patients with relapsed or refractory multiple myeloma who have received one to three lines of therapy. Carfilzomib is also indicated as a single agent in the US for the treatment of patients with relapsed or refractory MM who have received one or more lines of therapy ([Berenson, 2012a](#); [Siegel, 2012](#)).

**Pomalidomide:** Pomalidomide in combination with dexamethasone is approved in the US, Canada, Japan and many other countries around the world for the treatment of patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and have demonstrated disease progression on or within 60 days of completion of the last therapy ([Pomalidomide, 2018](#)).

**Ixazomib:** Ixazomib is a proteasome inhibitor approved in the US and other countries including Japan in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received at least 1 prior therapy ([Ixazomib, 2015](#)).

**Elotuzumab:** Elotuzumab is a SLAMF7-directed immunostimulatory antibody approved in the US, EU and other countries including Japan in combination with lenalidomide and dexamethasone for the treatment of patients with multiple myeloma who have received one to three prior therapies ([Elotuzumab, 2015](#)).

**Daratumumab:** Daratumumab is a CD38-directed cytolytic antibody approved in the US, EU, Japan and many other countries in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone for the treatment of patients with MM who have received at least one prior therapy. Daratumumab is approved in the US and EU with bortezomib, melphalan and prednisone for the treatment of patients with newly diagnosed MM who are ineligible for autologous stem transplant. Daratumumab is also approved in the US in combination with pomalidomide and dexamethasone for the treatment of patients with MM who have received at least two prior therapies including lenalidomide and a proteasome inhibitor and as monotherapy and as a monotherapy for the treatment of patients with multiple myeloma who have received at least three prior lines of therapy including a proteasome inhibitor (PI) and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent ([Daratumumab, 2018](#)).

**Panobinostat:** Panobinostat is a histone deacetylase inhibitor, approved in the US and many other countries in combination with bortezomib and dexamethasone is indicated for the treatment of patients with MM who have received at least two prior regimens, including bortezomib and in immunomodulatory agent ([Panobinostat, 2015](#)).

The main considerations for choosing an appropriate treatment for relapsed MM are: risk level, prior therapy, duration of response to prior therapy, residual toxicity, age, physical condition, and whether or not the patient is a candidate for allogeneic stem cell transplantation ([Kastritis, 2009](#); [NCCN, 2016](#)).

## 1.2. Pomalidomide (CC-4047)

Pomalidomide (POM) (CC-4047, 4-amino-2-(2,6-dioxopiperidin-3-yl)isoindoline-1,3-dione) is a novel immunomodulatory drug under development for the treatment of MM. Pomalidomide shares a number of the beneficial pharmacologic properties of thalidomide and LEN. An in vitro

model of anti-tumor necrosis factor (TNF) activity has shown that pomalidomide has a half maximal inhibitory concentration ( $IC_{50}$ ) of approximately 0.013  $\mu$ M (13 nM) against TNF produced by lipopolysaccharide (LPS)-stimulated human peripheral blood mononuclear cells. Thalidomide and LEN, by comparison, have an  $IC_{50}$  of ~194  $\mu$ M and 0.10  $\mu$ M (100 nM), respectively (Corral, 1999; Muller, 1999). In LPS-stimulated human whole blood,  $IC_{50}$  for pomalidomide is 0.025  $\mu$ M (25 nM) (Muller, 1999). In addition, pomalidomide has demonstrated a 10-fold higher potency for T-cell co-stimulation than LEN (Corral, 1999; Teo, 2005). Pomalidomide also augmented the activity of natural killer cells and enhanced antibody-dependent cell-mediated cytotoxicity of targeted tumor cells in combination with therapeutic antibodies to tumor-specific surface antigens (Hayashi, 2005; Hernandez-Ilizaturri, 2005). Moreover, pomalidomide is also a potent inhibitor of the proliferation of MM cell lines in vitro. Concentrations of 2.73 to 27.3 ng/mL (0.01 to 0.1  $\mu$ M) achieved a 50% inhibition of MM.1S and Hs Sultan cell proliferation. In contrast, at concentrations of 25.8  $\mu$ g/mL (100  $\mu$ M), thalidomide inhibited the proliferation of MM.1S and Hs Sultan cells by only 15% and 20%, respectively. Pomalidomide is also more potent than thalidomide or LEN in inducing G1 growth arrest and apoptosis in MM cell lines and in patient MM cells that are resistant to melphalan, doxorubicin, and dex as well as in enhancing the anti-MM activity of dex (Hideshima, 2000). However, pomalidomide does not inhibit the proliferation of normal B cells but rather protects them from apoptosis, suggesting an additive property of this compound in helping the repopulation of the normal blood cells (Verhelle, 2007).

Of potential relevance to the refractory MM setting, pomalidomide appears to retain antiproliferative activity against H929 and KMS-12-BM MM cells that have increased resistance to acute LEN treatment following chronic exposure to LEN (Adams, 2009; Rychak, 2011a). Pomalidomide and dex were also synergistic at inhibition of cell proliferation in LEN-resistant cell lines. Preliminary results from an in vitro experiment performed by the Celgene Research group (Adams, 2009; Rychak, 2011a) demonstrate that MM cells treated long-term with LEN plus dex and with POM + dex became resistant to LEN/dex but retained their sensitivity to POM/dex. This suggests that the combination of POM + dex may be useful in the treatment of MM that is refractory to LEN + dex.

### **Experience with Pomalidomide in Relapsed and/or Refractory MM**

#### **Celgene Phase 1b Study (CDC-407-00-001 / CC-4047-MM-001; Enrollment Completed):**

This was a phase 1b single-center, ascending dose (1, 2, 5, and 10 mg), open-label study to identify the maximum tolerated dose (MTD) and evaluate the safety and efficacy of pomalidomide given continuously ([cohort 1] Schey, 2004) or on alternate days ([cohort 2] Streetly, 2008) in 45 subjects with MM who were considered refractory to treatment after at least 2 cycles of treatment or who relapsed after previous treatment. The MTD was 2 mg continuously and 5 mg on alternate days; the most common dose-limiting toxicity (DLT) was grade 4 neutropenia. The most common adverse events (AEs) were neutropenia, thrombocytopenia, pharyngitis, cough, dyspnea, and hypoesthesia. Overall, 23 (51%) of 45 subjects had partial response (PR) or better, including 6 subjects with complete response (CR) and 12 with very good partial response (VGPR). In cohort 1, the PFS was 9.75 months and overall survival (OS) was 22.5 months; in cohort 2, the PFS was 10.5 months and OS was 35.9 months.

**Celgene Phase 1b/2 Study (CC-4047-MM-002; Enrollment Completed):** This was a phase 1b/2 multicenter, randomized, open-label, dose escalation (2, 3, 4, and 5 mg) study to evaluate the MTD of POM alone (Phase 1) and the safety and efficacy of POM alone using a cyclic regimen (21 of 28 days) and in combination with low-dose dexamethasone (LD-dex) (Phase 2) using a cyclic regimen (21 of 28 days) in subjects with relapsed and refractory MM who had received  $\geq 2$  prior anti-MM regimens. All subjects must have received prior treatment that included LEN and BTZ. In the phase 1b segment of the study, 38 subjects were enrolled. The MTD was 4 mg which was the dose selected for the phase 2 part of the study. The safety profile was similar across cohorts except for grade 4 neutropenia, which was the DLT and was experienced at the highest rate in the 5 mg cohort. A total of 221 subjects were enrolled in phase 2 (POM+LD-dex n = 113; POM n = 108); 219 received  $\geq 1$  cycle of study treatment and 191 subjects were evaluable for response. Baseline characteristics were comparable between the 2 arms with a median of 5 (range 2–13) prior therapies in both arms; 74% of subjects in POM+LD-dex and 76% of subjects in POM alone had prior autologous stem-cell transplantation (ASCT). The remaining subjects were elderly (aged  $> 75$  years) or ineligible for ASCT; all subjects were exposed to corticosteroids and 84% in the POM+LD-dex and 95% in POM alone arms were exposed to alkylators. Subjects were refractory to LEN, (POM+LD-dex 77% and POM alone 79%), BTZ (73% and 69%), or both drugs (61% and 59%). Among subjects who were randomized to receive POM alone, 61 (56%) subsequently went on to receive POM+LD-dex due to progressive disease (PD) per protocol. A median of 5 (range 1–17) treatment cycles were received by subjects in both arms. Median treatment duration was 5.0 months. Response of  $\geq$  PR was seen in 34% of subjects in the POM+LD-dex arm and 13% in the POM alone arm, including 1% CR in each arm;  $\geq$  minor response (MR) was 45% versus 29%, respectively. Median duration of response (DoR) was 7.7 months with POM+LD-dex and 8.3 months with POM alone, and median PFS was 4.6 and 2.6 months, respectively. Median OS was comparable for both arms (14.4 and 13.6 months). Results from independent adjudication were similar, with  $\geq$  PR in 30% of subjects in the POM+LD-dex arm and 9% in the POM alone arm, including 1% and 0% CR, respectively, in each arm. Greater-than-or-equal-to MR was achieved with POM+LD-dex in 45% and with POM alone in 25%; PFS was 3.8 and 2.5 months, respectively. In the subgroup of subjects refractory to both LEN and BTZ, 30% and 16% of subjects treated with POM+LD-dex or POM alone, respectively, achieved  $\geq$  PR;  $\geq$  MR was 45% and 30%, respectively. Median PFS was 3.8 months for POM+LD-dex and 2.0 months for POM alone; median OS showed a similar trend (13.5 and 10.8 months, respectively). The main reason for treatment discontinuation was PD in both arms (POM+LD-dex 51%; POM alone 44%); discontinuations due to AEs were 7% and 12%, respectively. Grade 3/4 AEs in POM+LD-dex versus POM alone, respectively, were: neutropenia 38% and 47%; febrile neutropenia 2% and 2%; thrombocytopenia 19% and 21%; anemia 21% and 17%; pneumonia 19% and 8%; and fatigue 10% and 8%. All grades of peripheral neuropathy, deep vein thrombosis, and renal failure occurred in 7% and 10%, 2% and 1%, and 2% and 1% of subjects for POM+LD-dex versus POM alone, respectively ([Richardson, 2011a](#)). This study formed the basis for the recent accelerated approval in the US of Pomalidomide (Pomalyst<sup>®</sup>) in patients with relapsed multiple myeloma.

**Celgene Phase 3 Study (CC-4047-MM-003; Enrollment Completed).** Dimopoulos et al reported on the phase 3, multicenter, randomized, open-label study comparing the efficacy and safety of POM in combination with low-dose dexamethasone (POM+LD-dex) versus high-dose

dexamethasone (HiDex) in patients with MM who were refractory to both LEN and BTZ (Dimopoulos, 2012). Patients in the POM+LD-dex arm (n=302) received POM 4 mg on Days 1-21 and Dex 40 mg on Days 1, 8, 15, and 22 in a 28-day cycle. Patients in the HiDex arm (n=153) received Dex 40 mg on Days 1-4, 9-12, and 17-20 in a 28-day cycle. Progression-free survival for the intent-to-treat (ITT) population: POM+LD-dex (3.6 months) versus HiDex (1.8 months); Hazard ratio (HR) = 0.45;  $P < .001$ . Progression-free survival for patients refractory to both LEN and BTZ: POM+LD-dex (3.2 months) versus HiDex (1.7 months); HR = 0.48;  $P < .001$ . Overall survival for the ITT population: POM+LD-dex (not reached) versus HiDex (7.8 months); HR = 0.53;  $P < .001$ . The most common Grade 3/4 AEs reported in the study for patients receiving POM+LD-dex were neutropenia (42%), anemia (27%) and thrombocytopenia (21%). Grade 3/4 non-hematologic AE included infections (24%), pneumonia (9%), fatigue (5%), hemorrhage and glucose intolerance (3% each).

**Celgene Phase 2 Study (CC-4047-MM-011; Enrollment Completed).** Ichinohe et al investigated pomalidomide plus low dose dexamethasone on 36 Japanese patients with relapsed or refractory multiple myeloma who had received two or more prior therapies. The ORR was 42%, which included 1 CR and 14 PRs as well as 44% (16 patients) who achieved stable disease (SD). The most frequent Grade 3/4 AEs reported were neutropenia (64%), anemia (42%) and thrombocytopenia (31%). Grade 3/4 non-hematologic AEs were pneumonia and decreased appetite (8% each) (Ichinohe, 2016).

**Investigator Initiated Phase 2 Study at the Mayo Clinic (PO-MM-PI-0010; Enrollment Completed).** This is a phase 2 open-label study of pomalidomide (2 mg continuous) +LD-dex (40 mg/day on Days 1, 8, 15, and 22) in subjects with relapsed or refractory MM who had received 1-3 prior regimens (Lacy, 2009). A total of 60 subjects were initially enrolled into this study. Thirty-eight (63%) of the 60 subjects had a confirmed response including 3 CR and 17 VGPR. Responses were seen in 8 of 12 (66.7%) LEN-refractory subjects, 6 of 16 (37%) thalidomide-refractory subjects, and 6 of 10 (60%) BTZ refractory subjects. The most common Grade 3/4 hematological toxicity was neutropenia, and the most common nonhematological Grade 3/4 toxicities were fatigue and pneumonia.

Since responses were observed in some patients who were refractory to LEN in the initial cohort of 60 subjects, an additional cohort of 34 subjects, who were refractory to prior LEN therapy, was enrolled from November 2008 to April 2009. The overall response rate ( $\geq$  PR) was 32% for this cohort of 34 subjects. The most common Grade 3/4 hematologic toxicity was neutropenia (29%) and the most common Grade 3/4 non-hematologic toxicity was fatigue (9%), which was consistent with that observed in the initial cohort of 60 subjects (Lacy, 2010b).

Based on a study conducted by Richardson, et al, (Richardson, 2009a) where the MTD of pomalidomide was determined to be 4 mg, a phase 2 study was initiated by Lacy, et al to compare the 2 different dosing regimens in MM subjects who were refractory to both LEN and BTZ. Pomalidomide was given orally 2 mg/day or 4 mg/day, on Days 1 to 28 of a 28-day cycle, with dex 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 ( $\geq$  PR) was 25% and 29% for the 2 mg and 4 mg cohorts, respectively (Lacy, 2011a).

**Investigator Initiated Phase 2 Study (PO-MM-PI-0024; Enrollment Completed).** This is a phase 2, multicenter, randomized, open-label study of POM + dex in subjects with relapsed and

refractory MM who have received BTZ and LEN, conducted by Intergroupe Français du Myelome (IFM). Subjects received a 4 mg dose of POM, given either in a continuous (28-day) or a cyclic (21-day out of 28-day cycles) regimen in combination with LD-dex. The primary endpoint is the response rate, and the secondary endpoints are safety, time to response, duration of response, time to disease progression, and OS. Eighty-four subjects were enrolled into this study, 43 in the 4 mg 21/28 days arm (Cohort A) and 41 in the 4 mg 28/28 days arm (Cohort B). At the cut-off of 01 Mar 2011, overall response rate (ORR) was 34.9% in Cohort A and 34.1% in Cohort B, including 4.7% and 7.3% VGPR, respectively. Overall, 40 (47.6%) subjects had SD (including minor response) and 3 subjects reached CR. The median PFS was 6.3 (4.1-9.1) months in either arm, and the median duration of response was 11.4 (3.7-13.6) months and 7.9 (4.0- not reached) months in Cohort A and in Cohort B, respectively. The median PFS was 4.2 (3.3-6.9) months for subjects with SD as compared to 12.6 (9.9-14.8) months in subjects that had a response. The primary toxicity was myelosuppression and was similar in both treatment arms (Leleu, 2011a).

### Conclusion

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 LEN and BTZ. Confirmed response rates range between 30% and 60% at POM doses of between 2 and 4 mg/day in combination with dex. Notably, pomalidomide produces responses in subjects who are refractory to LEN, another IMiDs<sup>®</sup> compound, aligning with the nonclinical results observed in LEN-resistant cells (Adams, 2009; Rychak, 2011a). 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.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of Pomalidomide.

### 1.3. Daratumumab

Daratumumab, is a human IgG1k anti-CD38 monoclonal antibody. CD38 is a transmembrane receptor with enzymatic activity that is highly and consistently expressed on the surface of myeloma cells (Deaglio, 2007). CD38 is involved in signal transduction for lymphoid and myeloid cells and presents a therapeutic target in MM because of low levels of expression on other hematologic and nonhematologic tissues. Daratumumab induces directed cell killing through complement dependent cytotoxicity, antibody-dependent cell cytotoxicity, and other potential mechanisms (Lokhorst, 2015).

#### Experience with Daratumumab in Relapsed and /or Refractory MM

**Genmab Phase 1/2 study (GEN 501; Enrollment Completed).** This was a phase 1/2 ascending dose (0.005, 0.05, 0.1, 0.5, 1, 2, 4, 8, 16 and 24 mg/kg), open-label study to identify the maximum tolerated dose (MTD) and evaluate the safety and efficacy of daratumumab given weekly for 8 weeks. In the expansion phase 2, forty-two patients received 16 mg/kg either once weekly or twice weekly (8 doses each) and then monthly for 24 months. The ORR was 36%. The most common grade 3/4 hematologic side effects were neutropenia 12%, thrombocytopenia

10% and grade 3/4 non-hematologic side effect were pneumonia 12% and pyrexia 2%. Daratumumab associated infusion related reactions occurred in 71% of patients ([Lokhorst, 2015](#)).

**Janssen Phase 1 (Enrollment Completed).** This is a phase 1, open label, multicenter dose escalation study in Japanese participants with  $\geq 2$  prior therapies. Daratumumab was administered at a dose of 8 mg/kg or 16 mg/kg weekly x 7, every 2 weeks x 8, then once every 4 weeks. Subjects received 8 mg/kg (n=4) and 16 mg/kg (n=5). Eight patients experienced Grade  $\geq 3$  AEs. Four serious AEs were observed in 3 patients. Infusion-related reactions occurred in four (44%) patients and were Grade 1 or 2. The ORR (44%) comprised 1 and 3 PR in 8 mg/kg and 16 mg/kg cohorts, respectively. The median PFS was 6 months for the 8 mg/kg cohort and 9.5 months for the 16/kg cohort ([Iida, 2017](#)).

**Janssen Phase 2 Study (SIRIUS MMY2002; Enrollment Completed).** This is a phase 2 open-label study of daratumumab in subjects who received 3 or more prior lines of therapy or were double refractory. A total of 106 subjects were enrolled into this study. Subjects received daratumumab 16 mg/kg weekly x 8, every 2 weeks x 8 and then every 4 weeks. The ORR was 29%. The most common Grade 3/4 hematological toxicities were thrombocytopenia (25%), anemia (24%), neutropenia (14%) and non-hematological were fatigue and back pain (3%) each. Daratumumab associated infusion related reactions occurred in 43% of patients, Grade 3 was 5% and no Grade 4 ([Lonial, 2016](#)).

**Janssen Phase 3 Study (POLLUX MMY3003; Enrollment Completed).** This is a phase 3 open-label, multicenter study of daratumumab, lenalidomide, and dexamethasone or lenalidomide and dexamethasone alone in subjects with relapsed or refractory MM who had received 1 or more lines of previous therapy. A total of 569 subjects were enrolled into this study. Patients in the DARA+LEN+dex arm (n=286) received DARA 16 mg/kg weekly x 8, then every 2 weeks for 16 weeks then every 4 weeks, LEN 25 mg on Days 1-21 and dex 40 mg on Days 1, 8, 15 and 21 in a 28-day cycle. Patients on the LEN+dex (n=283) received LEN 25 mg on Days 1-21 and dex 40 mg on Days 1, 8, 15, 21 in a 28-day cycle. PFS for the intent-to-treat (ITT) population at 12 months: DARA+LEN+dex 83.2% versus LEN+dex 60.1%. ORR in DARA+LEN+dex versus LEN+dex was 92.9% vs 76.4%,  $P < 0.001$ , VGPR or better 75.8% vs 44.2%,  $P < 0.001$ , and CR or better was 43.1% vs 19.2%,  $P < 0.001$ . Minimal residual disease (MRD) at  $10^{-5}$  in the DARA+LEN+dex was 22.4% vs LEN+dex 4.6%. The most common Grade 3/4 hematologic AEs reported in the study for patients receiving DARA+LEN+dex and in LEN+dex arm were neutropenia (51.9% and 37% respectively), thrombocytopenia (12.7% and 13.5% respectively) and anemia (12.4% and 19.6% respectively). Grade 3/4 non-hematologic AEs included infections (1.1% and 1.1% respectively), pneumonia (7.8% and 8.2% respectively) and fatigue (6.4% and 2.5% respectively). Daratumumab associated infusion-related reactions occurred in 47.7% of patients ([Dimopoulos, 2016](#)). A subgroup analysis of 36 Japanese patients was conducted, 21 patients to the DRd and 15 to Rd group. ORR DARA+LEN+dex and LEN+dex was (90% and 60% respectively). Responses to DARA+LEN+dex vs LEN+dex included 9(45%) vs 1(6.7%) stringent complete response, 1(5%) vs 0 (0%) CR, 5 (25%) vs 4(26.7%) VGPRs and 3(15%) vs 4(26.7%) PRs. MRD negative was higher in DARA+LEN+dex vs LEN+dex was 23.8% vs 6.7% at  $10^{-5}$ . These results demonstrate favorable efficacy and safety that are consistent with the findings in the overall population of Pollux ([Suzuki, 2018](#)).

**Janssen Phase 3 Study (CASTOR MMY3004; Enrollment Completed).** This is a phase 3 open-label, multicenter study of daratumumab, bortezomib and dexamethasone or bortezomib and dexamethasone alone in subjects with relapsed or refractory MM who had received 1 or more lines of previous therapy. A total of 498 subjects were enrolled into this study. Overall response in DARA+BTZ+dex versus BTZ+dex was 82.9% vs 63.2%,  $P < 0.001$ . The most common Grade 3/4 hematologic AEs reported in the daratumumab group and the control group were thrombocytopenia (45.3% and 32.9% respectively), anemia (14.4% and 16% respectively), neutropenia (12.8% and 4.2% respectively). Grade 3/4 non-hematologic AE included infections (1.1% vs 1.1%), pneumonia (7.8% vs 8.2%) and fatigue (6.4% vs 2.5%). Daratumumab associated infusion-related reactions occurred in 45.3% of patients ([Palumbo, 2016](#)).

**Janssen Phase 1b Study (JNJ-54767414; Enrollment Completed).** This is a phase 1 open-label study of daratumumab in combination with bortezomib and dexamethasone in Japanese patients with relapsed or refractory MM. Daratumumab was given 16 mg/kg weekly x 9 weeks, followed by every 3 weeks x 5 cycles, then every 4 weeks with bortezomib 1.3 mg/m<sup>2</sup> days 1, 4, 8, 11 every 21 days x 8 cycles and dexamethasone 20 mg days 1, 2, 4, 5, 8, 9, 11, 12 every 21 days x 8 cycles. Eight (8) Japanese patients were enrolled and the ORR was 100% (2 CRs or better, 2 VGPRs and 4 PRs). Mild Grade  $\leq 2$  infusion-related reactions were reported in 5 patients. All patients experienced Grade 3/4 treatment emergent adverse event (TEAE) with thrombocytopenia (n=6 patients, 75%) as well as serious TEAEs herpes zoster, nasopharyngitis and prostate cancer (n=1 each) ([Iida, 2018](#)).

**Janssen Phase 1b Study (EQUULEUS MMY1001; Enrollment Completed).** This is a phase 1b open-label, multicenter study of daratumumab, pomalidomide, and dexamethasone in subjects with relapsed or refractory MM who had received 2 more prior lines of therapy. A total of 103 subjects were enrolled into this study. Patients received daratumumab 16 mg/kg weekly x 8, then every 2 weeks for 16 weeks, then every 4 weeks, POM 4 mg on Days 1-21 and dex 40 mg weekly in a 28-day cycle. ORR was 60% and 58% in double refractory (PI and IMiD). In the CR or better MRD at  $10^{-5}$  was 29%. The most common Grade 3/4 hematologic AEs reported in the study were neutropenia (78%), anemia (28%), leukopenia (24%), thrombocytopenia (19%). Grade 3/4 non-hematologic AE included fatigue (12%), pneumonia (10%), febrile neutropenia and dyspnea (8% each). Daratumumab associated infusion-related AEs occurred in 50% of patients ([Chari, 2017](#)). A phase 3 study is currently under investigation comparing pomalidomide, dexamethasone with or without daratumumab in RRMM previously treated with lenalidomide and a PI (EMN14, NCT03180736)

## Conclusion

The results of studies conducted thus far indicate that daratumumab has activity in patients with relapsed and/or refractory MM, including patients who are refractory to LEN and BTZ. Confirmed response rates range between 29% and 36% for DARA monotherapy and for the Japanese participants response rates are 44%. Confirmed response rates range between 83% and 92% in combination therapy with LEN or BTZ and for Japanese patient population, the combination response rates range from 45% to 100%. The most common hematological toxicity experience by these subjects were thrombocytopenia and neutropenia, which can be managed by dose reductions or interruptions. The most common non-hematological toxicities are pneumonia and infusion related reactions.

Please refer to the Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies and adverse event profile of daratumumab.

## **2. STUDY OBJECTIVES**

### **2.1. Primary Objective**

The primary objective of the study is to evaluate the efficacy of the combination of POM + LD-dex or POM+DARA+LD-dex in subjects relapsing after or refractory to LEN-based therapy in the first or second line setting.

### **2.2. Secondary Objective**

The secondary objective of the study is to evaluate the safety of the combinations of POM + LD-dex or POM+DARA+LD-dex in subjects with relapsed or refractory MM.

### **2.3. Exploratory Objectives**

The exploratory objectives of the study are to investigate pharmacodynamic effects of POM+LD-dex or POM+DARA+LD-dex combination therapy, and potential biomarkers predictive of response or resistance to the therapy, in relation to the clinical endpoints from all enrolled subjects who provide informed consent in Cohort A and all enrolled subjects in Cohort B and Cohort C for participation in the exploratory biomarker portion of the trial.

### **3. STUDY ENDPOINTS**

#### **3.1. Primary Endpoint**

The primary study endpoint is the overall response rate (ORR).

#### **3.2. Secondary Endpoints**

The secondary endpoints include:

- Progression-free survival (PFS)
- Overall survival (OS)
- Duration of response (DoR)
- Time to response (TTR)
- Time to progression (TTP)
- Adverse event assessment (type, frequency, seriousness, severity, relationship to POM and/or DARA and/or LD-dex and outcomes), including second primary malignancies (SPM)

#### **3.3. Exploratory Endpoints**

The exploratory endpoints include:

- Molecular, immune and cellular markers that might predict response or resistance to POM+ LD-dex or POM+DARA+LD-dex combination therapy
- Pharmacodynamic and mechanistic biomarkers of pomalidomide-daratumumab-dexamethasone combination therapy
- Quality of life (for subjects enrolled in Cohort B only) as measured by the descriptive system of the EQ-5D

## 4. OVERALL STUDY DESIGN

### 4.1. Study Design

This is a multicenter, multi-cohort, open-label study of POM + LD-dex or POM+DARA+LD-dex in subjects relapsing after or refractory to LEN-based therapy in the first or second line setting.

The study is anticipated to enroll approximately 188 subjects with relapsed or refractory MM who fulfill the eligibility criteria. At the time of this amendment, enrollment to Cohort A and B already completed with 56 and 112 subjects respectively. Cohort C will enroll approximately 20 subjects.

This study consists of the following consecutive phases: A Screening phase within 28 days prior to Cycle 1 Day 1, a Treatment phase, and a Follow-up phase which starts within 28 days of discontinuation from study treatment, with continued follow-up every 3 months for up to 5 years after the last subject is enrolled in each respective cohort.

Each subject in Cohort A will receive POM administered orally at the starting dose of 4 mg/day on Days 1-21 of a 28-day cycle and LD-dex administered orally at the starting dose of 40 mg/day (for subjects  $\leq$  75 years old) or 20 mg/day (for subjects  $>$  75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle.

Each subject in Cohort B and Cohort C will also receive POM administered orally at the starting dose of 4 mg/day on Days 1-21 of a 28-day cycle and LD-dex administered orally at the starting dose of 40 mg/day (for subjects  $\leq$  75 years old) or 20 mg/day (for subjects  $>$  75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle. Additionally, subjects in Cohort B and Cohort C will receive DARA administered intravenously at a starting dose of 16 mg/kg on Days 1, 8, 15, and 22 of a 28-day cycle for Cycle 1 and Cycle 2; Days 1 and 15 for Cycle 3 through Cycle 6 and Day 1 for Cycle 7 and each cycle thereafter until disease progression.

Dose modifications and interruptions are permitted throughout the study as outlined in Section 8.2.

Subjects qualified to enroll in Cohort A will have had 2 prior lines of therapy with the most recent line of therapy containing lenalidomide. Subjects qualified to enroll in Cohort B and Cohort C will have had 1 or 2 prior lines of therapy with the most recent line of therapy containing lenalidomide.

Subjects will continue study treatment until the documentation of confirmed PD, intolerable toxicity, death, withdrawal of active participation in the study, withdrawal of consent, or are lost to follow-up, or as long as they benefit from therapy according to the opinion of responsible study investigator and approved by the sponsor.

Adverse events (secondary endpoint) will be recorded and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) (Version 4.03, June 2010). Second primary malignancies will be monitored 4 times per year (every 3 months) for up to 5 years after the last subject is enrolled in each respective cohort as events of interest throughout the course of the study. Safety data will be reviewed on an ongoing basis throughout the study by the study Medical Monitor and drug safety physician.

Tumor response, based on the investigator's assessment, will be evaluated according to the International Myeloma Working Group (IMWG) response criteria ([Durie, 2006](#)) and will be modified (mIMWG) to add criteria for MR ([Kyle, 2009](#)) (per [Appendix B](#)).

An interim analysis will be conducted 6 months after about 40% of subjects are enrolled in Cohort A. A positive efficacy conclusion at the interim is unlikely to lead to an early termination, and study recruitment will continue until the planned total enrollment with the objective of collecting complete safety data.

Analysis of biomarkers will also be explored in subjects who consent to participate in the exploratory biomarker study.

All subjects will be maintained on the Pomalidomide pregnancy prevention program ([Appendix D](#)) for the duration of the study.

For all subjects who enroll into this study, study visits and serial measurements of safety and efficacy will be performed as outlined in [Table 1](#), Table of Events. The overall study design is depicted in [Figure 1](#).

**Figure 1: Overall Study Design**

**Screening Phase**

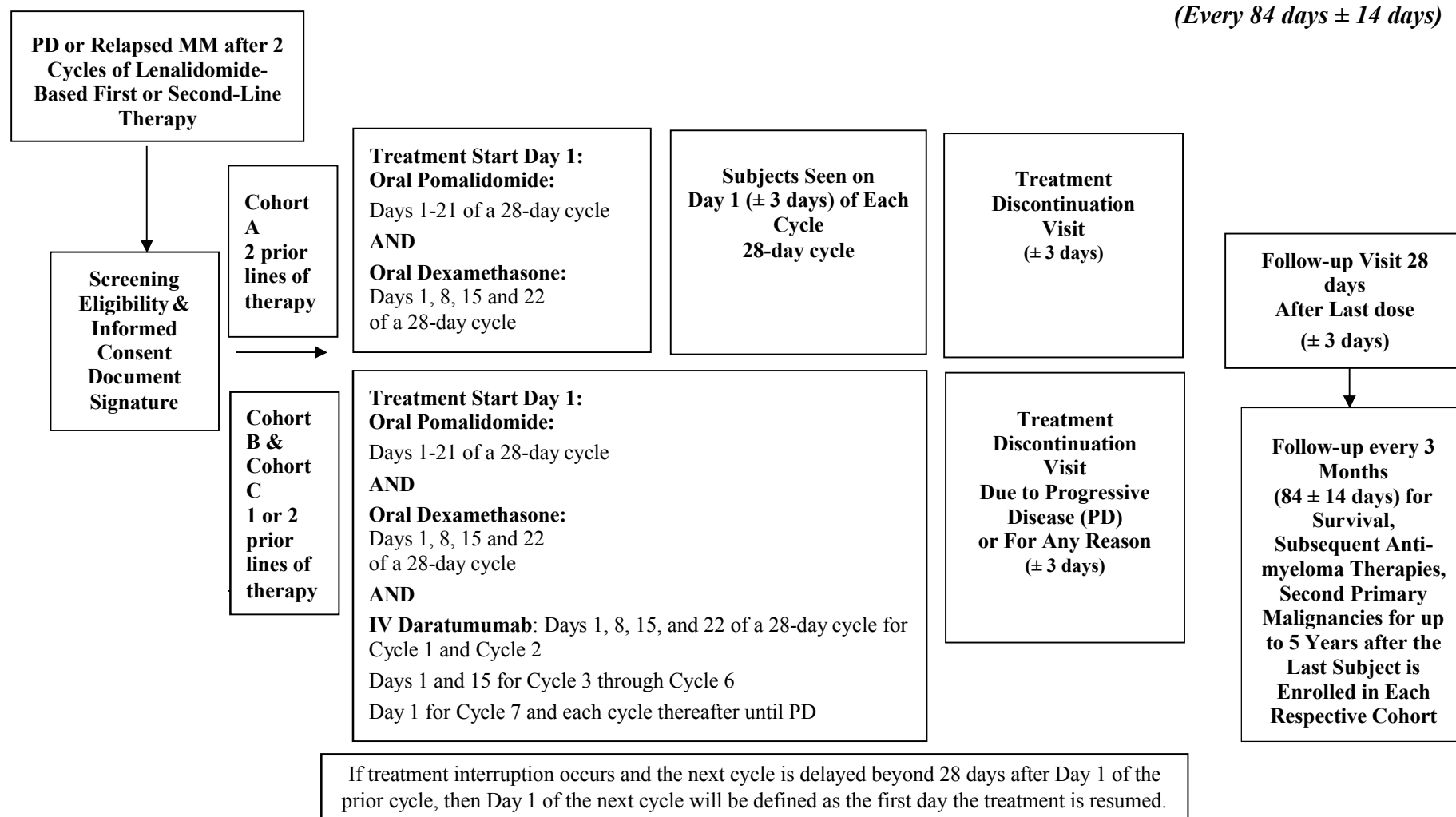
*Day -28 to 0*

**Treatment Phase**

*Day 1 – 28 ( $\pm 3$  days)*

**Follow-up Period**

*(Up to 5 years after enrollment of last subject in each respective cohort)  
(Every 84 days  $\pm 14$  days)*



## 4.2. Study Design Rationale

Pomalidomide + Dex has shown activity in several phase 1, phase 2 trials, and most recently in a randomized, phase 3 trial. The dose of 4 mg was established in a Phase 1 trial ([CC-4047-MM-002](#), [NCT00833833](#)) which also achieved 42% minimal response or better, 21% partial response or better and 3% complete response in a heavily pretreated population ([Richardson, 2013](#)). In a Phase 2 trial following this Phase 1, response rates of at least PR of 34% were achieved as well as a median PFS of 4.6 months ([Richardson, 2011a](#)). A Phase 2 trial conducted by the IFM confirmed high efficacy of the combination of POM and dex in subjects refractory to BTZ and LEN with response rates of 35% ([Leleu, 2013](#)). Recently, results of a Phase 3 trial comparing POM + Dex to high-dose dex in subjects refractory and heavily pretreated patients, including LEN and BTZ pretreatment, have shown significant improvement in PFS as well as OS ([Dimopoulos, 2012](#)).

The present study is a multicenter, multi-cohort, open-label, phase 2 study in the United States and Canada designed to further evaluate the efficacy and safety of combination POM + LD-dex or POM+DARA+LD-dex in the US, Canada and Japan in subjects with relapsed MM or refractory MM who received LEN-based therapy in the first or second line. Pomalidomide is efficacious in pretreated patients, especially those patients who are not only refractory to BTZ but also LEN and has shown statistically significant improvement in PFS. In a later line setting, the current treatment options are limited. Pomalidomide provides treatment control after LEN and BTZ, where there is still a high unmet medical need. The clinical efficacy of pomalidomide in advanced relapsed and refractory MM does not appear to be affected by prior refractory disease status ([Richardson, 2013](#)). In the MM-002 clinical trial, response rates (25%-30%) and overall survival (OS; median 13.4-14.4 months) were similar for patients refractory to LEN, BTZ, LEN + BTZ, and the overall patient population. Similarly, the Mayo Clinic trial has demonstrated response rates between 32% to 38% in patients refractory to LEN and 26% to 29% in patients refractory to LEN + BTZ ([Lacy, 2009](#)). In the Japanese phase 2, MM-011 clinical trial, response rates (33% - 43%) were similar for patients' refractory to LEN and LEN+BTZ and the overall patient population ([Ichinohe, 2016](#)). Additionally, in the phase 3 MM-003 clinical trial, POM + Dex treatment of dual refractory patients (LEN and BTZ) significantly improved PFS (3.2 months,  $P < 0.001$ ; HR = 0.48) and OS (not reached,  $P < 0.001$ ; HR = 0.53) compared with those treated with HiDex; 1.7 and 7.4 months, respectively). These phase 3 data met the primary PFS endpoint and crossed the upper boundary for superiority of OS ([Dimopoulos, 2012](#)).

Daratumumab is a human anti-CD38 IgG1 $\kappa$  monoclonal antibody with remarkable safety and activity as monotherapy in heavily treated relapsed and refractory multiple myeloma (MM) ([Lokhorst, 2014](#); [Lonial, 2016](#)). In the GEN 501 clinical trial, response rates (36% - 44%) were similar in patients LEN, BTZ, LEN+BTZ and the overall patient population ([Lokhorst, 2015](#); [Iida, 2017](#)). Daratumumab has demonstrated clinical activity in combination with LEN and Dex in relapsed or refractory MM and in Japanese subjects ([Plesner, 2014](#); [Dimopoulos, 2016](#); [Suzuki, 2018](#)). Daratumumab has also show clinical benefit in combination with BTZ and dex in relapsed and/or refractory MM ([Palumbo, 2016](#)).

Recently an open label multi-center phase 1b clinical trial assessed the combination of POM+DARA+Dex in 103 patients with relapsed or refractory multiple myeloma. The

combination demonstrated an ORR of 68% in a heavily pretreated patient population (median 4 prior lines of therapy) and ORR of 58% in double refractory (PI and IMiD). The toxicity profile of the three-drug combination was also well tolerated with most common Grade 3 toxicities being hematologic in nature including neutropenia (78%), anemia (28%), leukopenia (24%) and thrombocytopenia (19%) ([Chari, 2017](#)).

There have been no clinical trials evaluating the efficacy and safety of LEN following treatment with pomalidomide. Preclinical data in mice suggest that pomalidomide retains its antimyeloma activity in LEN-refractory disease to a much greater extent than LEN does in pomalidomide-refractory disease. Investigators at the Mayo Clinic have reported outcomes for patients who relapsed after treatment with Pomalidomide. Only 7 out of 52 (13%) patients received LEN-based therapy as first salvage, and 2 out of 7 (29%) achieved a partial response or better; 5 out of 7 (71%) had SD or PD ([Lacy, 2009](#)).

Data support the idea that pomalidomide provides consistent outcomes regardless of exposure to prior therapy. Results from the IFM 2009-02, MM-002, and Mayo Clinic trials demonstrated consistent responses across all subgroups (eg, LEN-refractory, BTZ refractory, and LEN/BTZ dual-refractory  $\pm$  prior stem cell transplantation). Additionally, preclinical data in mice suggest that POM + dex overcomes acquired resistance to LEN + dex. Taken together, these results suggest minimal cross resistance for POM following LEN.

Second primary malignancies will be monitored as events of interest and will be reported as a serious adverse event (SAE) regardless of causal relationship to investigational product (IP).

The multicenter nature as well as the inclusion of patients in Japan of the study provides reassurance that the results are likely to have general applicability and the size of the study allows accurate description of the nature, frequency, and severity of the AE profile.

Subjects will receive study treatment until PD or discontinuation. In studies evaluating agents for subjects with refractory MM or relapsed and refractory progressing or relapsed malignant diseases, it is common practice to continue study treatment until PD or intolerable toxicity develops. All subjects will be followed for OS, subsequent anti-myeloma therapies and SPMs.

### **4.3. Study Duration**

This study will consist of the following consecutive phases: Screening, Treatment and Follow-up. The study will remain open to enrollment until the target subject enrollment of approximately 188 subjects has been reached. Each subject will be followed for up to 5 years after the enrollment of the last subject in each respective cohort (unless the follow-up is shorter due to withdrawal of consent, loss to follow-up, or death).

### **4.4. End of Trial**

The End of Trial is defined as either the date of the last visit of the last subject to complete the study, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as pre-specified in the protocol and/or the Statistical Analysis Plan, whichever is the later date.

## 5. TABLE OF EVENTS

**Table 1: Table of Events**

Procedures	Screening (Days -28 to 0)	Day 1 ( $\pm 3$ days) of Every 28-day Cycle	Cycle 1 & 2 Day 8 ( $\pm 3$ days) Day 15 ( $\pm 3$ days) Day 22 ( $\pm 3$ days)	Cycle 3, 4, 5, 6 Day 15 ( $\pm 3$ days)	Treatment Discontinuation Visit ( $\pm 3$ days)	Follow-up Visit (Within 28 Days Post Treatment Discontinuation) ( $\pm 3$ days)	Long-term Follow-up Every 3 Months (84 $\pm$ 14 days) for Up to 5 Years After Last Subject Enrollment in each respective cohort
<b>Entry Assessments</b>							
Informed Consent Document (ICD)	X	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-
Demographics (age, gender)	X	-	-	-	-	-	-
Medical History	X	-	-	-	-	-	-
Cytogenetic data from medical history <sup>a</sup>	X	-	-	-	-	-	-
Prior anti-myeloma therapies, radiotherapy, surgeries	X	-	-	-	-	-	-
Disease Diagnosis <sup>b</sup>	X	-	-	-	-	-	-
<b>Safety Assessments</b>							
Adverse event	After Signing ICD and until 28 Days after Discontinuation from Treatment						
Second Primary Malignancy <sup>c</sup>	After Signing ICD and up to 5 years after last Subject Enrollment in each respective cohort or longer if Clinically Indicated						
Height/Weight <sup>d</sup>	X	-	-	-	-	-	-
Hematology <sup>e</sup>	X	X <sup>e</sup>	-	-	X	-	-
Serum Chemistry <sup>f</sup>	X	X <sup>e</sup>	-	-	X	-	-
Urinalysis <sup>g</sup>	X	-	-	-	X	-	-
Renal Function 24-hour Creatinine Clearance <sup>h</sup>	X	-	-	-	-	-	-

**Table 1: Table of Events (Continued)**

Procedures	Screening (Days -28 to 0)	Day 1 (± 3 days) of Every 28-day Cycle	Cycle 1 & 2 Day 8 (± 3 days) Day 15 (± 3 days) Day 22 (± 3 days)	Cycle 3, 4, 5, 6 Day 15 (± 3 days)	Treatment Discontinuation on Visit (± 3 days)	Follow-up Visit (Within 28 Days Post Treatment Discontinuation) (± 3 days)	Long-term Follow-up Every 3 Months (84 ± 14 days) for Up to 5 Years After Last Subject Enrollment in each respective cohort
VTE Monitoring	-	X	-	-	X	-	-
ECG <sup>1</sup> (only for subjects enrolled in Cohort A)	X	-	-	-	-	-	-
Blood Type & IAT (for subjects enrolling in Cohort B and Cohort C) <sup>w</sup>	X	-	-	-	-	-	-
Concomitant medications <sup>j</sup>	After Signing ICD and until 28 days after Discontinuation from Treatment						
Pregnancy testing for FCBP <sup>k</sup>	X	X	-	-	X	X	-
Pregnancy Counseling	X	X	-	-	X	X	-
<b>Efficacy Measurements</b>							
ECOG Performance Status	X	X	-	-	X	-	-
Bone Marrow Aspiration and/or Biopsy <sup>1</sup>	X	-	-	-	-	-	-
Serum Beta-2 Microglobulin	X	-	-	-	-	-	-
Quantitative Serum Immunoglobulin Levels <sup>m</sup>	X	X	-	-	X	-	-
Serum protein electrophoresis (SPEP) and 24-hour Urine electrophoresis (UPEP) <sup>n</sup>	X	X	-	-	X	-	-
Serum free light-chain (FLC) assay <sup>o</sup>	X	X	-	-	X	-	-
Extramedullary Plasmacytoma (EMP) Assessments <sup>p</sup>	X	X	-	-	X	-	-
Skeletal Survey (by x-ray) <sup>q</sup>	X	-	-	-	-	-	-
Assessment of Response <sup>r</sup>	-	X	-	-	X	-	-
Survival Status	-	-	-	-	-	-	X
Subsequent Anti-myeloma Regimens <sup>s</sup>	-	-	-	-	-	X	X

**Table 1: Table of Events (Continued)**

Procedures	Screening (Days -28 to 0)	Day 1 (± 3 days) of Every 28-day Cycle	Cycle 1 & 2 Day 8 (± 3 days) Day 15 (± 3 days) Day 22 (± 3 days)	Cycle 3, 4, 5, 6 Day 15 (± 3 days)	Treatment Discontinuation on Visit (± 3 days)	Follow-up Visit (Within 28 Days Post Treatment Discontinuation) (± 3 days)	Long-term Follow-up Every 3 Months (84 ± 14 days) for Up to 5 Years After Last Subject Enrollment in each respective cohort
<b>Other Assessments</b>							
Exploratory biomarker sampling: whole blood (at selected sites) <sup>t</sup>	X	X <sup>t</sup>	X <sup>t</sup>	-	X <sup>t</sup>	-	-
Exploratory biomarker sampling: bone marrow aspirate (at selected sites) <sup>t</sup>	X	-	-	-	X	-	-
Exploratory biomarker sampling: normal tissue (saliva samples) at selected sites <sup>u</sup>	X	-	-	-	-	-	-
EQ-5D (for subjects enrolling in Cohort B) <sup>v</sup>	X	X <sup>v</sup>	-	-	X	-	-
<b>Investigational Product Dispensation</b>							
Oral POM dispensation/ accountability	-	X	-	-	X	-	-
Oral dex dispensation/ accountability	-	X	-	-	X	-	-
DARA intravenous dispensation/infusion/ accountability	-	X	X	X	X	-	-

ANC = absolute neutrophil count; ALC = absolute lymphocyte count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CR = complete response; CT = computed tomography; dex = dexamethasone; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF = electronic case report forms; FCBP = females of childbearing potential; GGT = gamma glutamyl transferase; HGB = Hemoglobin; HCT = Hematocrit; IAT = indirect antiglobulin test; ICD = Informed Consent Document; LD = low-dose; LDH = lactate dehydrogenase; MCV = mean corpuscular volume; MM = multiple myeloma; MRI = magnetic resonance imaging; PD = progressive disease; POM = Pomalidomide; PR = partial response; RBC = red blood cell; SAE = serious adverse event; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvic transaminase; SPM = second primary malignancy; VTE = venous thromboembolism; WBC = white blood cell.

<sup>a</sup> Results for any local cytogenetic testing, if available as part of medical history, will be collected in the electronic case report forms (eCRFs).

<sup>b</sup> Date of initial diagnosis and myeloma stage per the International Staging System and/or the Durie-Salmon Staging System ([Appendix H](#)) at initial diagnosis (if available) will be collected as part of the disease diagnosis assessment.

<sup>c</sup> Second primary malignancies (SPM) will be monitored as events of interest and must be reported as SAEs regardless of causal relationship to IP (POM or LD-dex), occurring at any time from the time of signing the ICD up to and including the long-term follow-up period. Documentation of the diagnosis of the SPM must be provided at the time of

- reporting as a SAE (eg, any confirmatory pathology, histology or cytology results, cytogenetics, flow cytometry, x-rays, or CT scans). For all subjects who develop SPMs, all corresponding diagnostic reports (eg, pathology, cytogenetics, flow cytometry) from the MM diagnosis confirmation performed at screening and from the diagnostic tumor samples obtained at SPM determination, will be required for SPM confirmation. If the SPM determination is made at an institution besides the study institution, every effort will be made to collect these reports when performed locally or at other institutions.
- <sup>d</sup> The measurement of height and weight will be performed at screening only.
  - <sup>e</sup> Assessment of hematology includes: WBC count with differential, ANC, ALC, HGB, HCT, platelet count, and MCV.
  - <sup>f</sup> Assessment of serum chemistry includes: calcium, albumin, total bilirubin, alkaline phosphatase, AST/SGOT, ALT/SGPT, GGT, sodium, potassium, BUN, creatinine, and LDH.
  - <sup>g</sup> Assessment of urinalysis includes: specific gravity, pH, glucose, bilirubin, protein, ketones, blood, and microscopic analysis [casts, bacteria, RBCs, and WBCs].
  - <sup>h</sup> The assessment will be performed using the Cockcroft-Gault formula for estimation of creatinine clearance (CrCl). CrCl will be determined based on a 24-hour urine collection. A 24-hour urine sample obtained as a standard of care assessment prior to informed consent can be utilized for this study if it was performed  $\leq 7$  days prior to the Screening Visit and meets the protocol requirements for collection and analysis.
  - <sup>i</sup> ECGs will be performed at Screening visit and as clinically indicated at the discretion of the treating physician during the study.
  - <sup>j</sup> Concomitant medications including: anti-infectious agents, growth factors, antithrombotics, bisphosphonates or other agents used for the treatment of myeloma-associated bone disease, and transfusions.
  - <sup>k</sup> FCBP must have 2 negative serum or urine 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 subject may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative. All FCBP with regular or no menstrual cycles must agree to have pregnancy tests every 7 days (weekly) for the first 28 days of study participation and then every 28 days while on study, at treatment discontinuation, and 28 days following treatment 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 treatment discontinuation, and every Days 14 and 28 following treatment discontinuation. For subjects enrolled in Cohort B and Cohort C pregnancy prevention and testing will continue until 3 months after last dose of daratumumab.
  - <sup>l</sup> At screening, an adequate bone aspirate/or biopsy must be obtained (within 28 days of enrollment). After screening, bone marrow aspirate (or biopsy if necessary) must be performed to document a response of CR and may otherwise be repeated as clinically indicated at the discretion of the treating physician.
  - <sup>m</sup> Quantitative immunoglobulin assessment (IgG, IgA, IgM, IgE and IgD) should also be performed at the time of response confirmation (CR). All subjects will be evaluated for IgG, IgA and IgM. Testing for IgE and IgD is only required for subjects with the respective (IgE or IgD) subtype.
  - <sup>n</sup> If a response ( $\geq$  PR) or PD is noted based on SPEP and/or UPEP results, a repeat test should also be conducted as soon as possible to confirm the response or PD. Also, serum and urine immunofixation (IFE) tests are performed during screening to identify the immunoglobulin subtype of MM and thereafter are required to be performed whenever M-protein is undetectable in both serum and urine by protein electrophoresis studies. Serum and urine IFE tests should also be performed at the time of response confirmation (CR).
  - <sup>o</sup> Serum FLC assay should also be performed at the time of response confirmation (CR).
  - <sup>p</sup> Assessment/measurement at specified time-points only required if EMPs are present. If EMPs are clinically assessable, clinical assessment will be performed at screening, at every Cycle Day 1, and at treatment discontinuation. If EMPs are only assessable radiographically (x-ray and/or conventional [spiral] CT/MRI scan), scans are required at screening, at Cycle 3 Day 1, every 3 cycles thereafter (Cycle 6 Day 1, Cycle 9 Day 1, etc.) during treatment, at treatment discontinuation, and when clinically indicated to confirm response ( $\geq$  PR).
  - <sup>q</sup> A skeletal survey by x-ray will be performed at screening and when clinically indicated per the investigator's discretion. If a skeletal survey was performed within 60 days prior to the start of Cycle 1, it may be used for the screening assessment if approved by sponsor. Refer to [Appendix C](#) for detailed requirements.
  - <sup>r</sup> Response, including PD, will be assessed by investigators using the modified International Myeloma Working Group criteria ([Appendix B](#)). Response assessment should also be repeated at the time of response ( $\geq$  PR) or PD confirmation. The first response assessment will occur at Day 1 of Cycle 2.
  - <sup>s</sup> Subsequent anti-myeloma regimens: type of treatment, start and stop dates, date of progression and best response whenever possible.
  - <sup>t</sup> For Cohort A and Cohort B subjects who consent to participate in biomarker analysis may undergo collection of bone marrow aspirate and whole blood samples at screening, response assessment (confirm CR) and disease progression, and when clinically indicated. Additionally, whole blood samples will be collected at Day 1 of Cycle 3,5 and

treatment discontinuation for Cohort A and **C1D1, C1D8, C1D15, C2D1, C2D15, C3D1, C5D1 and treatment discontinuation** for Cohort B. For Cohort C, all subjects will provide bone marrow aspirate at screening and treatment discontinuation.

<sup>u</sup> For Cohort A and Cohort B subjects who consent to participate in biomarker analysis may undergo collection of normal tissue (which may include saliva samples) at screening only.

<sup>v</sup> For subjects enrolled in Cohort B, Quality of Life (QoL) measured with the descriptive system of the EQ-5D will be provided to each subject to complete on Day 1 of every cycle prior to any study treatment (POM, DARA, LD-dex) administration and at treatment discontinuation.

<sup>w</sup> Refer to Section 6 for details on the daratumumab IAT. Subjects are to be provided a blood type card to carry with them during the Treatment Phase.

## 6. PROCEDURES

### Study Entry

Prior to screening, subjects must sign an informed consent document. All screening assessments must be completed within 28 days prior to start of Cycle 1, with the exception of the skeletal survey, which may be performed within 60 days prior to initiation of study treatment, with the approval of sponsor.

Confirmation of diagnosis (including date of confirmed initial diagnosis and, if available, myeloma stage at time of initial diagnosis per the Salmon-Durie Criteria and/or the International Staging System [[Appendix H](#)]), medical history, prior cancer and surgical history, and review of prior medications should be documented during the screening period. All prior radiotherapy, surgeries, and anti-myeloma therapies must be recorded in the electronic case report form (eCRF), including approximate dates for each therapy and the date of progression for each regimen. Results for any local cytogenetic testing (prefer fluorescence in situ *hybridization* [FISH] results), if available, as part of medical history, will be collected in the eCRF. See [Table 1](#) (Table of Events) for a complete list of the required assessments during screening.

If the subject's safety and efficacy laboratory assessments performed at screening are within 7 days of enrollment into the study, they do not need to be repeated at Cycle 1 Day 1 and can be used as baseline results. The start of study drug dosing is designated as Cycle 1 Day 1. A 14-day wash-out period is required for any prior anti-myeloma therapy before study treatment is initiated.

### Safety Assessments

#### *Adverse Events*

All AEs should be assessed starting after the subject signs the informed consent document (ICD) until 28 days after treatment discontinuation. Adverse events that lead to study discontinuation should be followed until resolution or stabilization.

#### *Serious Adverse Events*

Serious adverse events, regardless of relationship to the IP (POM, DARA, or dex), that occur from the time the subject signs the ICD to at least 28 days after treatment discontinuation and those made known to the investigator at any time thereafter that are suspected of being related to the IP (POM, DARA, or dex) must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event.

#### *Second Primary Malignancies*

Second primary malignancies will be monitored every 3 months for up to 5 years after the last subject is enrolled in each respective cohort, as events of interest and must be reported as SAEs. This includes any SPM, regardless of causal relationship to the IP (POM, DARA, or dex), occurring at any time from the time of signing the ICD up to and including the long-term follow-up period. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" even if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the eCRF and subject's source documents.

Documentation of the diagnosis of the SPM must be provided at the time of reporting as a SAE

eg, any confirmatory pathology, histology or cytology results, cytogenetics, flow cytometry, x-rays, or computed tomography scans (CT scans). For all subjects who develop SPMs, all corresponding diagnostic reports (eg, pathology, cytogenetics, flow cytometry) from the MM diagnosis confirmation performed at screening and from the diagnostic tumor samples obtained at SPM determination, will be required for SPM confirmation.

For SPMs diagnosed at another institution, (outside of the investigational site) sites will be required to make every effort to obtain these reports for SPM confirmation.

### ***Prior and Concomitant Medications and Procedures***

The following prior and concomitant therapies will be collected and recorded in the subject's eCRF: Anti-infectious agents, antithrombotics, growth factors, and bisphosphonates or other agents used for the treatment of myeloma-associated bone disease. Any procedures performed, including transfusions, after the subject signs the ICD until 28 days after treatment discontinuation will be collected and recorded in the subject's eCRF. Drugs known to prolong the QT corrected (QTc) interval should be avoided unless deemed medically necessary. See [Appendix G](#) for a comprehensive list of drugs which are known to prolong QTc.

### ***Venous Thrombotic Events Assessment and Monitoring***

All prior venous thromboembolisms (VTEs) and pulmonary embolisms (PEs) that occurred will be collected with complete medical history during the screening period. The VTE assessment will be performed on Day 1 of every cycle starting at Cycle 1, and at treatment discontinuation. Subjects who develop symptomatic deep vein thrombosis will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method. See [Appendix A](#) for deep vein thrombosis (DVT) and PE diagnostic algorithms.

### ***Measurement of Height and Weight***

Measurement of height and weight will be performed at screening only.

### ***Electrocardiogram***

For subjects enrolled in Cohort A, electrocardiogram (ECG) (12-lead) monitoring will be performed at the Screening visit and as clinically indicated at the discretion of the treating physician during the study. All ECGs will be performed and reviewed locally.

### ***Laboratory Assessments for Safety Parameters***

With the exception of pregnancy tests, all laboratory assessments for safety parameters will be performed and reviewed by the central laboratory; however, tests that may result in dose interruption and/or modification should also be performed locally to allow for treatment related decisions during subject visits. Results from local laboratories will not be collected, unless specifically requested by the sponsor in which case they may be entered into an unscheduled visit on the eCRF. At Study Day 1 subject must meet eligibility criteria based on local or central lab results prior to initiating study therapy.

If screening visit results are  $\leq 7$  days prior to enrollment, these laboratory assessments are not required to be repeated at Cycle 1 Day 1.

- **Hematology Laboratory Tests.** Hematology includes: white blood cell (WBC) count with differential, absolute neutrophil count (ANC), absolute lymphocyte count

(ALC), hemoglobin, hematocrit, platelet count, and mean corpuscular volume. Hematology will be performed at screening, on Day 1 of each cycle, and at treatment discontinuation.

- **Serum Chemistry Laboratory Tests.** Serum chemistry includes: calcium (corrected), albumin, total bilirubin, alkaline phosphatase, aspartate aminotransferase (AST)/serum glutamic oxaloacetic transaminase (SGOT), alanine aminotransferase (ALT)/serum glutamic pyruvic transaminase (SGPT), gamma glutamyl transferase (GGT), sodium, potassium, blood urea nitrogen, creatinine, and lactate dehydrogenase. Serum chemistry labs will be performed at screening, on Day 1 ( $\pm$  3 days) of every cycle, and at treatment discontinuation. If PD is noted based on corrected serum calcium level, a repeat serum chemistry test should be performed as soon as possible to confirm PD.
- **Infectious Tests.** Human immunodeficiency virus (HIV), Hepatitis A, Hepatitis B and Hepatitis C. Infectious testing will be performed at screening for Cohort C only.
- **Urinalysis.** Urinalysis includes: specific gravity, pH, glucose, bilirubin, protein, ketones, blood and microscopic analysis (casts, bacteria, red blood cells [RBCs], and WBCs). Urinalysis will be performed at screening, and at treatment discontinuation.
- **Estimation of Renal Function.** The assessment will be performed using the Cockcroft-Gault estimate of creatinine clearance (CrCl).

*Cockcroft-Gault Formula* ([Cockcroft, 1976](#); [Luke, 1990](#))

$\text{CrCl (mL/min)} = (140 - \text{age}) (\text{weight [kg]}) / 72 (\text{serum creatinine [mg/dL]})$ ; for females, the formula is multiplied by 0.85.

CrCl will be determined based on a 24-hour urine collection at the Screening visit. A 24-hour urine sample obtained as a standard of care assessment prior to informed consent can be utilized for this study if it was performed  $\leq 7$  days prior to the Screening Visit.

Estimation of renal function will be performed at Screening only.

### ***Pregnancy Counseling (Males and Females)***

Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted for all subjects at screening, Day 1 of every cycle during treatment, at treatment discontinuation and at the follow-up visit for all subjects. Please refer to Pomalidomide Pregnancy Risk Minimization Plan in [Appendix D](#).

### ***Pregnancy Testing for Females of Child Bearing Potential (FCBP)***

All FCBP must have 2 medically supervised negative serum or urine pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting the study. The first pregnancy test must be performed within 10-14 days prior to the start of study treatment and the second pregnancy test must be performed within 24 hours prior to the start of study treatment. The subject may not receive study drug until the study doctor has verified that the results of these pregnancy tests are negative. Females of child bearing potential with regular or no menstrual cycles must agree to have pregnancy tests every 7 days (weekly) for the first 28 days of study participation and then

every 28 days while on study, at treatment discontinuation, and 28 days following treatment 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 treatment discontinuation, and at Days 14 and 28 following treatment discontinuation.

For subjects enrolled in Cohort B and Cohort C pregnancy prevention and testing will continue until 3 months after last dose of daratumumab.

**Blood Typing** - Blood typing of subjects is required during screening for subjects enrolling in Cohort B and Cohort C.

### ***Indirect Antiglobulin Test (IAT)***

Daratumumab interferes with the Indirect Antiglobulin Test (IAT), which is a routine pretransfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) ([Chapuy, 2015](#)).

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

1. Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping prior to daratumumab administration) or genotypically matched units
2. Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies. For additional details, refer to the Daratumumab Investigator's Brochure (IB).

### **Efficacy Assessments**

Disease progression status will be assessed by the Investigator at each treatment cycle and at treatment discontinuation. Tumor response including progressive disease will be assessed according to the IMWG uniform response criteria ([Durie, 2006](#)) and modified to add criteria for MR ([Kyle, 2009](#)). All treatment decisions will be made by the treating physician based on response as assessed using the mIMWG criteria (per [Appendix B](#)).

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPEP) and immunofixation (IFE) assays used for the clinical

monitoring of endogenous M-protein. This can lead to false positive SPEP and IFE assay results for subjects with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. In subjects with persistent very good partial response, consider other methods to evaluate the depth of response.

Survival status will be collected for all subjects during the long-term follow-up phase.

All efficacy laboratory assessments will be performed and reviewed by the central laboratory. These efficacy assessments include laboratory tests used as part of standard care: Serum beta-2 microglobulin (at screening only), myeloma paraprotein protein electrophoresis and immunofixation, serum immunoglobulins, and serum free light chain assay.

Efficacy assessments are to be performed at the start of each new cycle. If a new cycle is delayed more than 7 days (but less than 28 days) from the protocol-defined 28-day dosing cycle, an unscheduled visit should be performed for efficacy assessments prior to initiation of the next cycle. If the delay is greater than 28 days, these efficacy assessments should be performed every 28 days ( $\pm 3$  days) until a new cycle can begin. For subsequent cycles following a delayed cycle, efficacy assessments should be performed at the start of each new cycle.

The efficacy assessments will be documented in the source documents and recorded on the eCRF.

### ***Eastern Cooperative Oncology Group Performance Status***

Eastern Cooperative Oncology Group (ECOG) Performance Status will be assessed at screening, at Day 1 of every Cycle, and at treatment discontinuation. See [Appendix E](#) for the ECOG Performance Status Scale.

### ***Laboratory Assessments for Efficacy Parameters***

All laboratory assessments for efficacy parameters will be performed by central laboratory.

- **Serum beta-2 microglobulin.** The serum beta-2 microglobulin sample will be collected at screening only.
- **Myeloma Paraprotein (M-Proteins) Protein Electrophoresis.** Serum protein electrophoresis (quantified from the serum protein electrophoresis [SPEP] test) and urine protein electrophoresis (quantified from the urine protein electrophoresis [UPEP] test performed on the 24-hour urine collection), will be performed at screening, at every cycle on Day 1, and at treatment discontinuation. If a response or PD is noted based on SPEP and/or UPEP results, SPEP and UPEP tests should be repeated as soon as possible to confirm the response ( $\geq$  PR) or PD.
- **Myeloma Paraprotein (M-Proteins) Immunofixation.** Serum and urine immunofixation (IFE) tests are performed at screening to identify the immunoglobulin subtype of MM and thereafter are required to be performed whenever M-protein is undetectable in both serum and urine by protein electrophoresis studies. Serum and urine IFE tests should also be performed at the time of response confirmation for CR.
- **Serum Immunoglobulins** assessment will be performed at screening and at every cycle on Day 1, at treatment discontinuation, and at the time of response confirmation

for CR. All subjects will be evaluated for IgG, IgA, and IgM. Testing for IgE and IgD is only required for subjects with the respective (IgE or IgD) subtype.

- **Serum Free Light Chain** assay will be performed at screening, at every cycle on Day 1, at treatment discontinuation, and at the time of response confirmation for CR.

A 24-hour urine sample obtained as a standard of care assessment prior to informed consent can be utilized for this study if it was performed  $\leq 7$  days prior to the Screening Visit and meets the protocol requirements for collection and analysis. Additionally, if screening visit results are  $\leq 7$  days prior to enrollment, these laboratory assessments are not required to be repeated at Cycle 1 Day 1.

### ***Bone Marrow Aspiration and/or Biopsy***

A bone marrow aspirate (and biopsy if necessary) is mandatory and must be obtained within 28 days prior to enrollment to obtain a current estimate of the % plasma cells in the marrow. Analysis for % plasma cells in the marrow will be performed locally. After screening, a bone marrow aspirate (or biopsy if necessary) must be performed to document a CR response and may otherwise be repeated as clinically indicated at the discretion of the treating physician.

Subjects who provide informed consent for biomarker assessments will have samples collected and processed as per separate lab manual. Bone marrow aspirate material will be collected during the mandatory bone marrow assessment at screening and during other bone marrow assessments that are clinically indicated (Confirmation of CR, and at disease progression).

### ***Extramedullary Plasmacytoma Assessments***

Extramedullary plasmacytoma assessments/measurements at specified time-points are only required if extramedullary plasmacytomas (EMPs) are present.

If EMPs are clinically assessable, clinical assessment will be performed at screening, at every Cycle Day 1, and at treatment discontinuation.

If EMPs are only assessable radiographically (x-ray and/or conventional [spiral] CT/MRI [computed tomography/magnetic resonance imaging] scan), scans are required at screening, at Cycle 3 Day 1, every 3 cycles thereafter (Cycle 6 Day 1, Cycle 9 Day 1, etc.) during treatment, at treatment discontinuation, and when clinically indicated to confirm a response  $\geq$  PR. All scans will be reviewed locally only.

### ***Skeletal Survey***

A skeletal survey by x-ray will be performed at screening and when clinically indicated per the investigator's discretion. If a skeletal survey was performed within 60 days prior to the start of Cycle 1 as part of standard medical care, it may be used for the screening assessment. All skeletal survey films will be performed and analyzed locally by the site investigator/radiologist. The x-rays will not be collected for centralized review. Refer to [Appendix C](#) for detailed requirements.

### ***Assessment of Response***

Response, including PD, will be assessed using the mIMWG criteria ([Appendix B](#)) at Day 1 of each Cycle and at the treatment discontinuation visit.

### ***Overall Survival and Subsequent Anti-MM Therapies***

During the follow-up period, survival status and subsequent therapies for MM must be collected and entered into the eCRF. All subjects will be assessed 4 times a year (every 3 months) to determine survival status for up to 5 years after the last subject is enrolled in each respective cohort. Primary cause of death (medical condition) is to be recorded in the eCRF and the subject's medical record. All subsequent therapies given for MM must be collected and entered into the eCRF.

### ***Exploratory Biomarker Study***

Normal tissue (saliva), whole blood, and bone marrow aspirate material at defined time-points or events will be taken from subjects who give informed consent in Cohort A and all subjects in Cohort B at clinical sites that are able to collect and process the mandated samples. Only non-invasive approaches to collect normal tissue for comparative analysis with tumor specimens will be used. Samples will be collected and processed as per separate lab manuals.

The bone marrow aspirate will be collected at screening during the mandatory screening procedure and at other times on study when clinically indicated. All samples will be destroyed 5 years after completion of the study or earlier if required by law.

Samples to be collected:

- Excess bone marrow aspirate will be collected from the procedure mandated for study entry and also collected at other time points as response assessment or treatment discontinuation when clinically indicated for Cohort A and Cohort B. For Cohort C, bone marrow aspirate will be collected at screening and treatment discontinuation.
- For Cohort A and Cohort B, whole blood sample will be collected at screening, at time of response and/or at treatment discontinuation (disease progression) when a bone marrow procedure is being performed. Additionally, whole blood will be collected Day 1 of Cycle 3 and 5 for Cohort A and Cycle 1 Day 1, Cycle 1 Day 8, Cycle 1 Day 15, Cycle 2 Day 1, Cycle 2 Day 15, Cycle 3 Day 1, and Cycle 5 Day 1 for Cohort B.
- Normal tissue: Saliva samples collected at screening by noninvasive methods for Cohort A and Cohort B.

Bone marrow aspirates and cellular fractions isolated from them will be used for nucleic acid (eg, gene expression profiling and DNA sequencing), protein, and other biochemical analyses. These studies will focus on genomes, candidate genes, proteins, and signaling pathways identified by earlier work and will characterize aberrations associated with high-risk MM and changes induced by pomalidomide or pomalidomide/daratumumab based therapy. Serially collected samples may be used to study changes associated with clonal evolution and for measuring depth of responses to therapy. The analytical techniques involved will include methods such as cell sorting, immunohistochemistry, flow cytometry, Western blotting techniques, array-based and Quantitative polymerase chain reaction (QPCR) gene expression profiling, DNA sequencing and allele copy number measurements. The CD 138 + and CD 138- cells isolated from bone marrow mononuclear cells will be used for DNA, gene expression, and protein analysis. Analyses of DNA for subsets of genes and specific dysregulated pathways associated with pomalidomide/dexamethasone or pomalidomide/daratumumab/dexamethasone

activity or genetic aberrations associated with high-risk multiple myeloma will be evaluated for mutations, aberrations, or changes in copy number (ie, allelic loss or gain). Gene expression analyses will be conducted from baseline as well as subsequent samples for comparison of pomalidomide/dexamethasone or pomalidomide/daratumumab/dexamethasone treatment effect on the expression of genes, such as cereblon. Similarly, for proteins, targets (such as Cereblon, IRF 4, cMyc, etc) and other factors important for pomalidomide/daratumumab/dexamethasone synergistic activity will be measured by several techniques such as immunohistochemistry, western analysis or flow cytometry respectively. In some subjects, clonal evolution of MM cells or minimal residual disease (MRD) may be measured using bone marrow aspirates collected at diagnosis to study depth of response to pomalidomide, daratumumab and LD-dex and the sensitivity of different subclones of the MM disease to treatment by using sensitive next generation sequencing-based approaches.

### ***Quality of Life (QoL)***

For subjects enrolled in Cohort B, Quality of Life (QoL) as measured by the descriptive system of the EQ-5D will be provided to each subject to complete on Day 1 of every cycle prior to any study treatment (POM, DARA, LD-Dex) administration and at treatment discontinuation. See [Appendix I](#) for EQ-5D questionnaire to be used.

## 7. STUDY POPULATION

### 7.1. Number of Subjects and Sites

This is a multicenter, multi-cohort, open label, phase 2 study of POM + LD-dex or POM+DARA+LD-dex in adult subjects with relapsed or refractory MM.

This study is anticipated to enroll approximately 188 subjects with relapsed MM or refractory MM who fulfill the eligibility criteria. At the time of this amendment #4, enrollment to Cohort A and B already completed with 56 and 112 subjects respectively. Cohort C will enroll approximately 20 subjects in Japan.

### 7.2. Inclusion Criteria

Subjects must satisfy the following criteria to be enrolled in the study:

1. Adults (age  $\geq 18$  years at the time of signing the ICD) with documented diagnosis of MM and measurable disease (serum M-protein  $\geq 0.5$  g/dL or urine M-protein  $\geq 200$  mg/24 hours).
2. Subjects enrolling in Cohort A (POM+LD-dex) must have received 2 prior treatment lines of anti-myeloma therapy. Subjects enrolling in Cohort B and Cohort C (POM+DARA+LD-dex) must have received 1 or 2 prior treatment lines of anti-myeloma therapy.
3. All subjects must have received prior treatment with LEN or a LEN-containing regimen for at least 2 consecutive cycles as the most recent treatment regimen.
4. All subjects must have documented disease progression during or after their last anti-myeloma therapy.
5. Subjects must have an Eastern Cooperative Oncology Group (ECOG) performance status score of 0, 1, or 2.
6. Subjects must understand and voluntarily sign an ICD prior to any study related assessments/procedures being conducted.
7. Subjects must be able to adhere to the study visit schedule and other protocol requirements.
8. All subjects must provide an adequate bone marrow sample at screening that definitively evaluates the presence or absence of myelodysplastic changes.
9. Females with child-bearing potential (FCBP<sup>†</sup>) must agree to use 2 reliable forms of contraception\* simultaneously or practice complete abstinence from heterosexual contact for at least 28 days before starting study drug, while participating in the study (including

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<sup>†</sup> This protocol defines a female of childbearing potential as a female who: 1) has achieved menarche at some point, 2) has not undergone a hysterectomy or bilateral oophorectomy, or 3) has not been naturally postmenopausal (amenorrhea following cancer therapy does not rule out childbearing potential) for at least 24 consecutive months (ie, has had menses at any time in the preceding 24 consecutive months).

\* The two methods of birth control used may be selected from the following categories, but the two methods cannot be selected from any one category: barrier method: ie, condom (male or female) or diaphragm with spermicide; hormonal: eg, contraceptive pill, patch; intrauterine device (IUD); vasectomy; or tubal ligation.

during dose interruptions), and for at least 28 days after study treatment discontinuation and must agree to regular pregnancy testing during this timeframe. For subjects enrolled in Cohort B and Cohort C, pregnancy prevention and testing will continue until 3 months after last dose of daratumumab.

10. Females must agree to abstain from breastfeeding during study participation and 28 days after study drug discontinuation. Female subjects enrolled in Cohort B and Cohort C must agree to abstain from breastfeeding and donating eggs during study participation and until 3 months after last dose of daratumumab.
11. Males must agree to use a latex condom during any sexual contact with FCBP while participating in the study and for 28 days following discontinuation from this study, even if he has undergone a successful vasectomy. Male subjects enrolled in Cohort B and Cohort C must agree to use a latex condom during any sexual contact with FCBP while participating in the study and until 3 months after last dose of daratumumab.
12. Males must also agree to refrain from donating semen or sperm during the treatment phase and for 28 days after discontinuation from this study treatment. Male subjects enrolled in Cohort B and Cohort C must also agree to refrain from donating semen or sperm during the treatment phase and until 3 months after last dose of daratumumab.
13. All subjects must agree to refrain from donating blood while on study therapy and for 28 days after discontinuation from this study treatment.
14. All subjects must agree not to share medication.

### 7.3. Exclusion Criteria

The presence of any of the following will exclude a subject from study enrollment:

1. Any of the following laboratory abnormalities:
  - Absolute neutrophil count < 1,000/ $\mu$ L
  - Platelet count < 75,000/ $\mu$ L for subjects in whom < 50% of bone marrow nucleated cells are plasma cells; or a platelet count < 30,000/ $\mu$ L for subjects in whom  $\geq$  50% of bone marrow nucleated cells are plasma cells.
  - Severe renal impairment (Creatinine Clearance [CrCl] < 30 mL/min) requiring dialysis.
  - Corrected serum calcium > 11.5 mg/dL (> 2.8 mmol/L)
  - Hemoglobin < 8 g/dL (< 4.9 mmol/L; prior red blood cell transfusion or recombinant human erythropoietin use is permitted)
  - Serum SGOT/AST or SGPT/ALT > 3.0 x the upper limit of normal (ULN)
  - Serum total bilirubin > 2.0 mg/dL (34.2  $\mu$ mol/L); or > 3.0 x ULN for subjects with hereditary benign hyperbilirubinemia
2. Prior history of malignancies, other than MM, unless the subject has been free of the disease for more than 5 years. Allowed exceptions include the following:
  - Basal or squamous cell carcinoma of the skin

- Carcinoma in situ of the cervix or breast
  - Incidental histological finding of prostate cancer (TNM [tumor, nodes, metastasis] stage of T1a or T1b)
3. Previous therapy with pomalidomide or daratumumab
  4. Hypersensitivity to thalidomide, LEN, or dex (this includes  $\geq$  Grade 3 rash during prior thalidomide or LEN therapy)
  5. Subjects who received an allogeneic bone marrow or allogeneic peripheral blood stem cell transplant less than 12 months prior to initiation of study treatment and who have not discontinued immunosuppressive treatment for at least 4 weeks prior to initiation of study treatment and are currently dependent on such treatment.
  6. Subjects with any one of the following:
    - Congestive heart failure (NY Heart Association Class III or IV)
    - Myocardial infarction within 12 months prior to starting study treatment
    - Unstable or poorly controlled angina pectoris, including Prinzmetal's variant angina pectoris
  7. Subjects who received any of the following within 14 days of initiation of study treatment:
    - Major surgery (kyphoplasty is not considered major surgery)
    - Use of any anti-myeloma drug therapy
  8. Use of any investigational agents including for the treatment of multiple myeloma within 28 days or 5 half-lives (whichever is longer) of treatment, unless approved by the sponsor.
  9. Incidence of gastrointestinal disease that may significantly alter the oral absorption of Pomalidomide.
  10. Subjects unable or unwilling to undergo antithrombotic prophylactic treatment
  11. Any serious medical condition, laboratory abnormality, or psychiatric illness that would preclude participation in the study, or interfere with interpretation of the study results
  12. Pregnant or breastfeeding females
  13. Known human immunodeficiency virus (HIV) positivity; active infectious hepatitis A, B, or C; or chronic hepatitis B or C.

All subjects will be tested for hepatitis B surface antigen (HBsAg), hepatitis B surface antibody (antiHBs), and hepatitis B core antibody (antiHBc). Subjects with the following serological testing are considered not eligible:

- HBsAg positive
- HBsAg negative, anti-HBs positive and/or anti-HBc positive and detectable viral DNA

Note:

- Subjects who are HBsAg negative, anti-HBs positive, and/or anti-HBc positive, viral DNA negative are eligible. For these subjects, DNA monitoring and prophylactic medication for HBV reactivation are recommended per local practice.
- Subjects who are seropositive because of hepatitis B virus vaccination are eligible (anti-HBs positive, anti-HBc negative, and HBsAg negative).

All subjects will be tested for hepatitis C antibody. Subjects are not eligible if known seropositive for hepatitis C virus.

Note:

- Subjects who are hepatitis C antibody positive but show no detectable viral RNA for 6 months prior to initiation of study treatment are eligible.

14. For subjects enrolling in Cohort B and Cohort C - Subject has known allergies, hypersensitivity to mannitol, corticosteroids, monoclonal antibodies or human proteins, or their excipients (refer to the Daratumumab IB), or known sensitivity to mammalian-derived products.

## **8. DESCRIPTION OF STUDY TREATMENTS**

### **8.1. Description of Investigational Product(s)**

Pomalidomide will be supplied as Investigational Product by Celgene Corporation as 1 mg, 2 mg, 3 mg, and 4 mg capsules for oral administration. Investigational product will be packaged in bottles containing a 21-day supply of POM.

Daratumumab will be supplied as Investigational Product by Celgene Corporation in single-use vials in single-count cartons. Daratumumab is a colorless to pale yellow, preservative-free solution and will be supplied in as 400 mg/20 mL or 100 mg/5 mL vials for intravenous administration. For Cohort C, 400 mg/20 mL vials for intravenous administration will be supplied. For reconstitution, administration and storage after reconstitution information, please refer to the pharmacy manual.

Dexamethasone for oral administration is approved and commercially available for patients with MM. Investigative sites will use commercial oral dex for this study, which will be provided to subjects via prescription. For Cohort C, dexamethasone will be supplied as 2 mg or 4 mg tablets for oral administration as Investigational Product by Celgene Corporation. This protocol only contains summary information on dex administration, the full product information and labeling contained in the current dex Package Insert should be reviewed prior to administration.

Other recommended/required concomitant medications per the protocol such as aspirin (or other antithrombotic or anti-coagulants), antihistamines, antipyretics (or other medications administered for infusion of DARA) and growth factors are commercially available and will be provided at the site by investigator(s) prescription. Celgene will not provide these medications.

### **8.2. Treatment Administration and Schedule**

All study drug doses will be administered orally or intravenously, and subjects will be instructed about the dosing schedules for the study.

Subjects enrolled in Cohort A of this study will receive:

- Oral POM at the starting dose of 4 mg/day on Days 1-21 of a 28-day cycle
- Oral LD-dex at the starting dose of 40 mg/day ( $\leq$  75 years old) or 20 mg/day ( $>$  75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle.

Subjects enrolled in Cohort B and Cohort C of this study will receive:

- Oral POM at the starting dose of 4 mg/day on Days 1-21 of a 28-day cycle
- Oral LD-dex at the starting dose of 40 mg/day ( $\leq$  75 years old) or 20 mg/day ( $>$  75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle.
- DARA administered intravenously at a starting dose of 16 mg/kg at following schedule:
  - Days 1, 8, 15, and 22 of a 28-day cycle for Cycle 1 and Cycle 2
  - Days 1 and 15 for Cycle 3 through Cycle 6
  - Day 1 for Cycle 7 and each cycle thereafter until disease progression

Subjects will also be instructed to return the study drug bottles (and any remaining study drug) at the next visit for drug accountability purposes. For FCBP, study drug will not be dispensed until the investigator has verified that the results of the pregnancy test are negative. Females of childbearing potential other than the subject should not handle study drug unless wearing gloves.

All subjects enrolled into the study will continue study treatment until progressive disease or unacceptable toxicity, death, withdrawal of active participation in the study or withdrawal of consent, or lost to follow-up, or as long as they benefit from therapy according to the opinion of the responsible study investigator.

### Dose Modification and Interruption

Dosing interruptions and reductions are permitted throughout the study.

In the event of any dose reduction for POM, site staff must contact the Interactive Voice Response System (IVRS) to record the new dose level.

If the treatment has been interrupted and the next cycle is delayed beyond 28 days after Day 1 of the prior cycle, then Day 1 of the next cycle will be defined as the first day that treatment is resumed.

Subjects will be evaluated for AEs at each visit with the NCI-CTCAE (version 4.03) as a guide for the grading of severity.

- If POM is permanently discontinued, then the subject must be permanently discontinued from all study treatments.
- For Patients in Cohort B and Cohort C, if DARA is withheld or permanently discontinued, then POM, and LD-Dex dosing may be continued.
- If LD-dex dosing is withheld or permanently discontinued, then POM and DARA (for patients in Cohort B and Cohort C) dosing may be continued.

### Dose Modification Instructions for Pomalidomide

Detailed instructions for POM dose interruptions and reductions are provided in [Table 2](#). [Table 3](#) outlines the dose reduction steps for POM.

If POM administration is withheld, LD-dex should also be withheld.

**Table 2: Dose Modification Instructions for Pomalidomide**

Toxicity <sup>a</sup>	Dose Modification
Neutropenia Grade 4 neutropenia (ANC < 500/ $\mu$ L) or Febrile neutropenia (ANC < 1,000/ $\mu$ L with a single temperature of > 38.5 °C or a sustained temperature of $\geq$ 38 °C for more than one hour)	Withhold the dose and follow CBC weekly. If the subject was not receiving GCSF therapy, GCSF therapy may be started at the discretion of the treating physician. When dosing is resumed, the dose of POM may be maintained if neutropenia was the only POM-related toxicity requiring a dose modification and GCSF treatments are continued. Otherwise, decrease by one dose level. Note, ANC must be $\geq$ 500/ $\mu$ L to restart dosing For Cohort C, ANC must be $\geq$ 1000/ $\mu$ L to restart dosing
Thrombocytopenia Grade 4 thrombocytopenia (Platelets < 25,000/ $\mu$ L)	Withhold the dose and follow CBC weekly. Dosing may resume at one dose level lower once the platelet count has recovered to $\geq$ 50,000/ $\mu$ L.

**Table 2: Dose Modification Instructions for Pomalidomide (Continued)**

Toxicity	Dose Modification
Rash, Grade 3	Withhold dose for remainder of cycle. Decrease by one dose level when dosing restarted at next cycle (rash must resolve to $\leq$ Grade 1 before restarting dosing).
Rash, Grade 4 or Blistering	Discontinue subject from study treatment.
VTE $\geq$ Grade 3	Withhold dose for remainder of cycle. Assess anticoagulation treatment. Maintain dose level when dosing restarted at next cycle at discretion of treating physician.
Other $\geq$ Grade 3 POM-related <sup>b</sup> adverse events	Withhold dose. Decrease by one dose level when dosing restarted (adverse event must resolve to $\leq$ Grade 2 before restarting dosing).

ANC = absolute neutrophil count; GCSF = granulocyte colony-stimulating factor; POM = pomalidomide; VTE = venous thromboembolism.

<sup>a</sup> If recovery from toxicities is prolonged beyond 14 days, then the dose of POM will be decreased by one dose level when dosing is restarted.

<sup>b</sup> For Grade 3 or 4 AEs that are not considered to be related to study drug, the treating physician should consult with the sponsor for dose interruptions and reductions.

To initiate a new cycle of POM, the neutrophil count must be  $\geq 500/\mu\text{L}$  and for Cohort C, the neutrophil count must be  $\geq 1000/\mu\text{L}$  with or without granulocyte colony-stimulating factor (GCSF), the platelet count must be  $\geq 50,000/\mu\text{L}$ , and non-hematologic AEs must have recovered as outlined in [Table 2](#).

If recovery from toxicities is prolonged beyond 14 days, then the dose of POM will be decreased by one dose level when dosing is restarted. Prior to restarting treatment after a prolonged delay, subjects should be assessed to ensure they have not developed progressive disease.

**Table 3: Pomalidomide Dose Reduction Steps**

Dose Level <sup>a</sup>	Oral POM Dose Reduction (Days 1-21 of 28 days)
Starting dose	4 mg
Dose Level -1	3 mg
Dose Level -2	2 mg
Dose Level -3	1 mg

<sup>a</sup> The minimum permitted dose level for POM is 1.0 mg. No dose re-escalation is permitted for Pomalidomide.

### Dose Modification Instructions for Low-dose Dexamethasone

Dose Reductions for Low-dose dexamethasone-related Toxicities ([Table 4](#)) details instructions for LD-dex dose interruptions and reductions and [Table 5](#) outlines the dose reduction steps for LD-dex; however, the full product information and labeling contained in the current dex Package Insert should also be reviewed.

If LD-dex is held or permanently discontinued due to toxicity, POM, and (for patients in Cohort B and Cohort C) DARA may be continued.

**Table 4: Dose Reductions for Low-dose Dexamethasone-related Toxicities**

Toxicity <sup>a</sup>	LD-dex Dose Modification
Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist.
Dyspepsia ≥ Grade 3	Withhold dose until symptoms are controlled. Add H2 blocker or equivalent and decrease one dose level when dose restarted.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.
Confusion or mood alteration ≥ Grade 2	Withhold dose until symptoms resolve. When dose restarted, decrease dose by one dose level.
Muscle weakness (steroid myopathy) ≥ Grade 2	Withhold dose until muscle weakness ≤ Grade 1. When dose restarted decrease dose by one dose level.
Hyperglycemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycemic agents as needed.
Acute pancreatitis	Discontinue subject from dex treatment regimen.
Other ≥ Grade 3 dex-related adverse events	Stop dex dosing until the adverse event resolves to ≤ Grade 2. Decrease by one dose level when dex dosing is resumed.

<sup>a</sup> If recovery from toxicities is prolonged beyond 14 days, then the dose of dex will be decreased by one dose level when dose is restarted.

**Table 5: Dexamethasone Dose Reduction Steps**

Dose Level <sup>a</sup>	≤ 75 Years Old Dose (Days 1, 8, 15, 22 of a 28-day Cycle)	> 75 Years Old Dose (Days 1, 8, 15, 22 of a 28-day Cycle)
Starting Dose	40 mg	20 mg
Dose Level -1	20 mg	12 mg
Dose Level -2	10 mg	8 mg

<sup>a</sup> Dexamethasone should be discontinued if subject is unable to tolerate 10 mg if ≤ 75 years old or 8 mg if > 75 years old.

### 8.3. Daratumumab Administration

Preparation of the infusion bags should be done on the day of the planned infusion. The infusion solution will be prepared as a 1000-mL (first dose only) or 500-mL dilution of daratumumab in sterile, pyrogen free 0.9% NaCl. Preparation of the infusion bags should be done on the day of the planned infusion. Daratumumab must be administered as an IV infusion given through a well-functioning IV catheter by using an infusion pump or syringe pump. The study drug must be filtered by using an inline filter (0.2 µM) during the infusion.

Each subject's dose will be calculated based on the subject's weight rounded to the nearest kilogram. Dosing calculations do not need to be changed for weight changes that are < 10% from baseline. For reconstitution, administration and storage after reconstitution information, please refer to the pharmacy manual.

## Recommended Concomitant Medications

### Pre-infusion Medication

Administer pre-infusion medications to reduce the risk of infusion reactions to all subjects approximately 1 hour prior to every infusion of DARA as follows:

- Protocol specified dose of oral dexamethasone, plus
- oral antipyretics (acetaminophen 650 to 1000 mg), plus
- oral or intravenous antihistamine (diphenhydramine 25 to 50 mg or equivalent).
- Oral leukotriene receptor antagonist (10 mg montelukast or equivalent) is also recommended as this may reduce infusion related reactions ([Van de Donk, 2016](#)).

### Post-infusion Medication

For subjects with a history of obstructive pulmonary disorder, consider prescribing post-infusion medications such as short and long-acting bronchodilators, and inhaled corticosteroids.

Following the first four infusions, if the patient experiences no major infusion reactions, these additional inhaled post-infusion medications may be discontinued.

Where clinically indicated, at the discretion of the investigator, initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting DARA and continue for 3 months following treatment

### Daratumumab Dose Modifications

For infusion reactions of any grade/severity, immediately interrupt the DARA infusion and manage symptoms. Management of infusion reactions may further require reduction in the rate of infusion, or treatment discontinuation of DARA as outlined below ([Table 6](#)).

- Grade 1-2 (mild to moderate): Once reaction symptoms resolve, resume the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience any further reaction symptoms, infusion rate escalation may resume at increments and intervals as appropriate ([Table 6](#)).
- Grade 3 (severe): If the intensity of the reaction decreases to Grade 2 or lower, consider restarting the infusion at no more than half the rate at which the reaction occurred. If the patient does not experience additional symptoms, resume infusion rate escalation at increments and intervals as outlined in [Table 6](#). Repeat the procedure above in the event of recurrence of Grade 3 symptoms. Permanently discontinue DARA upon the third occurrence of a Grade 3 or greater infusion reaction.
- Grade 4 (life threatening): Permanently discontinue DARA treatment.

During a cycle, a daratumumab dose must be held if any of the following criteria below are met, to allow for recovery from toxicity. The criteria for a dose delay are:

- Grade 4 hematologic toxicity, or Grade 3 or higher thrombocytopenia with bleeding;
- Febrile neutropenia of any grade;
- Neutropenia with infection, of any grade;

- Grade 3 or higher nonhematologic toxicities with the following exceptions:
  - Grade 3 nausea or Grade 3 vomiting that responds to antiemetic treatment,
  - Grade 3 diarrhea that responds to antidiarrheal treatment,
  - Isolated Grade 3 Gamma-glutamyltransferase elevation
  - Grade 3 fatigue or asthenia that was present at baseline or that lasts for < 7 days after the last administration of daratumumab

If daratumumab administration does not commence within the prespecified window (Table 6) of the scheduled administration date, then the dose will be considered a missed dose.

Administration may resume at the next planned dosing date.

**Table 6: Daratumumab-Related Toxicity Management**

Frequency	Dose Miss	Dosing Resumption
Weekly	> 3 days	next planned weekly dosing date
Every 3 weeks	> 14 days	next planned every-third-week dosing date
Every 4 weeks	> 21 days	next planned every-4-weeks dosing date

A missed dose will not be made up. Any dose holds of more than 14 days due to toxicity will result in permanent discontinuation of daratumumab. Dose holds of more than 14 days for other reasons should be discussed with the sponsor. If a dose delay occurs, pharmacodynamic assessments should be performed on the actual day of study drug administration (only on days that PD samples are scheduled per protocol), not on the original scheduled administration day.

### **Daratumumab Interruption or Missed Doses**

A daratumumab dose that is held for more than 3 days per the per-protocol administration date for any reason other than toxicities suspected to be related to daratumumab should be brought to the attention of the sponsor's Study Manager at the earliest possible time. Subjects missing  $\geq 3$  consecutive planned doses of daratumumab should be withdrawn from study treatment, unless, upon consultation with the sponsor and the review of safety and efficacy, continuation is agreed upon.

**Table 7: Infusion Rates for Daratumumab Administration**

	Dilution Volume	Initial Rate (first hour)	Rate Increment	Maximum Rate
<b>First Infusion</b>	1000 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
<b>Second Infusion<sup>a</sup></b>	500 mL	50 mL/hour	50 mL/hour every hour	200 mL/hour
<b>Subsequent Infusions<sup>b</sup></b>	500 mL	100 mL/hour	50 mL/hour every hour	200 mL/hour

<sup>a</sup> Escalate only if there were no Grade 1 (mild) or greater infusion reactions during the first 3 hours of the first infusion.

<sup>b</sup> Escalate only if there were no Grade 1 (mild) or greater infusion reactions during a final infusion rate of  $\geq 100$  mL/hr in the first two infusions.

Infusion of daratumumab should be completed within approximately 15 hours.

### **Infusion Reactions**

Daratumumab can cause severe infusion reactions. Approximately half of all patients experienced a reaction, most during the first infusion. Infusion reactions can also occur with subsequent infusions. Nearly all reactions occurred during infusion or within 4 hours of completing DARA. Prior to the introduction of post-infusion medication in clinical trials, infusion reactions occurred up to 48 hours after infusion. Severe reactions have occurred, including bronchospasm, hypoxia, dyspnea, and hypertension. Signs and symptoms may include respiratory symptoms, such as cough, wheezing, larynx and throat tightness and irritation, laryngeal edema, pulmonary edema, nasal congestion, and allergic rhinitis. Less common symptoms were hypotension, headache, rash, urticaria, pruritus, nausea, vomiting, and chills.

Pre-medicate subjects with antihistamines, antipyretics, leukotriene receptor antagonist and corticosteroids. Frequently monitor subjects during the entire infusion. Interrupt DARA infusion for reactions of any severity and institute medical management as needed. Permanently discontinue DARA therapy for life-threatening (Grade 4) reactions. For subjects with Grade 1, 2, or 3 reactions, reduce the infusion rate when re-starting the infusion ([Table 7](#)).

### **Interference with Serological Testing:**

#### **Indirect Antiglobulin Test (IAT)**

Daratumumab interferes with the Indirect Antiglobulin Test (IAT), which is a routine pretransfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. Daratumumab does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. Daratumumab binds to the CD38 on erythrocytes, which results in a positive IAT (Indirect Coombs Test). This positive result masks the detection of antibodies to minor antigens and may prevent or delay blood banks from issuing donor blood for transfusion. This effect occurs during daratumumab treatment and for up to 6 months after treatment ends. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. Subjects are to carry this card throughout the treatment period and for at least 6 months after treatment ends. Blood banks can eliminate the daratumumab interference with IAT by treating reagent RBCs with dithiothreitol (DTT) ([Chapuy, 2015](#)).

Possible methods for blood banks to provide safe RBCs for transfusion to subjects receiving daratumumab include:

1. Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping prior to daratumumab administration) or genotypically matched units
2. Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using DTT-treated reagent RBCs

Uncrossmatched, ABO/RhD compatible RBC units should be administered if transfusion is needed emergently as per local blood bank practice.

Despite daratumumab binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in daratumumab studies ([Chari, 2017a](#)). For additional details, refer to the Daratumumab IB.

### **Overdose**

Overdose, as defined for this protocol, refers to pomalidomide, daratumumab and dexamethasone dosing only.

On a per dose basis, an overdose is defined as any amount over the protocol-specified dose of pomalidomide, daratumumab and dexamethasone assigned to a given patient, regardless of any associated adverse events or sequelae.

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form. See Section [11.1](#) for the reporting of adverse events associated with overdose.

## **8.4. Method of Treatment Assignment**

This study will use the IVRS for enrollment. Designated research personnel at each investigational sites will be assigned password protected, coded identification numbers which gives them the authorization to call into IVRS to enroll Celgene approved subjects.

Celgene trial staff will review and verify specific eligibility criteria for all screened subjects prior to allowing enrollment of subjects via the IVRS. Celgene trial staff will be required to activate subjects in the IVRS before site staff may enroll the subject. For drug assignment at each cycle start and in the event of any dose reduction, site staff must contact IVRS to record the new dose level and obtain the new study treatment assignment.

## **8.5. Packaging and Labeling**

The label(s) for IP (POM, DARA, dex) will include sponsor name, address and telephone number, the protocol number, IP name, dosage form, and strength amount of IP per container, lot number, expiry date (where applicable), medication identification/kit number, dosing instructions, storage conditions, and required caution statements and/or regulatory statements as applicable. Additional information may be included on the label as applicable per local regulations.

## **8.6. Investigational Product Accountability and Disposal**

Celgene will instruct the investigator on the return, disposal, and/or destruction of investigational product (POM, DARA, dex).

## **8.7. Investigational Product Compliance**

The investigator will document the number of capsules of POM issued to and returned by each subject at each study visit. The investigator will document the number of vials of DARA administered to each subject at each DARA administration visit. For Cohort C, the investigator

will document the number of tablets of dex issued to and returned by each subject at each study visit. The investigator will also be responsible for documenting subject compliance for POM, DARA and LD-dex.

## **9. CONCOMITANT MEDICATIONS AND PROCEDURES**

### **9.1. Permitted Concomitant Medications and Procedures**

Other therapies considered necessary for the subject's well-being may be administered at the discretion of the investigator. These therapies may include antibiotics, analgesics, antihistamines, or other medications and transfusions of RBC, platelets, or fresh frozen plasma given to assist in the management of complications associated with MM or its therapy. These therapies also include pre and post infusion medications required for the administration of DARA as per Section 8.2.

The prophylactic use of hematopoietic growth factors will be allowed throughout the study at the treating physician's discretion. Once allowed, the use of myeloid growth factors is encouraged when ANC is less than 1,000/ $\mu$ L at the discretion of the treating physician.

Subjects who met the ANC, hemoglobin, and platelet eligibility criteria due to growth factor treatment or platelet/blood transfusion received prior to the start of the screening period are acceptable. Platelet and RBC transfusions are also permitted during the study.

Adjunctive radiation therapy to a pathological fracture site or to treat bone pain is permitted.

Subjects with myeloma-associated bone disease may receive bisphosphonate therapy prior to study entry, as well as other agents that may be used for myeloma-associated bone disease such as denosumab and teriparatide, unless such therapy is contraindicated. The use of bisphosphonates, as well as other agents for the treatment of myeloma-associated bone disease, is permitted throughout the study.

Thromboembolism prophylaxis: Low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant will be given to all subjects.

The following therapies will be collected and recorded in the subject's Concomitant Medication eCRF page: Anti-infectious agents, antithrombotics, growth factors, and bisphosphonates or other agents used for the treatment of myeloma-associated bone disease. All procedures, including transfusions, will be collected and recorded in the subject's eCRF.

### **9.2. Prohibited Concomitant Medications and Procedures**

Concomitant use of other approved or investigational anti-myeloma therapy within 14 days of Cycle 1 Day 1 or while the subject is taking study drug (study treatment phase) is prohibited. Subsequent anti-myeloma treatment should not be initiated prior to PD or study treatment discontinuation.

Chronic use of steroids (other than dex) or any other immunosuppressive therapies is prohibited in this study without approval from the Medical Monitor.

Drugs known to prolong the QT corrected (QTc) interval should be avoided unless deemed medically necessary. See [Appendix G](#) for a comprehensive list of drugs known to prolong QTc.

### **9.3. Required Concomitant Medications and Procedures**

Recent or active cancer is a recognized prothrombotic risk factor for increasing the risk of VTE. Increased plasma viscosity related to monoclonal paraproteinemia has been implicated as a risk

factor for VTE in MM subjects. Clinical studies have shown that thalidomide and LEN in combination with dex or other chemotherapeutic agents increase the risk of VTE ([Baz, 2005](#); [Weber, 2007](#)). Aspirin has been reported to be effective in reducing the incidence of DVT in MM subjects treated with thalidomide or LEN ([Baz, 2005](#)).

For the current study, low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anti-coagulant will be given during the study to all subjects. Antithrombotic prophylaxis will be recorded on the eCRF.

Pre and post infusion medications required for the administration of DARA as per Section [8.2](#) will also be recorded on the eCRF. Subjects who develop symptomatic DVT will be assessed and diagnosed objectively by Doppler ultrasonography or a comparable method. Diagnostic algorithms are provided in [Appendix A](#).

## **10. STATISTICAL ANALYSES**

### **10.1. Overview**

This is a multi-cohort study separately evaluating efficacy and safety of the combinations of POM+LD-dex (Cohort A) and POM+DARA+LD-dex combination as therapy for subjects relapsing after or refractory to LEN-based therapy in the first or second line. The primary endpoint of overall response for Cohort A will be analyzed in 2 stages; once at 6 cycles after approximately 40% of the subjects are enrolled and again after the last subject is enrolled and adequate follow up is obtained. For Cohort B and Cohort C, the primary endpoint may be assessed at timepoints allowing for early dissemination of descriptive results and after the last subject is enrolled and adequate follow up is obtained. A third analysis is planned at the end of the long-term follow-up phase of the study.

### **10.2. Study Population Definitions**

#### **Safety Population**

The safety population is defined as all enrolled subjects who receive at least one dose of the study treatment. The safety population will be used for all safety analyses.

#### **ITT Population**

The ITT population is defined as all enrolled subjects regardless of whether they received any of the study treatment. The ITT population will be used for all efficacy analyses.

#### **Efficacy Evaluable (EE) Population**

This population will consist of all enrolled subjects who meet eligibility criteria, take at least one dose of study drug, and have at least one post-baseline response assessment. The EE population will be used to provide supporting sensitivity analyses for the primary endpoint and key secondary endpoints.

### **10.3. Sample Size and Power Considerations**

The primary analysis in Cohort A will test the hypothesis that the proportion of subjects in the intent-to-treat population with ORR of 30% or greater against the null hypothesis of a response no greater than an unacceptable ORR of 16%. The 16% unacceptable ORR assumption is based on experience with carfilzomib monotherapy and the 30% ORR under the alternate hypothesis is based on a limited cohort in the Celgene CC-4047-MM-002 study. An exact binomial test with a 2-sided alpha level of 0.05 will be used to test this hypothesis. The enrollment in Cohort A was terminated at 56 subjects. Cohort A sample size will curtail the power in assessing the original hypothesis to 71%. The overall response rate can be estimated within +/- 12% with a 95% confidence interval with 55 subjects. An interim analysis will be conducted at a target of about 40% of the original planned sample size of Cohort A. There is no intent to terminate the study at interim, and the study will continue to full enrollment in order to collect an adequate amount of safety information for the POM and LD-dex combination as a third-line therapy. In order to adequately assess the primary ITT patient population analysis, the final minimum enrollment in Cohort A is 55 subjects. Accounting for drop-outs, and non-eligibility a total of approximately

65 subjects may be enrolled in Cohort A in order to support the secondary EE patient population analysis.

The primary objective for Cohort B is to estimate the overall response rate for this triplet (POM+DARA+LD-dex). A sample size of approximately 100 subjects will be adequate to estimate the overall response rate with a 95% confidence interval of width  $\pm 9.7\%$  about the obtained rate. This calculation assumes an OR rate similar to the 70% reported for this triplet combination by Chari, et al (Chari, 2015). The minimum required enrollment in Cohort B is 85 subjects. Accounting for drop-outs and non-eligibility, a total of about 100 subjects could be enrolled in Cohort B.

The primary objective for Cohort C is to test the hypothesis that the ORR for this triplet (POM+DARA+LD-dex), in Japanese participants, exceeds 25% using an exact 1-sided binomial test conducted at an alpha level of 0.025. A sample size of  $n=17$  subjects will provide 80% power for an expected ORR of 60% (Ichinohe, 2016). Accounting for the drop-outs and non-eligibility, approximately 20 subjects will be enrolled in the study. The null ORR of 25% is based on Ichinohe (2016) and the expected 60% ORR under this triplet therapy is based on Chari, et al (Chari, 2017).

#### **10.4. Background and Demographic Characteristics**

Subjects' age, height, weight, and continuous baseline characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be summarized using frequency tabulations. Medical history data will be summarized using frequency tabulations by system organ class and preferred term.

#### **10.5. Subject Disposition**

For all enrolled subjects, disposition will be summarized by ITT, Safety, and EE population. Reasons for treatment termination will be summarized for all enrolled subjects according to the treatment termination reason collected in the eCRF. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

#### **10.6. Efficacy Analysis**

The primary efficacy analysis will be performed on both the ITT and EE populations. The exact binomial test will be used to test the hypothesis that the ORR for the Cohort A is greater than 16%. The final primary analysis on ORR will report exact 2-sided p-values with 95% Clopper-Pearson confidence intervals (Collett, 2003). For Cohort B point estimates of the ORR together with 95% confidence interval will be calculated using the normal approximation to the binomial distribution. Analysis for Cohort C will mirror the analysis for Cohort A except for a test of the hypothesis of an ORR greater than 25%.

The Kaplan-Meier procedures will be used to characterize the time-to-event curves (PFS, OS, TTP, and response duration) and the median and 95% confidence intervals of time to each of these events will be estimated. Univariate summary statistics will be provided for time to response. Progression-free survival and OS will be analyzed in the ITT as well as the EE populations. Other secondary efficacy endpoints will be analyzed in the ITT population only.

Analyses of PFS, OS, TTP, and response duration will be updated at the end of the long-term follow-up phase of the study.

### **Primary Efficacy Endpoint**

The primary endpoint will be the overall response rate (ORR) by mIMWG criteria and will be based on the best response prior to the data cut-offs. Data cut-offs for the primary endpoint for Cohort A are planned for 6 cycles after about 40% of the subjects enroll and 6 cycles after the last patient enrolls. For Cohort B and Cohort C the primary endpoint may be assessed at time points allowing for early dissemination of descriptive results, after the last subject is enrolled, and after adequate follow up of all subjects enrolled. The ORR will consist of the responses of PR or better (CR, VGPR, or PR). A response that is documented after the initiation of another anti-myeloma treatment will not be counted as a response. However, these subjects will be included in the denominator for the ORR calculation. Subjects without an assessment of response will be considered nonresponders.

### **Secondary Efficacy Endpoints**

#### **Time to Response**

Time to response, calculated for responders only, is calculated as the time from the start of treatment to the first documented response (PR or better) based on mIMWG criteria.

#### **Duration of Response**

Duration of response, calculated for responders only, is defined as time from the initial documented response (PR or better) to the first confirmed PD or until death from any cause. Subjects without documented progression will be censored at the time of their last response assessment.

#### **Time to Progression**

Time to progression will be calculated as the time from start of treatment until PD (as determined by the site investigator based on the mIMWG criteria). Subjects not experiencing a documented progression will be censored at the time of their last response assessment (or at the time of trial enrollment if no assessment was conducted).

#### **Progression-free Survival**

Progression-free survival will be calculated as the time from start of treatment until the time of PD (as determined by the site investigator based on the mIMWG criteria) or death from any cause on study treatment, whichever comes first. Subjects not experiencing a documented progression will be censored at the time of their last response assessment (or at the time of trial enrollment if no assessment was conducted).

#### **Overall Survival**

Overall survival will be calculated as the time from start of treatment until the time of death from any cause. If no death is recorded the subject will be censored at the time the subject was last known to be alive.

## **Quality of Life (QoL)**

Using EQ-5D scoring instructions, overall scores will be analyzed for subjects enrolled in Cohort B using change from the screening assessment at each post-screening time point. The worst change from baseline among all available post-baseline measurements for each subject will also be analyzed. Change scores from baselines will be analyzed using mixed model using baseline covariates as adjustment.

## **10.7. Safety Analysis**

All subjects who receive at least one dose of study medication will be included in the safety analyses. Graphical displays will be provided where useful in the interpretation of results.

### **Adverse Events**

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA). The severity of AEs will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events NCI-CTCAE (version 4.03, June 2010).

Treatment-emergent adverse events (TEAEs) are defined as in the International Conference on Harmonisation (ICH) E9 as “an event that emerges during treatment, having been absent pre-treatment, or worsens relative to the pre-treatment state”. The treatment phase is defined as starting from the first dose of the study medication through 28 days after the last dose. All TEAEs, NCI-CTCAE grade 3/4 AEs, Grade 5 AEs, AEs leading to study medication discontinuations, AEs leading to dose reduction/interruption, AEs leading to death, AEs related to study medication, and serious AEs will be summarized by system organ class, preferred term, and by NCI-CTCAE grade (worst grade).

Tables will be sorted by system organ class/preferred term and the overall frequency of the incidence. If a subject experiences the same preferred term multiple times, then the subject will be counted only once for this term and by the worst severity.

### **Deaths**

Deaths during treatment (defined as deaths from the first dose and within 28 days after the last dose of study medication) and during the long-term follow-up phase shall be summarized by frequency of occurrence and corresponding percentage by cause of death per period (during treatment or follow-up) as well as overall.

### **Study Drug**

Descriptive summaries of pomalidomide, daratumumab, and dexamethasone exposure duration, dosing information, and dose modification during the study will be provided.

### **Concomitant Therapy**

All concomitant medications and procedures documented during the study period will be summarized in frequency tabulations. The Anatomical Therapeutic Chemical coding scheme of the World Health Organization will be used to group medications into relevant categories for these tabulations.

### **Clinical Laboratories**

Clinical laboratory values will be graded according to NCI-CTCAE (version 4.03, June 2010) for applicable tests. Baseline grade and worst grade during treatment for selected laboratory results will be summarized. Shift from baseline to the worst grade observed during the treatment for selected laboratory results will also be provided.

### **Electrocardiogram**

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with 'Normal', 'Abnormal, not clinically significant' and 'Abnormal, clinically significant'. This analysis will only be conducted for subjects enrolled in Cohort A.

### **Second Primary Malignancies**

Second primary malignancies will be classified and tabled as hematological malignancies, solid tumor malignancies and non-melanoma skin cancers. The raw incidence and the incidence per 100 patient years will be summarized.

## **10.8. Interim Analysis**

In the interest of early dissemination of safety and efficacy data, an interim analysis will be conducted 6 months after about 40% of the planned enrollment for Cohort A. Clopper-Pearson confidence intervals and exact p-values will be provided. A positive efficacy conclusion at the interim will not lead to an early termination, and study recruitment will continue until the planned total enrollment with the objective of collecting complete safety data. Anti-myeloma activity of POM+DARA+Dex will be assessed at appropriate time points but no formal Interim analysis will be performed for Cohort B and Cohort C.

Pertinent safety analyses from those described in Section 10.7 will be conducted as part of the interim analysis.

## **10.9. Other Topics**

Questions emerging after study initiation and questions pertaining to biomarker data will be subjects of further exploratory analyses.

## **11. ADVERSE EVENTS**

### **11.1. Monitoring, Recording and Reporting of Adverse Events**

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values (as specified by the criteria in Section 11.3, regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF. (See Section 8.3 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself. In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for pomalidomide, daratumumab, or dexamethasone overdose. Actual treatment should depend on the severity of the clinical situation and the judgement and experience of the treating physician. All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or other appropriate tests and procedures.

All AEs will be recorded by the investigator from the time the subject signs informed consent to at least 28 days after the last dose of POM, DARA, or LD-dex, and those SAEs made known to the investigator at any time thereafter that are suspected of being related to study IPs (POM, DARA, or LD-dex). AEs and SAEs will be recorded on the AE page of the CRF and in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

### **11.2. Evaluation of Adverse Events**

A qualified investigator will evaluate all adverse events as to:

#### **11.2.1. Seriousness**

An SAE is any AE occurring at any dose that:

- Results in death;
- Is life-threatening (ie, in the opinion of the investigator, the subject is at immediate risk of death from the AE);

- Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization is defined as an inpatient admission, regardless of length of stay);
- Results in persistent or significant disability/incapacity (a substantial disruption of the subject's ability to conduct normal life functions);
- Is a congenital anomaly/birth defect;
- Constitutes an important medical event.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment cohort the subject is in (see Section 11.5). This includes any SPM, regardless of causal relationship to study IPs (POM, DARA, or LD-dex), occurring at any time for the duration of the study, from the time of signing the ICD for at least 5 years from the date the last subject is enrolled into each respective cohort. Events of SPM are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF (ie, AE and SPM CRF) and subject's source documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as an SAE (eg, any confirmatory histology or cytology results, x-rays, CT scans, etc.).

Events **not considered** to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (eg, surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (ie, planned prior to starting of treatment on study); must be documented in the source document and the eCRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of a pre-existing condition unrelated to the studied indication.

- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed.

For each SAE, the investigator will provide information on severity, start and stop dates, relationship to IP (POM, DARA, or LD-dex), action taken regarding IP (POM, DARA, or LD-dex), and outcome.

### 11.2.2. Severity / Intensity

For both AEs and SAEs, the investigator must assess the severity / intensity of the event.

The severity of AEs will be graded based upon the subject's symptoms according to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE, Version 4.0.3 or higher);

[http://ctep.cancer.gov/protocolDevelopment/electronic\\_applications/ctc.htm#ctc\\_40\\_](http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40_)

Adverse events that are not defined in the NCI CTCAE should be evaluated for severity according to the following scale:

- 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, hospitalization is possible
- Grade 4 = Life threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death – the event results in death

The term “severe” is often used to describe the intensity of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is *not* the same as “serious” which is based on subject/event *outcome* or *action* criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

### 11.2.3. Causality

The investigator must determine the relationship between the administration of IPs (POM, DARA, or LD-dex) and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: Means a causal relationship of the adverse event to IP (POM, DARA, or LD-dex) administration is **unlikely or remote**, or

other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

**Suspected:** Means there is a **reasonable possibility** that the administration of IP (POM, DARA, or LD-dex) caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary, or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

#### **11.2.4. Duration**

For both AEs and SAEs, the investigator will provide a record of the start and stop dates of the event.

#### **11.2.5. Action Taken**

The investigator will report the action taken with IPs (POM, DARA, or LD-dex) as a result of an AE or SAE, as applicable (eg, discontinuation or reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

#### **11.2.6. Outcome**

All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered, recovered with sequelae, not recovered (death due to another cause), or death (due to the SAE).

### **11.3. Abnormal Laboratory Values**

An abnormal laboratory value is considered to be an AE if the abnormality:

- results in discontinuation from the study;
- requires treatment, modification/ interruption of IPs (POM, DARA, or LD-dex) dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as a serious adverse event.

If a laboratory abnormality is one component of a diagnosis or syndrome, then only the diagnosis or syndrome should be recorded on the AE page/screen of the CRF. If the abnormality was not a part of a diagnosis or syndrome, then the laboratory abnormality should be recorded as the AE.

## **11.4. Pregnancy**

All pregnancies or suspected pregnancies occurring in either a female subject or partner of a male subject are immediately reportable events.

In the event of a pregnancy occurring in a female subject of childbearing potential or female partner of a male subject, Celgene will follow up with the clinical investigator each trimester of pregnancy and for 1 year following the birth of the infant (if applicable). Please reference the pregnancy information consent (permission) forms for data collection for additional information.

The exposure of any pregnant female (eg, caregiver or pharmacist) to pomalidomide is also an immediately reportable event.

### **11.4.1. Females of Childbearing Potential:**

Pregnancies and suspected pregnancies (including elevated beta human chorionic gonadotropin [ $\beta$ hCG] or positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study treatment, or within 28 days of the subject's last dose of POM or LD-dex or (for subjects enrolled in Cohort B and Cohort C) within 3 months of last dose of daratumumab, are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the IP to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the Initial Pregnancy Report Form, or approved equivalent form. The female should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The investigator will follow the female subject until completion of the pregnancy and must notify Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Follow-up Pregnancy Report Form or approved equivalent form.

If the outcome of the pregnancy was abnormal (eg, 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 by facsimile, or other appropriate method, within 24 hours of the investigator's knowledge of the event using the SAE Report Form or approved equivalent form.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the investigator suspects is related to the in utero exposure to the POM or LD-dex or (for subjects enrolled in Cohort B and Cohort C) within 3 months of last dose of daratumumab should also be reported to Celgene Drug Safety 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.

### **11.4.2. Male Subjects**

If a female partner of a male subject taking investigational product pomalidomide, daratumumab or dexamethasone becomes pregnant, the male subject taking IPs (POM, DARA, or LD-dex) should notify the investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

## **11.5. Reporting of Serious Adverse Events**

Any AE that meets any criterion for an SAE requires the completion of an SAE Report Form in addition to being recorded on the AE page/screen of the CRF. All SAEs must be reported to Celgene Drug Safety within 24 hours of the investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events. This includes any second primary malignancy, regardless of causal relationship to IP (POM, DARA, or LD-dex), occurring at any time for the duration of the study, from the time of signing the ICD for at least 5 years from the date the last subject is enrolled into each respective cohort. Events of second primary malignancy are to be reported using the SAE report form and must be considered an "Important Medical Event" if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF (ie, AE and SPM CRF) and subject's source documents. Documentation of the diagnosis of the SPM must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, x-rays, CT scans, etc.).

The investigator is required to ensure that the data on these forms is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IPs [POM, DARA, or LD-dex]) that occur during the study (from the time the subject signs informed consent to at least 28 days after the last dose of IPs [POM, DARA, or LD-dex]), and those made known to the investigator at any time thereafter that are suspected of being related to IPs (POM, DARA, or LD-dex). SAEs occurring prior to treatment will be captured.

The SAE report should provide a detailed description of the SAE and include summaries of hospital records and other relevant documents. If a subject died and an autopsy has been performed, copies of the autopsy report and death certificate are to be sent to Celgene Drug Safety as soon as these become available. Any follow-up data will be detailed in a subsequent SAE Report Form, or approved equivalent form, and sent to Celgene Drug Safety.

Where required by local legislation, the investigator is responsible for informing the Institutional Review Board (IRB)/Ethics Committee (EC) of the SAE and providing them with all relevant initial and follow-up information about the event. The investigator must keep copies of all SAE information on file including correspondence with Celgene and the IRB/EC.

### **11.5.1. Safety Queries**

Queries pertaining to SAEs will be communicated from Celgene Drug Safety to the site via facsimile or electronic mail. The response time is expected to be no more than 5 business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

## **11.6. Expedited Reporting of Adverse Events**

For the purpose of regulatory reporting, Celgene Drug Safety will determine the expectedness of events suspected of being related to pomalidomide and daratumumab based on the Investigator's Brochure.

In the United States, all suspected unexpected serious adverse reactions (SUSARs) will be reported in an expedited manner in accordance with 21 CFR 312.32.

Events of e.g. disease progression for the disease under study (including deaths due to disease progression for indications that are considered to be fatal) will be assessed as expected adverse events and will not be reported as expedited safety reports to regulatory authorities.

Celgene or its authorized representatives shall notify the Investigator of the following information. In Japan, Celgene KK shall notify the Heads of the Institutes in addition to the Investigators.

- Any AE suspected of being related to the use of IPs (POM, DARA, or LD-dex) in this study or in other studies that is both serious and unexpected (ie, SUSAR);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity;
- Other important safety information and periodic reports according to the local regulations.

Where required by local legislation, 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 pertinent safety information on file including correspondence with Celgene and the IRB/EC. (See Section 15.3 for record retention information).

#### **Celgene Drug Safety Contact Information:**

For Local Drug Safety Affiliate Office contact information, please refer to the Serious Adverse Event Report Form / Completion Guidelines or to the Pregnancy Report Form / Completion Guidelines.

## 12. DISCONTINUATIONS

The following events are considered sufficient reasons for discontinuing a subject from the investigational product and/or from the study:

- Adverse Event(s)
- Progressive Disease (PD)
- Withdrawal from active participation in the study (follow-up information may still be collected)
- Withdrawal of consent
- Death
- Lost to follow-up
- Protocol violation

The following events are considered sufficient reasons for discontinuing a subject from the Long-term follow-up phase:

- Withdrawal of consent
- Death
- Lost to follow-up
- Completion of 5-year after last subject enrollment follow-up for each respective cohort

The reason for discontinuation from each phase of the study will be captured in the eCRFs and source document

The decision to discontinue a subject remains the responsibility of the treating physician, which will not be delayed or refused by the sponsor. However, prior to discontinuing a subject, the investigator may contact the Medical Monitor and forward appropriate supporting documents for review and discussion.

- If POM is permanently discontinued, then the subject must be permanently discontinued from all study treatments.
- For Patients in Cohort B and Cohort C, if DARA is withheld or permanently discontinued, then POM, and LD-Dex dosing may be continued.
- If LD-dex dosing is withheld or permanently discontinued, then POM and DARA (for patients in Cohort B and Cohort C) dosing may be continued.

## **13. EMERGENCY PROCEDURES**

### **13.1. Emergency Contact**

In emergency situations, the investigator should contact the responsible Clinical Research Physician/Medical Monitor or designee by telephone at the number(s) listed on the Emergency Contact Information page of the protocol (after title page).

In the unlikely event that the Clinical Research Physician/Medical Monitor or designee cannot be reached, please contact the global Emergency Call Center by telephone at the number listed on the Emergency Contact Information page of the protocol (after title page). This global Emergency Call Center is available 24 hours a day and 7 days a week. The representatives are responsible for obtaining your call-back information and contacting the on-call Celgene/CRO Medical Monitor, who will then contact you promptly.

Note: The back-up 24-hour global emergency contact call center should only be used if you are not able to reach the Clinical Research Physician(s) or Medical Monitor or designee for emergency calls.

### **13.2. Emergency Identification of Investigational Products**

This is an open-label study; therefore, IP will be identified on the package labeling.

## **14. REGULATORY CONSIDERATIONS**

### **14.1. Good Clinical Practice**

The procedures set out in this study protocol pertaining to the conduct, evaluation, and documentation of this study are designed to ensure that Celgene, its authorized representative, and investigator abide by Good Clinical Practice (GCP), as described in International Conference on Harmonisation (ICH) Guideline E6 and in accordance with the general ethical principles outlined in the Declaration of Helsinki. The study will receive approval from an IRB/EC prior to commencement. The investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

### **14.2. Investigator Responsibilities**

Investigator responsibilities are set out in the ICH Guideline for Good Clinical Practice and in the local regulations. Celgene staff or an authorized representative will evaluate and approve all investigators who in turn will select their staff.

The investigator should ensure that all persons assisting with the study are adequately informed about the protocol, amendments, study treatments, as well as study-related duties and functions. The investigator should maintain a list of Sub-Investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

The investigator is responsible for keeping a record of all subjects who sign an informed consent document and are screened for entry into the study. Subjects who fail screening must have the reason(s) recorded in the subject's source documents.

The investigator, or a designated member of the investigator's staff, must be available during monitoring visits to review data, resolve queries and allow direct access to subject records (eg, medical records, office charts, hospital charts, and study-related charts) for source data verification. The investigator must ensure timely and accurate completion of CRFs and queries.

### **14.3. Subject Information and Informed Consent**

The investigator must obtain informed consent of a subject and/or a subject's legal representative prior to any study related procedures.

Documentation that informed consent occurred prior to the study subject's entry into the study and of the informed consent process should be recorded in the study subject's source documents including the date. The original informed consent document signed and dated by the study subject and by the person consenting the study subject prior to the study subject's entry into the study, must be maintained in the investigator's study files and a copy given to the study subject. In addition, if a protocol is amended and it impacts on the content of the informed consent, the informed consent document must be revised. Study subjects participating in the study when the amended protocol is implemented must be re-consented with the revised version of the informed consent document. The revised informed consent document signed and dated by the study subject and by the person consenting the study subject must be maintained in the investigator's study files and a copy given to the study subject.

#### **14.4. Confidentiality**

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the investigator to permit Celgene's representatives and, when necessary, representatives from 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 signed informed consent document, it is the responsibility of the investigator to obtain such permission in writing from the appropriate individual.

#### **14.5. Protocol Amendments**

Any amendment to this protocol must be approved by the Celgene Clinical Research Physician/Medical Monitor. Amendments will be submitted to the IRB/EC for written approval. Written approval must be obtained before implementation of the amended version occurs. The written signed approval from the IRB/EC should specifically reference the investigator name, protocol number, study title and amendment number(s) that is applicable. Amendments that are administrative in nature do not require IRB/IEC approval but will be submitted to the IRB/IEC for information purposes.

#### **14.6. Institutional Review Board/Independent Ethics Committee Review and Approval**

Before the start of the study, the study protocol, informed consent document, and any other appropriate documents will be submitted to the IRB/EC with a cover letter or a form listing the documents submitted, their dates of issue, and the site (or region or area of jurisdiction, as applicable) for which approval is sought. If applicable, the documents will also be submitted to the authorities in accordance with local legal requirements.

The IP can only be supplied to an investigator by Celgene or its authorized representative after documentation of all ethical and legal requirements for starting the study has been received by Celgene or its authorized representative. This documentation must also include a list of the members of the IRB/EC and their occupation and qualifications. If the IRB/EC will not disclose the names, occupations and qualifications of the committee members, it should be asked to issue a statement confirming that the composition of the committee is in accordance with GCP. For example, the IRB General Assurance Number may be accepted as a substitute for this list. Formal approval by the IRB/EC should mention the protocol title, number, amendment number (if applicable), study site (or region or area of jurisdiction, as applicable), and any other documents reviewed. It must mention the date on which the decision was made and must be officially signed by a committee member. Before the first subject is enrolled in the study, all ethical and legal requirements must be met.

The IRB/EC and, if applicable, the authorities, must be informed of all subsequent protocol amendments in accordance with local legal requirements. Amendments must be evaluated to determine whether formal approval must be sought and whether the informed consent document should also be revised.

The investigator must keep a record of all communication with the IRB/EC and, if applicable, between a Coordinating investigator and the IRB/EC. This statement also applies to any communication between the investigator (or Coordinating investigator, if applicable) and regulatory authorities.

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

#### **14.7. Ongoing Information for Institutional Review Board / Ethics Committee**

If required by legislation or the IRB/EC, the investigator must submit to the IRB/EC:

- Information on serious or unexpected adverse events as soon as possible;
- Periodic reports on the progress of the study;
- Deviations from the protocol or anything that may involve added risk to subjects.

#### **14.8. Closure of the Study**

Celgene reserves the right to terminate this study at any time for reasonable medical or administrative reasons. Any premature discontinuation will be appropriately documented according to local requirements (eg, IRB/EC, regulatory authorities).

In addition, the investigator or Celgene has the right to discontinue a single site at any time during the study for medical or administrative reasons such as:

- Unsatisfactory enrollment;
- GCP noncompliance;
- Inaccurate or incomplete data collection;
- Falsification of records;
- Failure to adhere to the study protocol.

## **15. DATA HANDLING AND RECORDKEEPING**

### **15.1. Data/Documents**

The investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the investigational product are complete, accurate, filed and retained. Examples of source documents include: hospital records; clinic and office charts; laboratory notes; memoranda; subject's diaries or evaluation checklists; dispensing records; recorded data from automated instruments; copies or transcriptions certified after verification as being accurate copies; microfiche; x-ray film and reports; and records kept at the pharmacy, and the laboratories, as well as copies of CRFs or CD-ROM.

### **15.2. Data Management**

Data will be collected via electronic CRF (eCRFs). This data will be electronically verified through use of programmed edit checks specified by the clinical team. Discrepancies in the data will be brought to the attention of the clinical team, and investigational site personnel, if necessary. Resolutions to these issues will be reflected in the database. An audit trail within the system will track all changes made to the data.

### **15.3. Record Retention**

Essential documents must be retained by the investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region, or at least 2 years have elapsed since the formal discontinuation of clinical development of the IP. The investigator must retain these documents for the time period described above or according to local laws or requirements, whichever is longer. Essential documents include, but are not limited to, the following:

- Signed informed consent documents for all subjects;
- Subject identification code list, screening log (if applicable), and enrollment log;
- Record of all communications between the investigator and the IRB/EC;
- Composition of the IRB/EC;
- Record of all communications between the investigator, Celgene, and their authorized representative(s);
- List of Sub-investigators and other appropriately qualified persons to whom the investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

- All other documents as listed in Section 8 of the ICH consolidated guideline on GCP (Essential Documents for the Conduct of a Clinical Trial).

The investigator must notify Celgene if he/she wishes to assign the essential documents to someone else, remove them to another location or is unable to retain them for a specified period. The investigator must obtain approval in writing from Celgene prior to destruction of any records. If the investigator is unable to meet this obligation, the investigator must ask Celgene for permission to make alternative arrangements. Details of these arrangements should be documented.

All study documents should be made available if required by relevant health authorities. Investigator/Institution should take measures to prevent accidental or premature destruction of these documents.

#### **15.4. Product Quality Complaint**

A Product Quality Complaint (PQC) is any written, electronic, or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, purity, or performance of any drug product manufactured by or on behalf of Celgene Corporation after it is released for distribution. PQCs may reduce the usability of the product for its intended function or affect performance of the product and therefore pose a significant risk to the subject. Examples of PQCs include (but are not limited to): mixed product, mislabeling, lack of effect, seal/packaging breach, product missing/short/overage, contamination, suspected falsified, tampered, diverted or stolen material, and general product/packaging damage. If you become aware of a suspected PQC, you are obligated to report the issue immediately. You can do so by emailing [customercomplaints@celgene.com](mailto:customercomplaints@celgene.com) or by contacting the Celgene Customer Care Center (1-888-423-5436).

## **16. QUALITY CONTROL AND QUALITY ASSURANCE**

All aspects of the study will be carefully monitored by Celgene or its authorized representative for compliance with applicable government regulations with respect to current GCP and standard operating procedures.

### **16.1. Study Monitoring and Source Data Verification**

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. Before the study is initiated at a site visit or at an Investigator meeting, all aspects of the study are reviewed with the investigator and the staff. Prior to enrolling subjects into the study, a Celgene representative will review the protocol, CRFs, procedures for obtaining informed consent, record keeping, and reporting of AEs/SAEs with the investigator. Monitoring will include on-site visits with the investigator and his/her staff as well as any appropriate communications by mail, email, fax, or telephone. At each monitoring visit, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative for accuracy, adherence to the protocol and Good Clinical Practice.

Accuracy will be checked by performing source data verification that is a direct comparison of the entries made onto the CRFs against the appropriate source documentation. Any resulting discrepancies will be reviewed with the investigator and/or his/her staff. Any necessary corrections will be made directly to the CRFs or via queries by the investigator and/or his/her staff. Monitoring procedures require that informed consents, adherence to inclusion/exclusion criteria and documentation of SAEs and their proper recording be verified. Additional monitoring activities may be outlined in a study-specific monitoring plan.

### **16.2. Audits and Inspections**

In addition to the routine monitoring procedures, a Good Clinical Practice Quality Assurance unit exists within Celgene. Representatives of this unit will conduct audits of clinical research activities in accordance with Celgene SOPs to evaluate compliance with Good Clinical Practice guidelines and regulations.

The investigator is required to permit direct access to the facilities where the study took place, source documents, CRFs and applicable supporting records of study subject participation for audits and inspections by IRB/IECs, regulatory authorities (eg, FDA, EMA, Health Canada, Pharmaceuticals and Medical Devices Agency) and company authorized representatives. The investigator should make every effort to be available for the audits and/or inspections. If the investigator is contacted by any regulatory authority regarding an inspection, he/she should contact Celgene immediately.

## **17. PUBLICATIONS**

The results of this study may be published in a medical publication, journal, or may be used for teaching purposes. Additionally, this study and its results may be submitted for inclusion in all appropriate health authority study registries, as well as publication on health authority study registry websites, as required by local health authority regulations. Selection of first authorship will be based on several considerations, including, but not limited to study participation, contribution to the protocol development, and analysis and input into the manuscript, related abstracts, and presentations in a study.

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## 19. APPENDICES

### Appendix A: Venous Thromboembolism (VTE) Algorithms

#### VTE Diagnostic Procedure

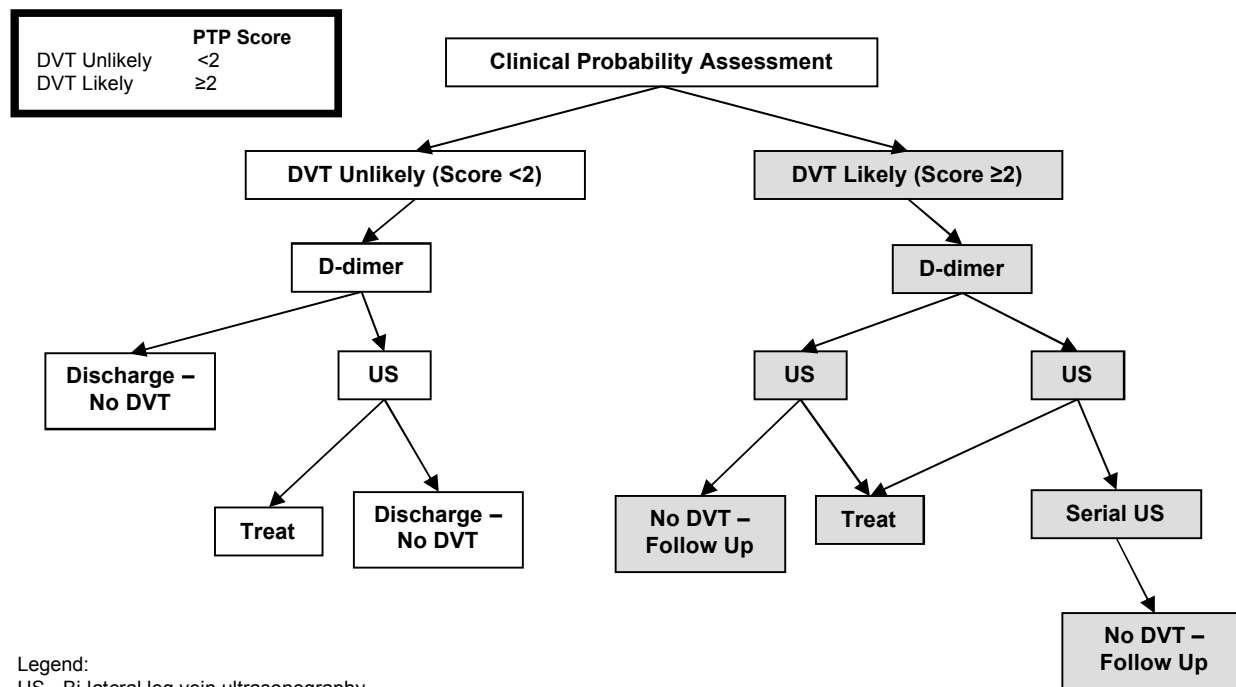
1. Refer to the DVT Pre-Test Probability Score Table. Add up the score and determine the patient's pre-test probability for DVT.
2. Refer to the DVT Diagnostic Algorithm. According to the pre-test probability follow the relevant diagnostic algorithm.

**Table 8: Wells Deep Vein Thrombosis (DVT) Pre-test Probability (PTP) Score**

Clinical Characteristic	Score
Active cancer (treatment ongoing or within previous 6 months or palliative)	1
Paralysis, paresis, or recent plaster immobilization of the lower extremities	1
Recently bedridden for 3 days or more or major surgery within the previous 12 weeks requiring general or regional anesthesia	1
Localized tenderness along the distribution of the deep venous system	1
Entire leg swollen	1
Calf swelling 3 cm > asymptomatic side (measured 10 cm below tibial tuberosity)	1
Pitting edema confined to the symptomatic leg	1
Collateral superficial veins (nonvaricose)	1
Previously documented deep-vein thrombosis	1
Alternative diagnosis as likely or greater than that of DVT	-2

Source: [Wells, 2003](#).

## Appendix A: Venous Thromboembolism (VTE) Algorithms (Continued)



Adapted from 6B6 D-Dimer™ The Essential Element Wall Chart

## Appendix A: Venous Thromboembolism (VTE) Algorithms (Continued)

### PE Diagnostic Procedure

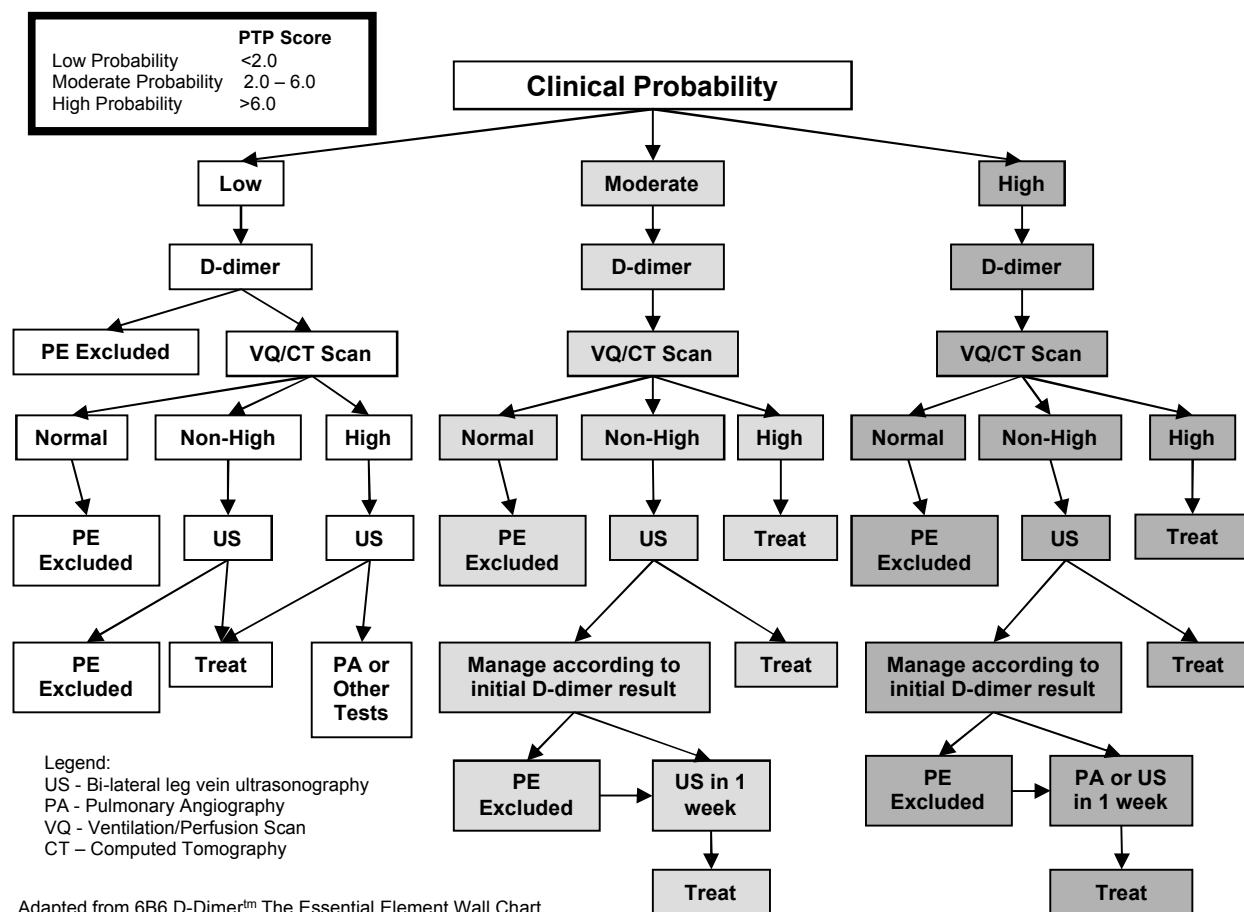
1. Refer to the PE Pre-Test Probability Score Table. Add up the score and determine the patient's pre-test probability for PE.
2. Refer to the PE Diagnostic Algorithm. According to the pre-test probability follow the relevant diagnostic algorithm.

**Table 9: Wells Pulmonary Embolism Pre-test Probability (PTP) Score**

Clinical Characteristic	Score
Clinical signs and symptoms of DVT (minimum of leg swelling and pain with palpation of the deep veins)	3.0
An alternative diagnosis is less likely than PE	3.0
Heart rate greater than 100 beats/min	1.5
Immobilization or surgery in the previous 4 weeks	1.5
Previous DVT/PE	1.5
Hemoptysis	1.0
Malignancy (at treatment, treated in the last 6 months or palliative)	1.0

Source: [Wells, 2000](#).

## Appendix A: Venous Thromboembolism (VTE) Algorithms (Continued)



## Appendix B: International Myeloma Working Group Response Criteria

**Table 10: International Myeloma Working Group Response Criteria**

Response Category	Response Criteria <sup>a</sup>
<b>CR<sup>b</sup></b>	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and $\leq 5\%$ plasma cells in bone marrow <sup>c</sup>
<b>VGPR</b>	Serum and urine M-protein detectable by immunofixation but not on electrophoresis or 90% or greater reduction in serum M-protein plus urine M-protein level $< 100$ mg per 24 hours
<b>PR</b>	<p><math>\geq 50\%</math> reduction of serum M-Protein and reduction in 24-hour urinary M-protein by <math>\geq 90\%</math> or to <math>&lt; 200</math> mg per 24 hours</p> <p>If the serum and urine M-protein are unmeasurable<sup>d</sup> a <math>\geq 50\%</math> decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria</p> <p>If serum and urine M-protein are unmeasurable, and the serum free light assay is also unmeasurable, <math>\geq 50\%</math> reduction in plasma cells is required in place of M-protein provided baseline bone marrow plasma cell percentage was <math>\geq 30\%</math></p> <p>In addition to the above, if present at baseline a <math>\geq 50\%</math> reduction in the size of soft tissue plasmacytomas is also required</p>
<b>MR</b>	<p><math>\geq 25\%</math> but <math>&lt; 49\%</math> reduction of serum M-Protein and reduction in 24-hour urinary M-protein by 50-89%, which still exceeds 200 mg per 24 hours</p> <p>In addition to the above criteria, if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required</p> <p>No increase in the size or number of lytic bone lesions (development of compression fracture does not exclude response)</p>
<b>SD<sup>e</sup></b>	Not meeting criteria for CR, VGPR, PR, or progressive disease

<sup>a</sup> All response categories require 2 consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response criteria.

<sup>b</sup> Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPEP) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This can lead to false positive SPEP and IFE assay results for subjects with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria. For subjects with daratumumab interference on serum immunofixation (IFE), the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test will be used to distinguish a positive SPEP/IFE due to the presence of daratumumab versus the presence of underlying (endogenous) monoclonal protein. . Subjects that meet all other IMWG criteria for CR, and whose positive IFE is confirmed to be daratumumab, will be considered complete responders. For subjects with light chain multiple myeloma, both serum and urine immunofixation test and serum free light chain assay will be performed routinely. As daratumumab is a monoclonal IgG antibody, additional serum samples may be utilized to monitor for potential daratumumab interference with the IFE.

<sup>c</sup> Confirmation with repeat biopsy not necessary.

<sup>d</sup> Applicable only to subjects who have 'measurable' disease defined by at least 1 of the following 3 measurements: Serum M-protein  $\geq 0.5$  g/dL, Urine M-protein  $\geq 200$  mg/24 hour, Serum FLC assay involved FLC level  $\geq 10$  mg/dL provided serum FLC ration is abnormal.

<sup>e</sup> Not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates.

## Appendix B: International Myeloma Working Group Response Criteria (Continued)

**Table 11: International Myeloma Working Group Relapse Criteria**

Relapse Category <sup>a</sup>	Relapse Criteria
<b>Progressive Disease</b>	<p><b>Requires only one of the following:</b></p> <p>Increase of <math>\geq 25\%</math> from nadir in:</p> <p>Serum M-component and/or (the absolute increase must be <math>\geq 0.5</math> g/dL)<sup>b</sup></p> <p>Urine M-component and/or (the absolute increase must be <math>\geq 200</math> mg/24 hours)</p> <p>In subjects without measurable serum and urine M-protein levels the difference between involved and uninvolved FLC levels, the absolute increase must be <math>&gt; 100</math> mg/dL.</p> <p>Bone marrow plasma cell percentage, the absolute % must be <math>\geq 10\%</math><sup>c</sup></p> <p>Definite development of new bone lesions or soft tissue plasmacytomas increase in the size of existing bone lesions or soft tissue plasmacytomas.</p> <p>Development of hypercalcemia (corrected serum calcium <math>&gt; 11.5</math> mg/dL or 2.65 mmol/l) that can be attributed solely to the plasma cell proliferative disorder.</p>
<b>Clinical Relapse</b> (Not used for TTP or PFS)	<p><b>Clinical relapse<sup>b</sup> requires one or more of:</b></p> <p>Development of new soft tissue plasmacytoma or bone lesions</p> <p>Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion</p> <p>Hypercalcemia (<math>&gt; 11.5</math> mg/dL [2.65 mmol/l])</p> <p>Decrease in hemoglobin of <math>\geq 2</math> g/dL (1.25 mmol/l)</p> <p>Rise in serum creatinine by 2 mg/dL or more (177 <math>\mu</math>mol/l or more)</p>
<b>Relapse from CR<sup>d</sup></b>	<p><b>Any one or more of the following:</b></p> <p>Reappearance of serum or urine M-protein by immunofixation or electrophoresis</p> <p>Development of <math>\geq 5\%</math> plasma cells in the bone marrow<sup>c</sup></p> <p>Appearance of any other sign or progression (ie, new plasmacytoma, lytic bone lesion, or hypercalcaemia)</p>

<sup>a</sup> All relapse categories require 2 consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy.

<sup>b</sup> For progressive disease, serum M-component increases of  $\geq 1$  g/dl are sufficient to define relapse if starting M-component is  $\geq 5$  g/dL.

<sup>c</sup> Relapse from CR has the 5% cutoff versus 10% for other categories or relapse.

<sup>d</sup> To only be used if the endpoint studied is disease free survival. For purposes of calculating time to progression and progression-free survival, CR subjects should also be evaluated using criteria listed above for progressive disease.

Daratumumab is a human IgG kappa monoclonal antibody that can be detected on both, the serum protein electrophoresis (SPEP) and immunofixation (IFE) assays used for the clinical monitoring of endogenous M-protein. This can lead to false positive SPEP and IFE assay results for subjects with IgG kappa myeloma protein impacting initial assessment of complete responses by International Myeloma Working Group (IMWG) criteria.

For subjects with daratumumab interference on serum immunofixation (IFE), the SEBIA Hydrashift 2/4 Daratumumab IFE Interference test will be used to distinguish a positive SPEP/IFE due to the presence of daratumumab versus the presence of underlying (endogenous) monoclonal protein.. Subjects that meet all other IMWG criteria (refer to [Table 10](#)) for CR, and whose positive IFE is confirmed to be daratumumab, will be considered complete responders. For subjects with light chain multiple myeloma, both serum and urine immunofixation test and serum free light chain assay will be performed routinely. As daratumumab is a monoclonal IgG antibody, additional serum samples may be utilized to monitor for potential daratumumab interference with the IFE.

## **Appendix C: Skeletal (Bone) Survey Films**

The following are the minimum plain radiological films required for the skeletal (bone) survey:

- Lateral skull
- AP and lateral cervical spine
- AP and lateral thoracic spine
- AP and lateral lumbar spine
- PA chest
- AP pelvis
- AP upper extremities, shoulder to elbow
- AP lower extremities, hip to knee

Other radiological films may be necessary to view symptomatic areas or known pre-existing lesions in skeletal regions not included in the films above.

## **Appendix D: Pomalidomide Pregnancy Risk Minimization Plan for Celgene Clinical Trials**

The Pomalidomide Pregnancy Risk Minimization Plan is a standalone document.

## Appendix E: ECOG Performance Status Scale

**Table 12: ECOG Performance Status Scale**

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

## Appendix F: Estimation of Renal Function

The primary assessment for renal function will be performed using the by Cockcroft-Gault formula for estimation of creatinine clearance (CrCl):  $\text{CrCl (mL/min)} = (140 - \text{age}) (\text{weight [kg]}) / 72 (\text{serum creatinine [mg/dL]})$ ; for females, the formula is multiplied by 0.85 ([Cockcroft, 1976](#); [Luke, 1990](#)).

Creatinine clearance also need be determined based on a 24-hour urine collection at Screening visit; for all other visits, a 24-hour urine collection may also be used as the primary assessment for renal function at the investigator's discretion.

## **Appendix G: QT Drugs by Risk Group**

To access a current list of QT-prolonging drugs grouped by risk of torsades, possible risk of torsades, and conditional risk of torsades visit <http://www.qtdrugs.org/>.

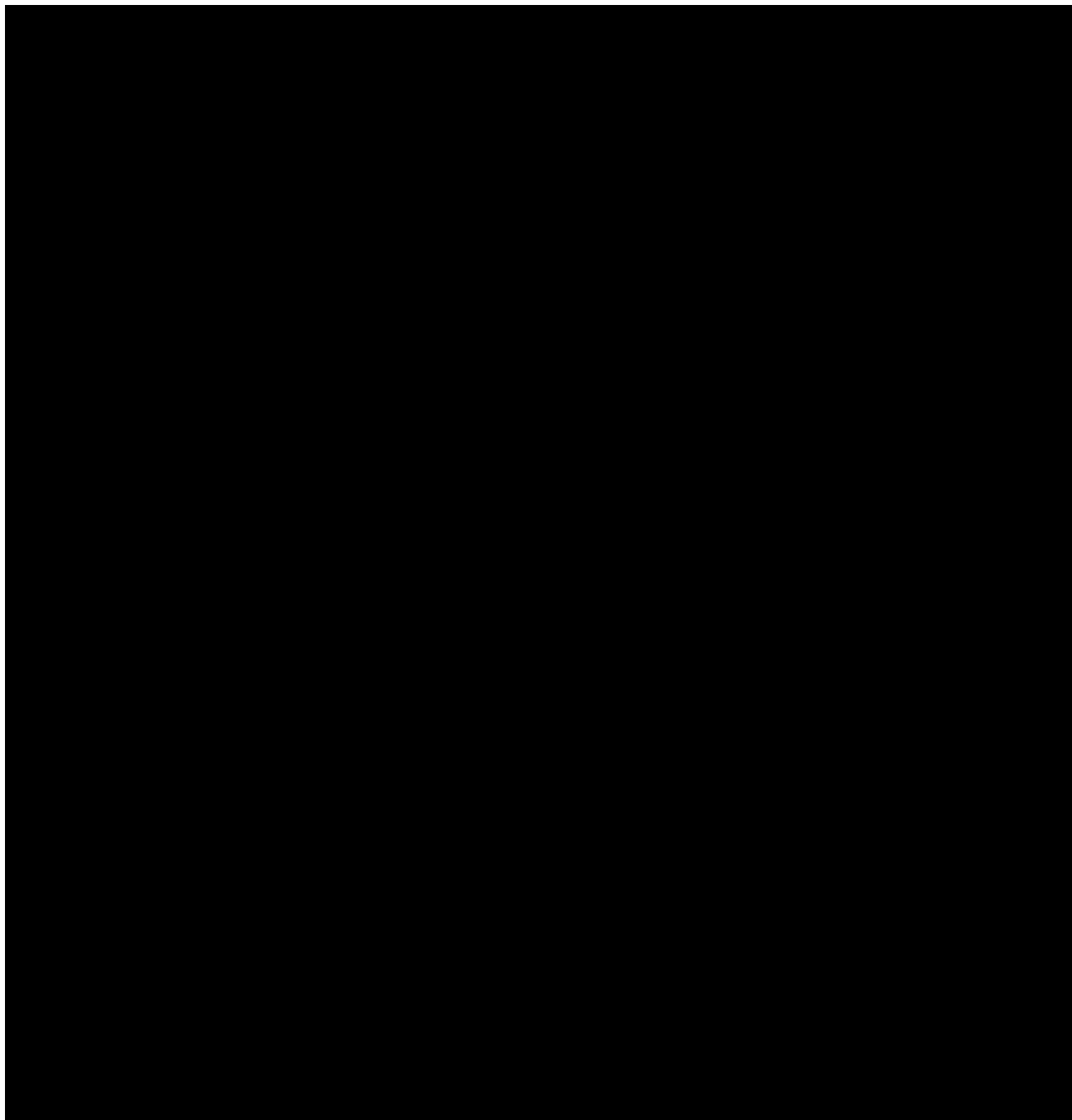
## Appendix H: Staging Systems for Multiple Myeloma

**Table 13: Staging Systems for Multiple Myeloma**

Stage	Durie-Salmon Criteria	ISS Criteria
I	<i>All of the following:</i> Hemoglobin value > 10 g/dL Serum calcium value normal or < 12 mg/dL Bone x-ray, normal bone structure (scale 0), or solitary bone plasmacytoma only Low M-component production rates IgG value < 5 mg/dL; IgA value < 3 mg/dL Urine light chain M-component on electrophoresis < 4 g/24 h	Serum beta-2 microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Neither Stage I nor Stage III	Neither Stage I nor Stage III
III	<i>One or more of the following:</i> Hemoglobin value < 8.5 g/dL Serum calcium value normal or > 12 mg/dL Advanced lytic bone lesions (scale 3) High M-component production rates IgG value > 7 mg/dL; IgA value > 5 mg/dL Urine light chain M-component on electrophoresis > 12 g/24 h	Serum beta-2 microglobulin ≥ 5.5 mg/L
Subclassification Criteria A Normal renal function (serum creatinine value < 2.0 mg/dL) B Abnormal renal function (serum creatinine value ≥ 2.0 mg/dL)		Not applicable

Source: [Durie, 1975](#); [Greipp, 2005](#).

## Appendix I: EQ-5D



## Appendix J: List of Abbreviations

**Table 14: List of Abbreviations**

Abbreviation	Definition
AE	Adverse Event
ALC	Absolute Lymphocyte Count
ALT	Alanine Aminotransferase
ANC	Absolute Neutrophil Count
ASCO	American Society of Clinical Oncologists
ASCT	Autologous Stem-cell Transplantation
AST	Aspartate Aminotransferase
BTZ	Bortezomib
CR	Complete Response
CrCl	Creatinine Clearance
CT	Computed Tomography
DARA	Daratumumab
dex	Dexamethasone
DLT	Dose-limiting Toxicity
DoR	Duration of Response
DTT	Dithiothreitol
DVT	Deep Vein Thrombosis
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EE	Efficacy Evaluable
EMP	Extramedullary Plasmacytoma
EU	European Union
FCBP	Female of Child Bearing Potential
FDA	Food and Drug Administration
FISH	Fluorescence In Situ Hybridization
FLC	Free Light-Chain
GCP	Good Clinical Practice
GCSF	Granulocyte Colony-Stimulating Factor

## Appendix J: List of Abbreviations (Continued)

**Table 14: List of Abbreviations (Continued)**

Abbreviation	Definition
GGT	Gamma Glutamyl Transferase
HDAC	Histone deacetylase
HiDex	High-dose Dexamethasone
HIV	Human Immunodeficiency Virus
IAT	Indirect Antiglobulin Test (also known as indirect Coombs test)
IB	Investigator's Brochure
IC <sub>50</sub>	Half Maximal Inhibitory Concentration
ICD	Informed Consent Document
ICH	International Conference on Harmonisation
IFE	Immunofixation
IFM	Intergroupe Francais du Myelome
IMiDs	Immunomodulating drugs
IMWG	International Myeloma Working Group
IP	Investigational Product
IRB	Institutional Review Board
IRR	Infusion Related Reaction
ITT	Intent-to-treat
IVRS/IWRS	Interactive Voice Response System/Web Response System
LD-dex	Low-dose Dexamethasone
LEN	Lenalidomide
LPS	Lipopolysaccharide
MedDRA	Medical Dictionary for Regulatory Activities
mIMWG	Modified International Myeloma Working Group
MM	Multiple Myeloma
MR	Minor Response
MRD	Minimal Residual Disease
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI-CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

## Appendix J: List of Abbreviations (Continued)

**Table 14: List of Abbreviations (Continued)**

Abbreviation	Definition
ORR	Overall Response Rate
OS	Overall Survival
PD	Progressive Disease
PE	Pulmonary Embolism
PFS	Progression-Free Survival
PI	Proteasome Inhibitors
POM	Pomalidomide
PR	Partial Response
QoL	Quality of Life
QTc	QT Corrected
RBC	Red Blood Cell
SAE	Serious Adverse Event
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
SPEP	Serum Protein Electrophoresis
SPM	Second Primary Malignancy
SUSAR	Suspected Unexpected Serious Adverse Reaction
TEAE	Treatment-Emergent Adverse Event
TNM	Tumor, Nodes, Metastasis
TNF	Tumor Necrosis Factor
TTP	Time to Progression
TTR	Time to Response
ULN	Upper Limit of Normal
UPEP	Urine Protein Electrophoresis
US	United States
VGPR	Very Good Partial Response
VTE	Venous Thromboembolism
WBC	White Blood Cell



## **Celgene Signing Page**

**This is a representation of an electronic record that was signed electronically in Livelink.**

**This page is the manifestation of the electronic signature(s) used in compliance with  
the organizations electronic signature policies and procedures.**

UserName: [REDACTED]

Title: [REDACTED]

Date: Friday, 12 April 2019, 12:04 AM Eastern Daylight Time

Meaning: Approved, no changes necessary.

=====

## 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Exploratory Biomarker Assessments (Protocol Summary, Section 5 and 6)**

Deleted the collection of bone marrow clot sample from subjects in Cohort C.

- **Exclusion Criteria (Section 7.3)**

Added exclusion criterion number 13 to clarify the requirements for subjects with known seropositive for hepatitis B or C virus.

Removed social condition from exclusion criterion number 11.

- **Follow Up Phase and Length of Study in the Protocol Summary, Study Design (Section 4.1), Study Duration (Section 4.3), Procedures (Section 6, Secondary Primary Malignancies, Overall Survival, Subsequent Anti-MM Therapies), Seriousness (Section 11.2.1), Reporting of Serious Adverse Events (Section 11.5), Discontinuations (Section 12), Overall Study Design (Figure 1), and Table of Events (Section 5, Table 1)**

Clarified the follow up period for each cohort of up to 5 years after the last subject is enrolled for each respective cohort.

- **Description of Investigational Product(s) (Section 8.1)**

Clarified the investigational product supplied to Cohort C. For Cohort C, 400 mg/20 mL vials for intravenous administration will be supplied.

## 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- **Introduction (Section 1.1)**

In the present study, cancer statistics were from 2010. The statistics were updated, and Japan cancer statistics were included. In addition, new drug classes were included to reflect current guidelines.

- **Treatment Options for Relapsed or Refractory Multiple Myeloma (Section 1.1)**

New drug approvals and combination regimens were included to reflect current practice.

- **Pomalidomide (CC-4047) (Section 1.2)**

Data on Japanese study was added to reflect the data available in clinical experience in this patient population.

- **Daratumumab (Section 1.3)**

Updated Daratumumab studies were added, including recent combination approval therapies.

- **Addition of Cohort C for Japan (Protocol Summary, Sections 2.1, 4.1, 5, 6, 7.1, 7.2, 7.3, 8.1, 8.2, 8.7, 10.1, 10.3, 10.6, 10.8, 11.4.1, 12)**

The primary purpose of this protocol amendment is the addition of Cohort C to provide efficacy and safety data for Japanese patients. Lenalidomide is being utilized frequently as doublet- or triplet-based induction therapy and/or maintenance therapy for newly diagnosed and early relapse patients. Multiple myeloma remains an incurable disease and when patients relapse or become refractory to lenalidomide, there is a limited number of treatment options. This represents a growing unmet need and pomalidomide has been exclusively studied in the lenalidomide exposed patient population and has shown statistically significant improvement in progression free survival. There is growing data for the combination therapy of pomalidomide and low-dose dexamethasone in combination with daratumumab. The number of Asian patients enrolled in previous studies is small. The additional Cohort C will address the need for clinical data for the previously lenalidomide-exposed Japanese patient.

- **Change to reflect the actual number of patients enrolled in Cohort A and Cohort B, (Sections 4.1, 4.3, 7.1, 10.3)**

In the present study, there is an approximate enrollment of 55 subjects for Cohort A and an approximate enrollment of 100 subjects for Cohort B, for a total of 155 subjects. The numbers have been updated to reflect the number of enrolled subjects for Cohort A was 56 and for Cohort B was 112. The number of patients to be approximately enrolled in the study will be 188.

▪ **Study Design Rationale (Section 4.2)**

Data for a Japanese patient study was added to explain the need for the creation of Cohort C to obtain clinical data on Japanese patients with the combination of POM-DEX-DARA.

▪ **Description of Investigational Product(s) (Section 8.1)**

In the present study, dexamethasone is commercially available in the US and Canada. Celgene Corporation will supply oral dexamethasone for administration as an Investigational Product for Cohort C.

▪ **Treatment Administration and Schedule (Section 8.2)**

Modification of Dosing Cycle (Table 2)

In addition, this amendment changes the ANC count to  $\geq 1000 \mu\text{L}$  to restart dosing days of oral Pomalidomide. This change will allow Cohort C sites to remain consistent with the country Pomalidomide label.

▪ **Statistical Analysis (Section 10.3)**

- Adjusted to reflect the new plan for Cohort C of collected data of 17 subjects enrolled in the study. Below are the major changes:
  - Overview and population updatedEfficacy analysis updated to reflect overall response rate analysis

▪ **Expedited Reporting of Adverse Events (Section 11.6)**

- Language was added to reflect inclusion of reporting for Cohort C and local Japan requirements, Celgene KK shall notify the Heads of Institutes in addition to investigators for suspected unexpected serious adverse events.
- Other important safety information and reports according to local regulations

▪ **Product Quality Complaint (Section 15.4)**

- This section was added to define product quality complaint and contact information is also included on reporting of any issues relating to product quality.

▪ **Overall Study Design (Figure 1)**

- Cohort C added to the schema box

▪ **The amendment also includes several other minor clarifications and corrections:**

- Additional references were added as appropriate

- Change of Medical Monitor
- Update of Figure 1
- Section 6
  - Update of blood typing
  - Clarification of samples collected for Biomarkers
- Update for Cohort C subjects enrolling (Inclusion criteria 7.2)
- Exclusion criteria 7.3
  - Changes of severe renal impairment and update of drug sensitivity
  - Clarification of investigation drug for multiple myeloma, prior history of malignancies and capacity to participate
- Update of Treatment Administration and Schedule (Section 8.2)
- Clarification of gamma-glutamyltransferase elevation (Section 8.3)

## 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

### **Addition of Cohort to Study Pomalidomide+Daratumumab+Dexamethasone**

The primary purpose of this protocol amendment is to add a Cohort to the trial consisting of approximately 100 patients where patients will receive pomalidomide and daratumumab and dexamethasone (Pom+Dara+Dex). This is due to a change in the treatment landscape for multiple myeloma where daratumumab and other medications such as elotuzumab and ixazomib are now approved for treating multiple myeloma in various treatment settings. The standard of care for treating multiple myeloma in the 2<sup>nd</sup> and 3<sup>rd</sup> line setting now includes three-drug combination regimens vs two-drug combination regimens prior to the new agents being approved. Furthermore, the standard of care in the front line setting now includes three-drug combination regimens that include an immunomodulatory (IMiD) and a proteasome inhibitor (Durie, 2015). As a result of these recent changes in the standard of care, the enrollment of patients into the trial as currently designed (a two-drug combination regimen) will be increasingly difficult.

As part of the planned interim analysis of the previous version of the protocol (Protocol Amendment #2, 02 April 2014), it was demonstrated that the pomalidomide plus dexamethasone (Pom+LD-Dex) regimen following lenalidomide base regimen in the second line setting had an overall response rate of 29.6% and a clinical benefit rate of 37%. This is consistent with previously reported data in a similar patient population (San Miguel, 2015). This response rate may be improved upon by adding additional therapy to the (Pom+LD-Dex) the patient population being studied.

Recently, Chari et al (Chari, 2015) reported the preliminary results of an open label, multi-center, phase 1b clinical trial which assessed the combination of Pom+Dara+LD-Dex in 98 patients with relapsed or refractory multiple myeloma. The combination demonstrated an overall response rate (ORR) of 71% in a heavily pretreated patient population (median 4 prior lines of therapy). This is an improvement of the ORR of 29.2% in the daratumumab package insert. While this patient population was described as having failed multiple treatments it is not clear what treatment the patients received immediately prior to the combination studied in this trial.

External experts have stated that studies leading to the approval of the new medications in the relapsed and refractory patient setting have left many questions unanswered about how to sequence and combine the medications in order to achieve the best outcomes for patients. In particular many of the registration studies conducted with the new medications did not include many patients who were relapsed or refractory to lenalidomide treatment (Lonial, 2015; Moreau 2015).

The study team feels that outcomes of patients relapsed or refractory to lenalidomide-based regimens can be improved by adding a third agent to the Pom+Dex regimen. Given the data presented by Chari, et al (Chari, 2015), the team feels daratumumab may be the best combination agent for this regimen. Expanding the body of evidence using Pom+Dara+Dex in patients

relapsed or refractory to a lenalidomide-based regimen in the 1<sup>st</sup> or 2<sup>nd</sup> line setting will answer critical questions regarding the disease outcomes of sequencing pomalidomide-based regimens after lenalidomide-based regimens. Furthermore, as Chari et al reported an improved ORR in a more heavily pre-treated population, it is possible that this trial may show deeper and more durable responses as well as a higher ORR.

It is important to note that the treatment used in this the clinical trial remains experimental as it is not an approved regimen. As a result, data will continue to be collected on subjects during the trial in much the same manner as per the previous version of the protocol (Protocol Amendment #2 02 April 2014).

#### **Revised Sections:**

- The following sections have been impacted by this change:
- Title Page; Protocol Summary; Sections 1.1, 1.3, 2, 3.2, 3.3, 4.1, 4.2, 5, 6, 7, 8 (except 8.4), 9.1, 9.3, 10.1, 10.3, 10.6, 10.7, 10.8, 11.1, 11.2.1, 11.2.3, 11.2.5, 11.3, 11.4, 11.5, 11.6, 18, Appendix B, Appendix I, Appendix J

#### **Modification of Inclusion/Exclusion Criteria**

One goal of this protocol amendment is to gain experience with the pomalidomide+daratumumab+dexamethasone regimen in subjects who are less heavily pre-treated than has been previously reported by Chari, et al (Chari, 2015). As a result, a modification to the criteria for number of prior lines of therapy has been modified. The modification is as follows:

For the inclusion criteria:

- Subjects must have received 2 prior treatment lines of anti-myeloma therapy. (previous version)  
Modified to:
- Subjects enrolling in Cohort A (Pom+LD-Dex) must have received 2 prior treatment lines of anti-myeloma therapy. Subjects enrolling in Cohort B (Pom+Dara+LD-Dex) must have received 1 or 2 prior treatment lines of anti-myeloma therapy.

#### **Revised Sections:**

- Protocol Summary
- Section 4.1 including Figure 1.
- Section 7

#### **Modification of Sample Size for Original Study Cohort (Pomalidomide+Dexamethasone)**

In the previous version of the protocol (Protocol Amendment #2, 02 April 2014) the sample size for the pomalidomide plus dexamethasone patient population was calculated to be 85 patients. As per the interim analysis conducted on the initial 40% of patients enrolled, the probability of the trial achieving success of the primary endpoint of the trial for this patient population is high.

As enrollment has been impacted by the change in landscape the statistical assumptions leading to the sample size for the pomalidomide plus dexamethasone population have been adjusted to maintain the possibility of analyzing the patient population for all endpoints with only 55 eligible patients being enrolled in this portion of the trial. Reducing the cohort A sample size will curtail the power in assessing the original hypothesis to 71%. The overall response rate can be estimated within +/- 12% with a 95% confidence interval with 55 subjects.

#### **Revised Sections:**

- Protocol Summary;
- Section 10.1
- Section 10.3
- Section 10.6
- Section 10.7
- Section 10.8

#### **Other changes to the protocol**

These major changes as well as minor changes in language have been made throughout multiple sections of the protocol.

#### **References**

Chari A, Lonial S, Suvannasankha A, Fay J, Arnulf B, Ifthikharuddin JJ, et al. Open-Label, Multicenter, Phase 1b Study of Daratumumab in Combination with Pomalidomide and Dexamethasone in Patients with  $\geq 2$  Lines of Prior Therapy and Relapsed or Relapsed and Refractory Multiple Myeloma. [abstract] ASH 2015, abstract 508.

Durie B, Hoering A, Rajukumar SV, Abidi MH, Epstein J, Kahanic SP, et al. Bortezomib, Lenalidomide and Dexamethasone Vs. Lenalidomide and Dexamethasone in Patients (Pts) with Previously Untreated Multiple Myeloma without an Intent for Immediate Autologous Stem Cell Transplant (ASCT): Results of the Randomized Phase III Trial SWOG S0777. [abstract] ASH 2015, abstract 25.

Lonial S, Dimopoulos M, Palumbo A, White D, Grosicki S, Spicka I, et al. Elotuzumab Therapy for Relapsed or Refractory Multiple Myeloma. N Engl J Med 2015;373:621-31.

Moreau P, Masszi T, Grzasko N, Bhalis NJ, Hansson M, Pour L, et al. Ixazomib, an Investigational Oral Proteasome Inhibitor (PI), in Combination with Lenalidomide and Dexamethasone (IRd), Significantly Extends Progression-Free Survival (PFS) for Patients (Pts) with Relapsed and/or Refractory Multiple Myeloma (RRMM): The Phase 3 Tourmaline-MM1 Study (NCT01564537). [abstract] ASH 2015, abstract 727.

San Miguel JF, Weisel KC, Song KW, Delforge M, Karlin L, Goldschmidt H, et al. Impact of prior treatment and depth of response on survival in MM-003, a randomized phase 3 study comparing pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone in relapsed/refractory multiple myeloma. Haematologica 2015;100:1334-9.

## 1. JUSTIFICATION FOR AMENDMENT

This amendment is in response to feedback from study investigators and key opinion leaders on the current treatment paradigms and use of pomalidomide with low-dose dexamethasone. In order to expand our eligible patient population, and to be reflective of current practice, we are allowing subjects who have received any lenalidomide-based regimen to be used as the immediate prior anti-myeloma therapy. In addition, revisions to the dose modification guidelines have been made in order to be in accordance with the prescribing information and administrative changes to clarify the table of events.

Significant changes included in this amendment are summarized below:

- Section 7. STUDY POPULATION. Protocol is amended to expand the patient population to allow a lenalidomide-based regimen as the immediate prior line of therapy.

The amendment also includes other clarifications and corrections.

- Page 2. MEDICAL MONITOR / EMERGENCY CONTACT INFORMATION. Rosanna Ricafort, MD will replace Yasir Nagarwala, MD as the Medical Monitor.
- Section 5. TABLE OF EVENTS, Table 1 (page 28-31). Updated row on urinalysis and footnote “c” regarding second primary malignancies (SPM) to align with protocol-specified procedures.
- Section 8.2. Treatment Administration and Schedule. Table 2: Dose Modification Instructions for Pomalidomide, Neutropenia (page 42). Revised dose modification guidelines to be in accordance with prescribing information to allow physicians to follow CBCs weekly and re-initiate pomalidomide at the appropriate dose when the toxicity resolves.
- Section 8.2. Treatment Administration and Schedule. Table 2: Dose Modification Instructions for Pomalidomide, Thrombocytopenia (page 42). Revised dose modification guidelines to be in accordance with prescribing information allow physicians to follow CBCs weekly, and re-initiate pomalidomide, at the appropriate dose when the toxicity resolves.
- Section 8.2. Treatment Administration and Schedule. Table 2: Dose Modification Instructions for Pomalidomide, Other  $\geq$  Grade 3 Pom-related adverse events (page 42). Revised dose modification guidelines to be in accordance with prescribing information to allow physicians to restart treatment at modified dose upon resolution of toxicity to less than or equal to Grade 2.

## 1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

- Section 7. STUDY POPULATION. Protocol is amended to enroll subjects in North America which includes United States and Canada.

The amendment also includes other clarifications and corrections.

- Section 5. TABLE OF EVENTS Updated (page 28-31)
- Section 6. PROCEDURES, Study Entry, (page 32). Corrected sentence in second paragraph, first sentence. “...[Appendix H], medical history, ...”
- Section 6. PROCEDURES, Estimation of Renal Function, (page 34). Added “only” after Screening and deleted “...on Day 1 of every cycle, and at treatment discontinuation.”
- Section 6. PROCEDURES, Exploratory Biomarker Study, (page 37). Added to paragraph starting with “Whole blood sample...” “...at treatment discontinuation (disease progression)...”
- Section 10.6 Efficacy Analysis, Duration of Response (page 48). Added “...or until death from any cause.” to the end of the first sentence.
- Section 10.6 Efficacy Analysis, Time to Progression (page 48). Deleted “...or death from progressive disease.” from the end of the first sentence.
- Section 11.2.2 Severity/Intensity (page 53). Corrected version of CTCAE and added CTCAE link.