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MEDI4736-MM-005

MULTICENTER, SINGLE-ARM, PHASE 2 STUDY TO DETERMINE THE EFFICACY FOR THE COMBINATION OF DARATUMUMAB (DARA) PLUS DURVALUMAB (DURVA) (D^2) IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM) WHO HAVE PROGRESSED ON DARA WHILE ON A DARA-CONTAINING REGIMEN AS THE MOST RECENT MULTIPLE MYELOMA THERAPY. "FUSION MM-005"

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PROTOCOL SUMMARY

Study Title

MEDI4736-MM-005 (FUSION MM-005): A Multicenter, Single-arm, Phase 2 Study to Determine the Efficacy of the Combination of Daratumumab (DARA) Plus Durvalumab (DURVA) (D^2) in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM) who have Progressed on DARA While on a DARA-containing Regimen as the Most Recent MM Therapy.

Indication

Relapsed and refractory multiple myeloma (RRMM) after treatment with at least 3 prior anti-myeloma therapies, including a proteasome inhibitor (PI) and an immunomodulatory drug (IMiD®) or after development of double-refractoriness to a both a PI and an IMiD.

- *The most recent multiple myeloma (MM) treatment regimen should contain daratumumab (DARA) and subjects must have progressed on DARA while on this regimen.*
- *Induction, bone marrow transplant with or without maintenance therapy is considered one regimen*
- ***Refractory is defined** as disease that is nonresponsive on therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease while on therapy.*
- *For subjects who received more than 1 regimen containing a PI their disease must be refractory to the most recent PI containing regimen.*
- *For subjects who received more than 1 regimen containing a IMiD their disease must be refractory to the most recent IMiD containing regimen*

Objectives

Primary:

- To determine the efficacy of DARA plus durvalumab (DURVA) in subjects with RRMM who have progressed on DARA while on a DARA-containing regimen as the most recent MM treatment.

Secondary:

- Determine the safety of DARA plus DURVA in subjects with RRMM who have progressed on DARA while on a DARA-containing regimen as the most recent MM treatment.
- Further evaluate the efficacy of the combination of DARA plus DURVA in subjects with RRMM who have progressed on DARA while on a DARA-containing regimen as the most recent MM treatment. Key efficacy measures include time-to-response [TTR], duration of response [DOR], progression-free survival [PFS], and overall survival [OS].

- Evaluate the pharmacokinetics (PK) of DARA and DURVA in subjects with RRMM who have progressed on DARA while on a DARA-containing regimen as the most recent MM treatment.

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Study Design

This is a single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of the combination regimen of DARA plus DURVA (D^2) in subjects with relapsed and refractory multiple myeloma after failure of prior therapies containing a PI, immunomodulatory drug and DARA. The study will be conducted in 2 parts: Part 1 and Part 2. Part 1 has a 2-stage design while Part 2 consists of an expansion phase. Subjects will receive intravenous (IV) DARA at 16 mg/kg on the same dosing schedule (weekly [QW], every 2 weeks [Q2W], or every 4 weeks [Q4W] of each 28-day treatment cycle) received during their last prior therapy containing DARA at the time of DARA progression. Dosing schedules, for the administration of DARA, may be adjusted during the course of the study, as detailed in Section 7.2, provided that the subject has a response of stable disease (SD) or better. Subjects will also receive IV DURVA at 1500 mg on Day 2 (Cycle 1) and on Day 1 (Cycles $\geq$ 2) of each 28-day treatment cycle.

Part 1:

Stage 1

A cohort of 18 subjects will be enrolled to determine the safety and preliminary efficacy of DARA plus DURVA. Once 6 subjects have been enrolled in MEDI4736-MM-005 and completed the first treatment cycle in Stage 1 of this study, the enrollment continuity would depend on the availability of additional safety data from the ongoing Phase 2 study (MEDI4736-MM-003) of DARA and DURVA in previously DARA-naïve subjects.

- If MEDI4736-MM-003 safety data are available and the tolerability profile of DARA plus DURVA is determined to be adequate, then enrollment will continue as planned in Stage 1 of MEDI4736-MM-005.
- If safety data are not available in MEDI4736-MM-003, enrollment in MEDI4736-MM-005 will be paused for a review of the safety profile of DARA plus DURVA by

a Dose Review Team (DRT), using the data from the first 6 patients. See Section 3.1.1.1.1.

Once the 18 subjects have been enrolled in MEDI4736-MM-005 (end of Stage 1), an interim analysis for futility purpose will be conducted to determine if the study can proceed to Stage 2.

Stage 2

If 3 or more subjects achieved a response (partial response [PR] or better) out of the 18 subjects at the end of Stage 1, an additional 32 subjects will be enrolled to evaluate the safety and efficacy of DARA plus DURVA.

Part 2:

Expansion

Upon completion of Part 1, if there are at least 9 subjects who achieved a response (PR or better) out of a total of 50 subjects and it is determined by the Sponsor to further confirm the efficacy and safety of DARA plus DURVA, an additional 70 subjects may be enrolled.

An Independent Response Adjudication Committee (IRAC) will be set up for this trial to perform an independent assessment of the efficacy data. The IRAC will determine tumor response to therapy and to confirm the time of disease progression (PD) (if disease progressed) at scheduled or unscheduled visits for each subject.

The safety and efficacy of the study will be monitored by an independent Data Monitoring Committee (DMC) who are not involved in the trial conduct. The DMC will meet up and review study data at pre-specified intervals throughout the trial. At time of the interim analysis, the DMC will assess the study data for futility. In addition to the DMC review, safety data will be monitored by the Celgene Medical Monitor and Safety Physician on an ongoing basis throughout the study. Should a significant safety issue be identified, the DMC will be convened to make a recommendation as to the future conduct of the study.

The study will be conducted globally and in compliance with the International Council on Harmonisation (ICH) Good Clinical Practices (GCPs).

Study Population

The study population will include subjects with multiple myeloma who have received at least 3 prior lines of anti-myeloma regimens including a PI and an IMiD, or who are double-refractory to a PI and an IMiD. In addition, eligible subjects must have had progressive disease while on a DARA-containing regimen as the most recent MM therapy.

Approximately 120 subjects will be enrolled into this study.

- Part 1, Stage 1: ~18 subjects
- Part 1, Stage 2: ~32 subjects
- Part 2, Expansion: ~70 subjects

Length of Study

The study will consist of the following consecutive phases: Screening, Treatment, and Follow-up. The Screening Phase may not exceed a 28-day window prior to start of study treatment (Cycle 1 Day 1). Subjects may continue on study treatment until PD or unacceptable toxicity. All subjects will have an End of Treatment (EOT) visit within 7 days after discontinuation of all study treatment. Subjects are to return to the study site 28 (+3) days after the EOT visit and 90 (+3) days after the last dose of DURVA or DARA, whichever is later, for safety follow-up visits.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, 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, whichever is the later date.

Study Treatments

All subjects will receive:

- IV DARA at 16 mg/kg starting at the same dosing schedule as their immediate prior DARA regimen. (QW, Q2W, or Q4W of each 28-day cycle). The dosing schedule may be adjusted during the course of the study as outlined in Section 7.2.
- IV DURVA at 1500 mg on Cycle 1 Day 2/28-day cycle then ≥Cycle 2 on Day 1/28-day cycle

Overview of Key Efficacy Assessments

- Myeloma paraprotein
- Serum immunoglobulins
- Serum free light chains
- Corrected serum calcium
- Percent of plasma cells in the bone marrow
- Radiographic assessments of lytic bone lesions
- Extramedullary plasmacytoma (EMP) assessments
- Response per the International Myeloma Working Group (IMWG) criteria

Overview of Key Safety Assessments

- Complete physical examination including vital signs
- Clinical laboratory evaluations
- Pregnancy testing (FCBP only; see
- Electrocardiogram (ECG)
- Concomitant medications and procedures
- Adverse events (AEs)

Overview of Key Pharmacokinetic Assessments

- Serum samples will be collected to assay plasma concentrations of DURVA and DARA

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Other

- CCI
- Eastern Cooperative Oncology Group (ECOG) Performance Status

Statistical Methods

The study will be conducted in 2 parts.

In Part 1, a 2-stage design is used with 1 interim analysis for futility at the end of Stage 1.

In Stage 1, 18 subjects will be enrolled and if at least 3 subjects out of 18 achieve a response (PR or better) by end of Cycle 3, the study will continue to Stage 2. If there are 2 or less subjects who achieved a response out of 18 subjects in Stage 1, the study will be terminated for futility and will not proceed to Stage 2.

In Stage 2, an additional 32 subjects will be enrolled.

If it is determined at the end of Part 1 to further evaluate the efficacy and safety of the combination regimen of DARA plus DURVA, then up to an additional 70 subjects will be enrolled in Part 2. In total, approximately 120 subjects will be included in this study.

The primary statistical analysis will be based on the full analysis set patient population, following the intent-to-treat (ITT) principle. For binary endpoints, the observed rate and 2-sided exact 95% confidence intervals (CIs) will be provided. For time-to-event type of endpoints, Kaplan-Meier method will be used. The Kaplan-Meier, as well as the median and its 95% CIs will be provided. Safety analysis will be based on all subjects who received at least 1 dose of DARA plus DURVA.

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1. INTRODUCTION

1.1. Disease Background

Multiple myeloma (MM) is a rare and incurable progressive neoplastic disease that accounts for 10% of all hematological malignancies. It has been estimated that 63,700 incident cases and 79,410 deaths from MM occurred globally in 2013 (GBD, 2015).

Significant progress has been made in the treatment of MM with various combinations of melphalan, prednisone, dexamethasone, doxorubicin, cyclophosphamide, etoposide, cisplatin, immunomodulatory agents (thalidomide, lenalidomide and pomalidomide), and proteasome inhibitors (eg, bortezomib, carfilzomib, and ixazomab) or with autologous stem cell transplant following high-dose chemotherapy and more recently monoclonal antibodies (eg, daratumumab, elotuzumab) (National Comprehensive Cancer Network [NCCN]-MM Guidelines, 2016). The main considerations for choosing an appropriate treatment for relapsed and refractory multiple myeloma (RRMM) are: risk level, prior therapy, duration of response to prior therapy, residual toxicity, age, physical condition, and whether the patient is a candidate for stem cell transplantation (NCCN-MM Guidelines, 2016).

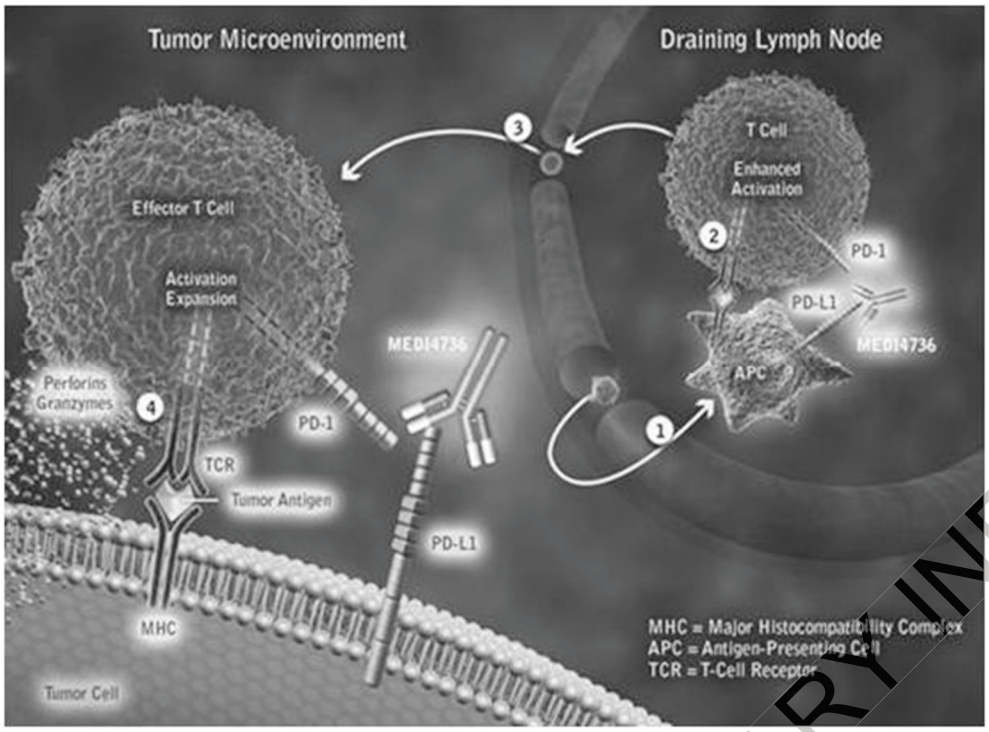
Despite the progress in treatment options for MM, the disease follows a relapsing course in the majority of patients, regardless of treatment regimen or initial response to treatment. Multiple myeloma remains incurable using conventional treatments, with an overall 5-year relative survival rate of 48.5% (Howlader, 2016). New therapies are needed to treat RRMM patients.

1.2. Compound Background

1.2.1. Durvalumab (MEDI4736)

Durvalumab (MEDI4736; DURVA) is a human immunoglobulin (Ig) G1 kappa monoclonal antibody (mAb) directed against human programmed death ligand-1 (PD-L1) protein. Durvalumab is expressed in Chinese hamster ovary cells and has an overall molecular weight of approximately 149 kDa. Durvalumab selectively binds human PD-L1 with high affinity and blocks its ability to bind to programmed cell death 1 (PD-1) protein and cluster of differentiation (CD)80. The fragment crystallizable (Fc) domain of DURVA contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fc gamma receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC) (Oganesyan, 2008).

Figure 1: Mechanism of Action for Durvalumab



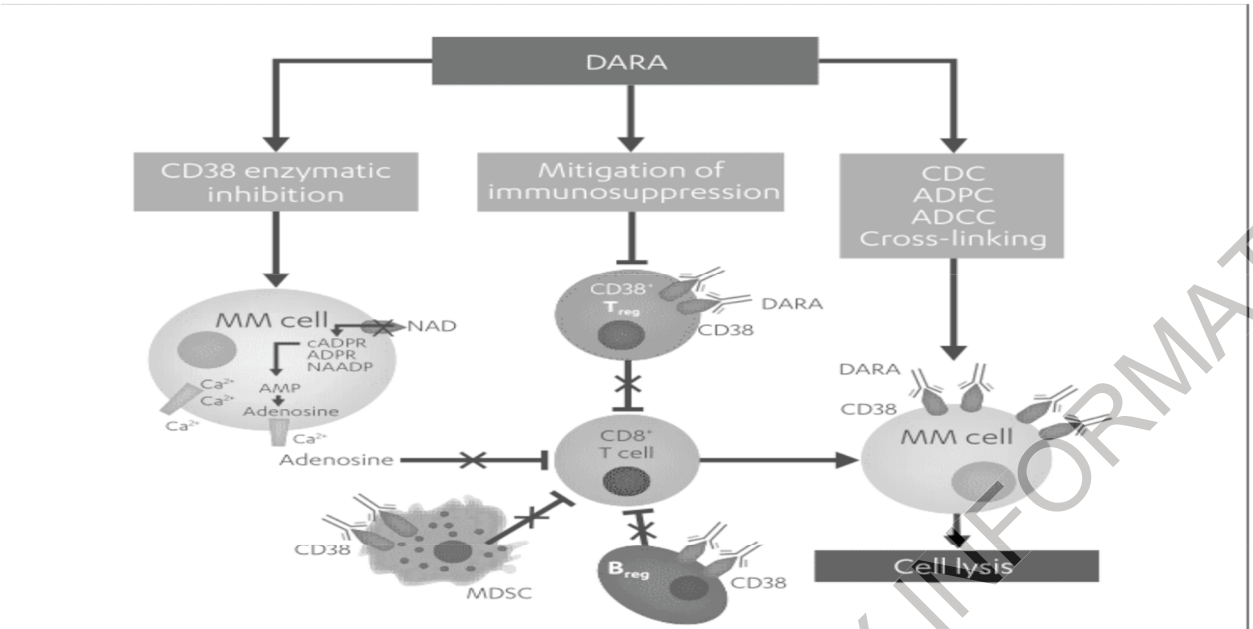
Refer to the DURVA Investigator's Brochure (IB) for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event (AE) profile of the investigational product (IP).

1.2.2. Daratumumab

Daratumumab (DARA) is a human $IgG1_k$ monoclonal antibody that binds with high affinity to a unique epitope on CD38. It is a targeted immunotherapy that attacks tumor cells that overexpress CD38, a transmembrane glycoprotein, in a variety of hematological malignancies including multiple myeloma. Daratumumab was approved under the accelerated approval regulations in the United States (US) on 16 November 2015, and in the European Union (EU) on 24 May 2016, 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 induces tumor cell death through diverse mechanisms of action, which include complement-dependent cytotoxicity (CDC), antibody dependent cell-mediated cytotoxicity (ADCC), antibody-dependent cellular phagocytosis, and induction of apoptosis (de Weers, 2011; Lammerts van Bueren, 2014; Overdijk, 2015; Jansen 2012).

Figure 2: Mechanisms of Daratumumab Activity



DARA, daratumumab; MM, multiple myeloma; CDC, complement-dependent cytotoxicity; ADPC, antibody-dependent cellular phagocytosis; ADCC, antibody-dependent cell-mediated cytotoxicity; NAD, nicotinamide adenine dinucleotide; Ca^{2+}, calcium ion; MDSC, myeloid-derived suppressor cell; B_{reg}, regulatory B cell; T_{reg}, regulatory T cell; cADPR, cyclic adenosine diphosphate-ribose; NAADP, nicotinic acid adenine dinucleotide phosphate; AMP, adenosine monophosphate.

Krejcik, 2015

Daratumamab was shown as a single agent, in heavily pretreated patients with relapsed or relapsed and refractory multiple myeloma, to have an overall response rate of 31% and a median overall survival of 20.1 months (Usmani, 2016). In addition, daratumamab in combination with bortezomib and dexamethasone (Vd) as well as Revlimid® and dexamethasone (Rd) have been shown to be effective. The DARA plus Vd (DVd) combination was tested in the CASTOR trial, where 498 patients were randomized between Vd and DVd (Palumbo, 2016). A prespecified interim analysis showed that the rate of progression-free survival (PFS) was significantly higher in the DVd group than in the control group; the 12-month rate of PFS was 60.7% in the DVd group versus 26.9% in Vd group. After a median follow-up period of 7.4 months, the median PFS was not reached in the DVd group and was 7.2 months in the Vd group (hazard ratio for progression or death with daratumumab versus control, 0.39; 95% confidence interval (CI), 0.28 to 0.53; p<0.001). The rate of overall response (ORR) was higher in the DVd group than in the Vd group (82.9% versus. 63.2%, p<0.001), as were the rates of very good partial response (VGPR) or better (59.2% versus. 29.1%, p<0.001) and complete response (CR) or better (19.2% versus. 9.0%, p = 0.001). In the POLLUX trial (Dimopoulos, 2016), the DARA plus Rd (DRd) regimen was tested against Rd in a population of 569 patients with at least one prior therapy and maintaining sensitivity to Revlimid®. After a median follow-up of 13.5 months, DRd significantly improved patients' median PFS, with the median PFS in the DRd group being not reached, compared with 18.4 months in the Rd arm (p<0.0001), translating to a 63% reduced risk of disease progression or death compared with Rd (hazard ratio = 0.37; 95% CI 0.27-0.52;

p<0.0001). Similarly, overall survival at 18 months was higher for daratumumab-treated patients: 86 % for DRd and 76 % for Rd. Daratumumab led to a higher ORR, more than doubling the rate of CRs or better: ORR: 93% versus. 76% (p<0.0001), ≥ VGPR: 76% versus. 44% (p<0.0001) and ≥ CR: 43% versus. 19% (p<0.0001). The median duration of response was longer in the DRd group (not reached versus. 17.4 months) and the median time to response was shorter (1 month versus. 1.3 months),

Refer to the DARA IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile; as well as the current US label (Darzalex™ Prescribing Information [PI], 2015) and Summary of Product Characteristics [SmPC] for the EU.

1.3. Rationale

1.3.1. Study Rationale and Purpose

The importance of the immune system in cancer development and progression has been recognized during the past decade (Hanahan, 2000). Failure of immune surveillance of pre-neoplastic lesions and micro-metastases is a key step in cancer development. Chronically immunosuppressed individuals show higher rates of cancer. This observation led to the hypothesis that sporadic cancers among immune-competent individuals are likely to be minimally immunogenic, allowing for passive escape from immune surveillance. Recent data suggest that this may be an oversimplification. Some sporadic tumors are highly immunogenic, but actively suppress the local immune environment through production of immunosuppressive cytokines (Shields, 2010). As such, the local tumor environment is likely a highly dynamic environment where most tumors grow and metastasize through adaptive responses that modulate antitumor immunity. The complexity and redundancy of the immune system offers multiple targets that may be manipulated to maximize the body's inherent immune response to a tumor. Immune response may be augmented by directly stimulating effector cells, indirectly stimulating effectors by augmenting antigen presentation activity or costimulation, or by suppressing immunosuppressive factors, cells, or messages (Monti, 2005).

DARA acts through multiple immune effector-mediated mechanisms, including CDC, ADCC, and antibody-dependent cellular phagocytosis. In addition to direct targeting of CD38+ myeloma cells, recently published data suggests an immune stimulating/modulatory role of DARA. Increases in CD8+, CD4+ T cell ratios, antiviral responses, and T cell clonality were all observed after DARA treatment in a heavily pretreated, relapsed, and refractory patient population not expected to have strong immune responses (Krejcik, 2015). Improved clinical responses were associated with changes in these parameters. In addition, DARA was shown to deplete regulatory T cells (Tregs) that express high levels of CD38. Reduction of these immune suppressive Tregs may promote expansion of cytotoxic CD8+ T cells which could have additional anti-tumor effects. These data suggest an immune modulatory role of DARA that may contribute to its efficacy. (Krejcik, 2015).

The mechanism of resistance to DARA remains to be fully explained, but immune escape by upregulation of PD-L1 signaling through PD-1 is hypothesized to contribute to resistance. Adding durvalumab, while continuing daratumumab is hypothesized to potentially reverse this mechanism of resistance.

Durvalumab (MEDI4736; DURVA) is a human IgG1 kappa mAb directed against human PD-L1 protein. Durvalumab selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 protein and cluster of differentiation (CD) 80. PD-1 is highly expressed on MM patient's T cells and natural killer (NK) cells; and both plasmacytoid dendritic cells (pDCs) and MM cells express PD-L1. Dysfunctional T cells, NK cells, and functionally defective pDCs contribute to the immune suppression in MM (Chauhan, 2009; Ray, 2015). It has been shown that pDCs produce T cell and NK cell immune suppression in the MM bone marrow (BM) milieu by engaging immune checkpoints via the PD-L1/PD-1 signaling axis (Ray, 2015). Blockade of PD-L1/PD-1 using anti-PD-L1 antibody generates MM-specific CD8+ cytotoxic T lymphocyte activity, as well as enhances NK-cell-mediated MM cell cytolytic activity.

As PD-L1-expressing pDCs are increased in MM bone marrow and localize with PD-L1-positive MM cells (Chauhan, 2009), PD-L1 expression may correlate with progression of disease, with highest levels in relapsed or relapsed/refractory MM. Indeed, a recent study showed that PD-L1 expression positively correlates with increased proliferative potential of tumor cells and resistance to therapies in MM (Tamura, 2013). Combination treatment of anti-PD-L1 mAb, like DURVA, with other anti-MM therapies that modulate MM-host immune responses, like DARA will potentially enhance both host anti-MM immunity and clinical response and warrant further exploration in the relapsed/refractory population being considered in this study.

The future of successful MM treatment lies in both the development of novel agents targeting the MM cells or the bone marrow microenvironment, and the development of rationally based combination therapies. As DARA use post approval, either alone, or in combination, increases, it is expected that patients who fail DARA-containing regimens will require new therapeutic options.

Targeted immunotherapy based on monoclonal antibodies against relevant tumor antigens has not only shown to be feasible, but also an effective approach in treating hematological malignancies. However, treatment options for heavily treated patients are limited, especially for those with disease that is double refractory to a PI and an immunomodulatory drug (IMiD®) (Laubach, 2016). To date, targeting MM cells by a combination-therapy approach has demonstrated superior clinical response as compared with that of single agents (Cavo, 2011). In theory, combination treatment of anti-PD-L1 mAb, like DURVA, with other anti-MM therapies that modulate MM-host immune responses, like DARA, may enhance both host anti-MM immunity and clinical response and warrant further exploration in a relapsed/refractory population being considered in this study. The importance of the PD-L1:PD-1 interaction has been recently further substantiated. In a recent study, PD-L1–expressing myeloma cells treated with PD-1 molecules were shown to have induction of drug resistance through activation of the Akt signaling pathway (Ishibashi, 2016). These results suggest that in the bone marrow microenvironment, the interaction between PD-L1 on myeloma cells and PD-1 on tumor-specific CTLs not only inhibits CTL activity via the PD-1 signaling pathway but also induces drug resistance via PD-L1mediated reverse signals.

Current treatments may mitigate, but are unable to completely circumvent, the inherent genomic instability and clonal heterogeneity that leads to recurrent relapses and ultimately refractory MM. In addition, in the era of novel agents, where MM patients are surviving longer, physicians are encountering more resistant and atypical relapses. Salvaging such patients becomes particularly

challenging and their prognosis often remains dismal (Phipps, 2015). There remains an unmet need for novel therapies that target different mechanisms of action.

The principle of overcoming resistance to an agent through continuation of that agent alone or in conjunction with the addition of a second agent or combination has been explored more extensively in the area of solid tumors. In lung cancer, discontinuation of epidermal growth factor receptor inhibitors (erlotinib and gefitinib) for radiographic progression resulted in increased rapidity of radiographic progression and onset of symptomatic progression that could be controlled by reinstitution of the same agents (Riely, 2007) with reduction in maximum standardized uptake value measurements. In melanoma, withdrawal of treatment after isolated progression of MAPK inhibitors in preparation for a new clinical trial sometimes led to rapid growth of remaining disease which had been controlled prior to that time point (Carlino, 2013). Multiple retrospective and prospective reports have described the clinical benefit potentially accruing from continuing particular agents in terms of PFS or overall survival (OS) in breast and colorectal cancers. Specific examples include continuation of bevacizumab or cetuximab while switching to differing chemotherapy regimens in colon cancer (Masi, 2015; Ciardiello, 2016), and continuation of trastuzumab beyond progression in breast cancer (von Minckwitz, 2011; Jackish, 2014).

Overcoming resistance and restoring a functional immune- surveillance system requires leveraging multiple, complementary mechanisms of action and agents that act in multiple phases of the cancer-immunity cycle. As such, combination immunotherapies that involve various phases of the cancer–immunity cycle may enhance the ability to prevent immune escape by targeting multiple mechanisms by which tumor cells avoid elimination by the immune system and with synergistic effects that may offer improved efficacy in broader patient populations (Morrissey, 2016). As CD38 expression is tied to response in patients with prior DARA treatment, and loss of CD38 correlates with development of resistance (Nijhof, 2016), it may be the case that controlling disease after progression with DARA treatment may also require continuation of DARA to continue control of sensitive disease clones, with the addition of DURVA providing additional therapeutic benefit for control of remaining clones no longer expressing CD38.

1.3.2. Rationale for the Study Design

The study will be conducted in 2 parts: Part 1 and Part 2.

Part 1 has a selected 2-stage design, where a limited number of subjects will be enrolled in Stage 1 to ensure a sufficient efficacy signal is seen prior to enrolling additional subjects in Stage 2.

While durvalumab has been dosed to over 1,910 patients and is currently being evaluated in over 30 Phase 3 clinical trials and daratumumab has received marketing approval, the combination of these two agents has not yet been extensively studied. An ongoing Phase 2 clinical study, MEDI4736-MM-003, is evaluating this two drug combination and is expected to provide evidence of safety and tolerability prior to the initiation of this study. However, if these safety data to clearly support the expected Phase 2 dose and schedule are not available prior to initiation of this study, a safety run-in phase will be conducted prior to further enrollment of this study.

Once 6 subjects have been enrolled and completed the first treatment cycle in Stage 1 of this study, the enrollment continuity would depend on the availability of safety data from the ongoing

Phase 2 study (MEDI4736-MM-003) of DARA and DURVA in previously DARA-naïve patients. Details are provided in Section 3.1.

If data are available and the safety profile of DARA plus DURVA has been evaluated as tolerable, enrollment in Part 1 Stage 1 will not be paused.

Part 2 will consist of an expansion phase and will be initiated once Part 1 has been completed and if a sufficient efficacy signal has been determined by the Sponsor at the end of Part 1, Stage 2.

1.3.3. Rationale for Dose, Schedule and Regimen Selection

1.3.3.1. Durvalumab

Nonclinical safety of DURVA was assessed in the pivotal Good Laboratory Practice (GLP) 13-week intravenous (IV) repeat-dose toxicity study in sexually mature cynomolgus monkeys. Animals received an IV loading dose of 30, 60 or 200 mg/kg of DURVA on Day 1, followed by 13 weekly IV doses of 15, 30 or 100 mg/kg, respectively. Animals were euthanized 3 days after the final dose, or after an 8-week treatment-free period. In the majority of animals exposure to DURVA and pharmacodynamics (as assessed by serum levels of free soluble PD-L1) were maintained throughout the dosing period. The IV administration of DURVA was not associated with any treatment-related effects on any of the endpoints studied (including clinical signs, bodyweights, ophthalmology, safety pharmacology endpoints (electrocardiograms [ECGs], respiratory rate, blood pressure and neurological examinations), peripheral blood leukocyte counts, clinical pathology parameters or gross and microscopic histopathology). The no observed adverse effect level (NOAEL) for DURVA in this study was therefore considered to be the 200/100 mg/kg dose (area under the curve [AUC] = 34,900 µg·d/mL, maximum plasma concentration [C_{max}] of drug = 7,470 µg/mL), the highest dose tested.

Based on the data from the GLP 3-month toxicity study in cynomolgus monkeys and the resultant safety margins, the Sponsor believes that the safety of these doses is supported by the existing nonclinical safety data.

As per the latest IB (Version 9), with data cut off dates of 15 April 2015 to 18 September 2015, 1,910 subjects have been treated across 30 ongoing DURVA studies, including 20 sponsored (6 monotherapy and 14 combination therapy) and 10 collaborative studies. Of the 1,910 subjects, 1,279 received DURVA monotherapy, 468 received DURVA in combination with other agents, and 163 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

The maximally administered dose of DURVA to humans in clinical trials conducted to date has been 20 mg/kg, which is equivalent to the 1500 mg every 4 weeks (Q4W) starting dose proposed in study MEDI4736-MM-003. Doses of DURVA up to 20 mg/kg as monotherapy did not define a non tolerated dose.

1.3.3.2. Daratumumab

The DARA dose/schedule will be as per the current approved label in the US (Darzalex PI) and Summary of Product Characteristics [SmPC] for the EU.

1.3.3.3. Potential for Synergistic Toxicities

There are no completed studies of anti-CD38 combined with PD-1 or PD-L1 inhibitors. These molecular targets do not have known mechanistic synergies, although variation in the co-expression of CD38/PD-1 has been studied as a marker of human immunodeficiency virus (HIV) infection, as a possible sign immune activation (Vollbrecht, 2010). Related cases of pneumonia or interstitial lung disease (ILD) have been reported with DARA (11%) (Darzalex PI), targeting CD38, and durvalumab (2%) (DURVA IB), targeting PD-L1. However, infections, and specifically pneumonias and ILDs, are well known clinical conditions in MM patients. With the exception of infusion-related reactions, the addition of DARA to standard MM treatment regimens did not seem to add toxicity to the safety profiles previously reported with these backbone regimens (Darzalex PI). No other known synergistic toxicities are expected with DURVA and DARA.

CCI [redacted]

CCI [redacted]

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to determine the efficacy of daratumumab (DARA) plus durvalumab (DURVA) in subjects with relapsed and refractory multiple myeloma (RRMM) who have progressed on a current treatment regimen containing DARA.
Secondary Objective(s)
The secondary objectives are to: • Determine the safety of DARA plus DURVA in subjects with RRMM who have progressed while on a current treatment regimen containing DARA. • Evaluate additional measures of efficacy of DARA plus DURVA in subjects with RRMM who have progressed on a current treatment regimen containing DARA. • Evaluate the pharmacokinetics (PK) of DARA plus DURVA in subjects with RRMM who have progressed on a current treatment regimen containing DARA.
CCI [redacted]
[redacted]

Table 2: Study Endpoints

Endpoint	Name	Description
Primary	Overall response rate (ORR)	Tumor response (partial response [PR] or better), and the rate of progressive disease (PD) according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Rajkumar, 2011).
Secondary	Safety	Type, frequency, seriousness and severity of adverse events (AEs), and relationship of AEs to study treatment
Secondary	Time-to-response (TTR)	Time from treatment initiation to the first documentation of response (PR or greater)

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description
Secondary	Duration of response (DOR)	Time from the first documentation of response (PR or greater) to the first documentation of PD or death, whichever is earlier, based on the investigator assessments according to the IMWG Uniform Response Criteria.
	Progression-free survival (PFS)	Time from treatment initiation to the first documentation of PD or death from any cause during study, whichever occurs earlier
	Overall survival (OS)	Time from treatment initiation to death due to any cause
Secondary	Pharmacokinetic (PK) parameters	Typical serum/plasma PK parameters for DURVA and DARA, such as maximum observed concentration (C_{max}), area under the concentration-time curve (AUC), time to maximum concentration (T_{max}), terminal elimination half-life ($t_{1/2}$), clearance (CL/F), and volume of distribution (V_Z/F)
CCI [redacted]	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of the combination regimen of daratumumab plus durvalumab (D^2). The study will consist of 2 parts; Part 1 has a 2-stage design while Part 2 consists of an expansion phase. Subjects will receive intravenous (IV) DARA at 16 mg/kg on the same dosing schedule (weekly [QW], every 2 weeks [Q2W]or every 4 weeks [Q4W] of each 28-day cycle) received on their last prior therapy containing DARA. The dosing schedule for DARA may be adjusted during the course of the study as outlined in Section 7.2.2.1. Subjects will also receive IV DURVA at 1500 mg on Day 2 (Cycle 1) and on Day 1 (Cycles ≥ 2) of each 28-day treatment cycle. The dosing schedule is outlined in Table 3.

3.1.1. Part 1: Selected 2-Stage

3.1.1.1. Stage 1

A cohort of 18 subjects will be enrolled to determine the preliminary efficacy of DARA plus DURVA. Once the 18 subjects have been enrolled, an interim analysis for futility purpose will be conducted to determine if the study can proceed to Stage 2.

3.1.1.1.1. Early Safety Monitoring

Once 6 subjects have been enrolled and completed the first treatment cycle in Stage 1 of this study, the enrollment continuity would depend on the availability of safety data from the on-going Phase 2 study (MEDI4736-MM-003) of DARA and DURVA in previously DARA-naïve patients.

- If MEDI4736-MM-003 safety data are available and the tolerability profile of DARA plus DURVA has been determined to be adequate, then enrollment will continue as planned in Stage 1 without an early safety monitoring review of the data.
- If safety data are not available enrollment in this study will be paused for a review of the safety profile of DARA plus DURVA by a Dose Review Team (DRT), using the data from the first 6 patients.
  - If ≥ 1 of the first 6 patients experiences a dose-limiting toxicity (DLT) as outlined in Section 3.1.1.1.1.1, the study will be halted for review and a change in the dosing regimen may be implemented.
  - The DRT will consist of the Celgene Medical Monitor, Celgene lead Safety Physician, Celgene biostatistician, other Celgene functional area representatives, as appropriate, and site investigator and/or designees who have enrolled subjects to the study.
  - All available safety and, if applicable, PK/([redacted] and preliminary efficacy data will be reviewed and can be considered in the DRT's decisions.

– A DRT meeting will be held to review all data and make decisions regarding continuity of the study.

3.1.1.1.1.1. Dose-limiting Toxicity

Dose-limiting toxicities (DLTs) may be evaluated during the DLT evaluation period for the initial 6 patients in Part 1 of the study. The DLT evaluation period will be defined as the first treatment cycle. Subjects are considered evaluable for assessment of DLT if they:

- Receive at least 1 dose of study treatments and experience a DLT

  OR

- Receive 1 dose of DURVA, 4 doses of DARA and complete the safety follow-up through the end of the DLT evaluation period.

Grading of DLTs will be according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) Version 4.03.

A DLT will be defined as below:

Hematologic DLT

a. Grade 4 neutropenia observed for greater than 5 days duration
b. Grade 3 neutropenia associated with fever (≥ 38.5 °C) of any duration.
c. Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding, or any requirement for platelets transfusion.
d. Any other Grade 4 hematologic toxicity that does not resolve to subject's pretreatment baseline level within 72 hours
e. Grade 4 anemia, unexplained by underlying disease.

Non-hematologic DLT

a. Any nonhematological toxicity ≥ Grade 3 except for alopecia and nausea controlled by medical management
b. Any treatment interruption greater than 2 weeks due to an AE.

While the rules for adjudicating DLTs in the context of dose escalation are specified above, an AE not listed above may be defined as a DLT after consultation with the Sponsor and investigators, based on the emerging safety profile.

3.1.1.2. Stage 2

If 3 or more subjects achieved a response (PR or better) out of the 18 subjects at the end of Stage 1, an additional 32 subjects will be enrolled to evaluate the safety and efficacy of DARA plus DURVA.

3.1.1.3. Part 2: Expansion

Upon completion of Part 1, if at least 9 subjects achieve a response (PR or better) out of a total of 50 subjects and it is determined to further confirm the efficacy and safety of DARA plus DURVA, an additional 70 subjects may be enrolled.

An Independent Response Adjudication Committee (IRAC) will be set up for this trial to review study data. The IRAC will determine tumor response to therapy and to confirm the time of disease progression (PD) (if disease progressed) at scheduled or unscheduled visits for each subject.

The safety and efficacy of the study will be monitored by an independent Data Monitoring Committee (DMC) who are not involved in the trial conduct. The DMC will meet up and review study data at pre specified intervals throughout the trial.

In the event that the trial is halted for early safety monitoring, as outlined in Section 3.1.1.1.1, evaluation of the emerging safety data from the initial 6 patients enrolled in Part 1 will be performed by the Dose Review Team (DRT).

Safety data will be monitored by the Celgene Medical Monitor and Safety Physician on an ongoing basis throughout the study. Should a significant safety issue be identified, the DMC will be convened to make a recommendation as to the future conduct of the study.

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

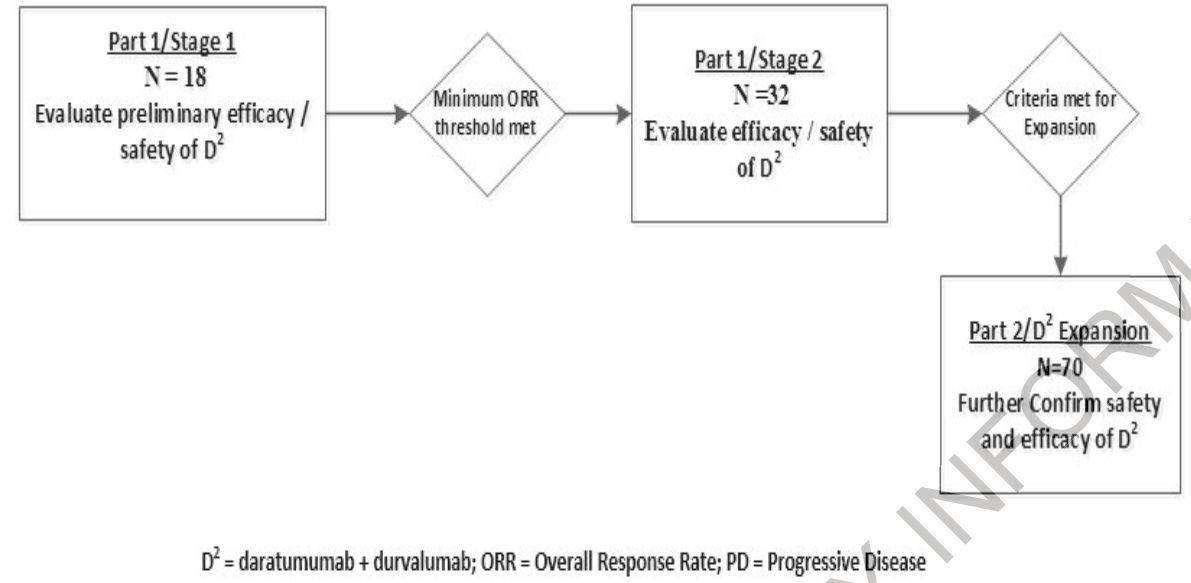
The study will be conducted in compliance with the International Council on Harmonisation (ICH) of Technical Requirements for Registration of Pharmaceuticals for Human Use/Good Clinical Practice (GCP) and applicable regulatory requirements.

Table 3: Dosing Schedules

IV DURVA (Dose: 1500 mg)	IV DARA (Dose: 16 mg/kg)
Cycle 1: Day 2 / 28-day cycle Cycle ≥ 2: Day 1 / 28-day cycle	Subjects should start study treatment on the same dosing schedule as their last DARA-containing regimen (QW, Q2W, or Q4W) The dosing schedule should be modified, during the course of the study, as shown below, provided that the subject has a response of stable disease (SD) or better: QW frequency (Days 1, 8, 15, and 22/ 28-day cycle): Weeks 1 to 8 then Q2W Weeks 9 to 24 Q2W frequency (Days 1, 15/ 28-day cycle): Weeks 1 to 16 then Q4W Q4W frequency (Day 1/28-day cycle): Week 1 onwards until disease progression

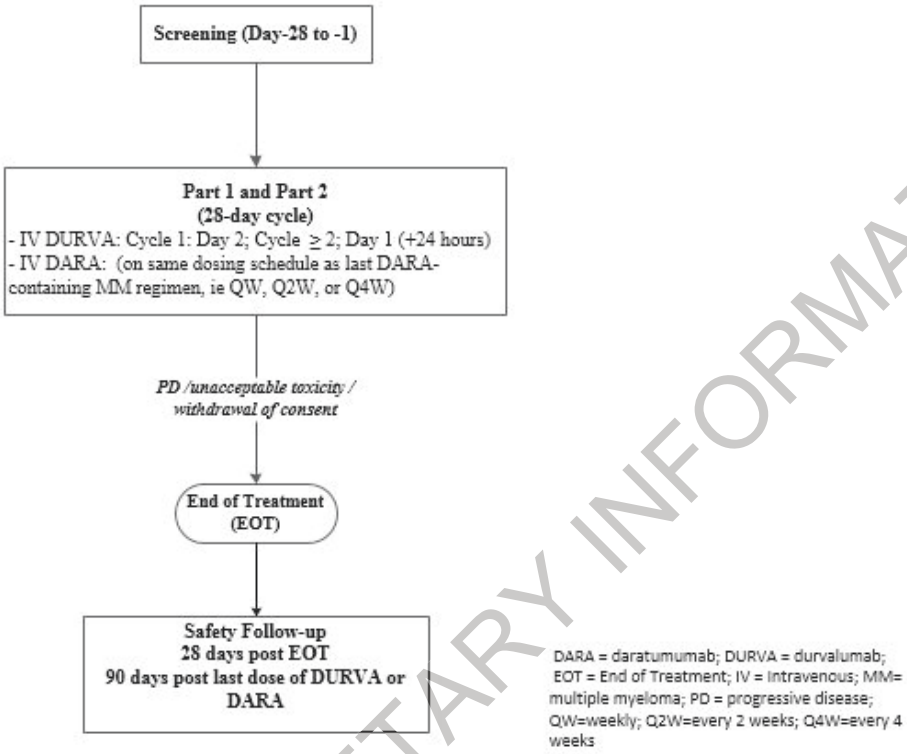
DARA= daratumumab; DURVA=durvalumab; IV= intravenously; QW=weekly; Q2W=every 2 weeks; Q4W=every 4 weeks.

Figure 3: Overall Study Design



D^2 = daratumumab + durvalumab; ORR = Overall Response Rate; PD = Progressive Disease

Figure 4: Study Schematic



3.2. Study Duration for Subjects

The study will consist of the following consecutive phases: Screening, Treatment, and Follow-up. The Screening Phase may not exceed a 28-day window prior to start of study treatment (Cycle 1 Day 1). Subjects may continue on study treatment until PD or unacceptable toxicity. All subjects will have an End of Treatment (EOT) visit within 7 days after discontinuation of all study treatment. Subjects are to return to the study site 28 (+3) days after the EOT visit and 90 (+3) days after the last dose of DURVA or DARA for safety follow-up visits.

3.3. End of Trial

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, 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, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

Up to approximately 120 subjects with RRMM will be enrolled worldwide.

- Part 1, Stage 1: Up to 18 subjects
- Part 1, Stage 2: Up to 32 subjects
- Part 2, Expansion: Up to 70 subjects

4.2. Inclusion Criteria

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

1. Subject received at least 3 prior anti-myeloma regimens including a PI and an immunomodulatory agent or is double-refractory to a PI and an immunomodulatory agent.
   - *Induction, bone marrow transplant with or without maintenance therapy is considered one regimen.*
   - ***Refractory** is defined as disease that is nonresponsive on therapy, or progresses within 60 days of last therapy. Nonresponsive disease is defined as either failure to achieve minimal response or development of progressive disease while on therapy.*
   - *For subjects who received more than 1 regimen containing a PI their disease must be refractory to the most recent PI containing regimen.*
   - *For subjects who received more than 1 regimen containing a immunomodulatory agent their disease must be refractory to the most recent immunomodulatory agent containing regimen.*
2. All subjects must have failed DARA either as a single agent or in combination on last MM therapy. Failure is defined as PD on DARA either as a single agent or in combination.
3. Subject has measurable disease defined as:
   a. M-protein (serum protein electrophoresis (sPEP) or urine protein electrophoresis (uPEP): sPEP ≥ 0.5 g/dL or uPEP ≥ 200 mg/24 hours) *and/or*
   b. Light chain MM without measurable disease in the serum or the urine: serum immunoglobulin free light chain ≥10 mg/dL and abnormal serum immunoglobulin kappa lambda free light chain ratio
4. Subject achieved a response (minimal response [MR] or better) to at least 1 prior treatment regimen.
5. Subject has an Eastern Cooperative Oncology Group (ECOG) Performance Status score of 2 or less.
6. Subject's toxicities resulting from previous therapy (including peripheral neuropathy) have resolved or stabilized to ≤ Grade 1.

7. Subject is at least 18 years of age at the time of signing the informed consent form (ICF).
8. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
9. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
10. Females of childbearing potential (FCBP[1]) must:
    a. Have 2 negative pregnancy tests as verified by the investigator prior to starting study treatment. This applies even if the subject practices true abstinence from heterosexual contact.
        i. Negative serum pregnancy test at screening
        ii. Negative serum or urine pregnancy test (investigator's discretion) within 72 hours prior to starting study treatment (Cycle 1, Day 1), and before beginning each subsequent cycle of treatment, and after end of study treatment.
            1. Note: Pregnancy testing does not need to be repeated prior to Cycle 1 if the serum pregnancy test for screening was performed within 72 hours of the first dose of study treatment.
    b. Either practice true abstinence[2] from heterosexual contact (which must be reviewed on a monthly basis and source documented) or agree to use, and be able to comply with, effective contraception without interruption (eg, oral, injectable, or implantable hormonal contraceptive; tubal ligation; intra-uterine device; barrier contraceptive with spermicide; true abstinence; or vasectomized partner), 28 days prior to starting study treatment, during the study therapy (including dose interruptions), and for at least 90 days after discontinuation of study treatment.
    c. Agree to abstain from breastfeeding during study participation and for at least 90 days after the last dose of DARA or DURVA, whichever is later.
    d. Refrain from egg cell donation for at least 90 days after the final dose of DURVA or DARA, whichever is later.
11. Male subjects must:
    a. Either practice true abstinence[2] (which must be reviewed on a monthly basis) or agree to use a condom during sexual contact with a pregnant female or a female of childbearing potential while participating in the study, during dose interruptions and for at least 90 days following study treatment discontinuation, even if he has undergone a successful vasectomy.
    b. Refrain from sperm donation for at least 90 days after the final dose of DURVA or DARA, whichever is later.

[1] A female of childbearing potential (FCBP) is 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).

[2] True abstinence is acceptable when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (eg, calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.

4.3. Exclusion Criteria

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

1. Subject has had prior exposure to anti-CTLA-4, anti-PD-1, anti-PD-L1 mAbs, or cancer vaccines
2. Subject has received autologous stem cell transplantation (ASCT) within 12 weeks before the date of randomization.
3. History of organ or allogeneic stem cell transplantation
4. Subject received any of the following within the last 14 days of initiating study treatment:
    a. Plasmapheresis
    b. Major surgery (as defined by the investigator)
    c. Radiation therapy other than local therapy for myeloma associated bone lesions
    d. Use of any systemic anti-myeloma drug therapy (except for DARA either alone or in combination with other agents given with it)
5. Subject received prior treatment with a monoclonal antibody within 5 half-lives of initiating study treatment, other than DARA.
6. Subject is receiving concurrent chemotherapy or biologic or hormonal therapy for cancer treatment. Note: Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.
7. Subject has any of the following laboratory abnormalities:
    a. Absolute neutrophil count (ANC) < 1,000/µL
    b. Platelet count: < 75,000/µL (it is not permissible to transfuse a subject to reach this level)
    c. Hemoglobin < 8 g/dL (< 4.9 mmol/L)(it is not permissible to transfuse a subject to reach this level)
    d. Creatinine clearance (CrCl) < 45 mL/min (calculated using the Cockcroft-Gault formula or directly calculated from the 24-hour urine collection method)
    e. Corrected serum calcium > 13.5 mg/dL (> 3.4 mmol/L)
    f. Serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) > 2.5 × upper limit of normal (ULN)
    g. Serum total bilirubin > 1.5 × upper limit of normal (ULN) or > 3.0 mg/dL for subjects with documented Gilbert's syndrome
8. Subject has clinical evidence of central nervous system (CNS) or pulmonary leukostasis, disseminated intravascular coagulation, or CNS MM
9. Subject has known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) 50% of predicted normal. *Note that forced expiratory testing (FEV1)is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is < 50% of predicted normal.*
10. Subject has known moderate or severe persistent asthma within the past 2 years (see Appendix F) or uncontrolled asthma of any classification. Note that subjects who

currently have controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.

11. Subject has plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or amyloidosis
12. Subject has nonsecretory MM
13. Subject has known allergy or hypersensitivity to study drug formulations
14. Subject has active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis, celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea; systemic lupus erythematosus; Wegener syndrome; myasthenia gravis; Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
    a. Subjects with vitiligo or alopecia.
    b. Subjects with hypothyroidism (eg, following Hashimoto's disease) stable on hormone replacement.
    c. Psoriasis not requiring systemic treatment.
15. Subject has history of primary immunodeficiency
16. Subject is positive for human immunodeficiency virus (HIV-1), chronic or active hepatitis B or active hepatitis A or C.
17. Subject has received live, attenuated vaccine within 30 days prior to the first dose of DURVA (NOTE: Subjects, if enrolled, should not receive live vaccine during the study and through 30 days after the last dose of DURVA)
18. Subject is currently using or has used immunosuppressive medication within 14 days prior to the first study dose of study treatment. The following are exceptions to this criterion:
    a. Intranasal, topical, inhaled, or local steroid injections (eg, intra-articular injection).
    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent.
    c. Steroids as premedication for hypersensitivity reactions (eg, infusion-related reactions, computed tomography [CT] scan premedication).
19. Subject has any one of the following:
    a. Clinically significant abnormal ECG finding at screening
    b. Congestive heart failure (New York Heart Association Class III or IV)
    c. Myocardial infarction within 12 months prior to starting study treatment
    d. Unstable or poorly controlled angina pectoris, including Prinzmetal variant angina pectoris
20. Subject has prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years with the exception of the following noninvasive malignancies:

a. Basal cell carcinoma of the skin
b. Squamous cell carcinoma of the skin
c. Carcinoma in situ of the cervix
d. Carcinoma in situ of the breast
e. Incidental histologic finding of prostate cancer (T1a or T1b using the TNM [tumor, nodes, metastasis] clinical staging system) or prostate cancer that is curative

21. Subject is a female who is pregnant, nursing, or breastfeeding, or who intends to become pregnant during the participation in the study.
22. Subject has any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
23. Subject has any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
24. Subject has any condition that confounds the ability to interpret data from the study

5. TABLE OF EVENTS

Table 4: Table of Events

Events	Screening Period	Treatment Period									Follow-up Period	
		C 1-2 (±3 days)					C 3-6 (±3 days)		≥ C7 (±3 days)	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DURVA/ DARA dose
	-28 to -1	D1[a]	D 2	D8	D 15	D 22	D 1	D 15	D 1			
Informed consent	X	-	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-	-	-	-	-	-
IRT registration	X	X	-	-	-	-	-	-	-	X	-	-
Complete medical history	X	-	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-	-
Prior disease history	X	-	-	-	-	-	-	-	-	-	-	-
Prior disease therapies	X	-	-	-	-	-	-	-	-	-	-	-
Forced expiratory volume test, (subjects with COPD)	X	-	-	-	-	-	-	-	-	-	-	-
Prior/concomitant medication evaluation	X (-28 days from the date when ICF was signed)	Continuous, until 90 days after last dose of DURVA or DARA, whichever is later										
Blood Type, Rh, and IAT	-	X	-	-	-	-	-	-	-	-	-	-
Prior/concomitant procedures evaluation	X (-28 days from the date when ICF was signed)	Continuous, until 90 days after last dose of DURVA or DARA, whichever is later										
AE evaluation	Continuous starting after informed consent signature, until 90 days after last dose of DURVA or DARA, whichever is later											
Physical examination	X	X	-	-	-	-	X	-	X	X	-	-

Table 4: Table of Events (Continued)

Events	Screening Period	Treatment Period									Follow-up Period	
		C 1-2 (±3 days)					C 3-6 (±3 days)		≥ C7 (±3 days)	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DURVA/ DARA dose
	-28 to -1	D1[a]	D 2	D8	D 15	D 22	D 1	D 15	D 1			
Vital signs	X	X	X	X	X	X	X	X	X	X	X	X
Height	X	-	-	-	-	-	-	-	-	-	-	-
Weight	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG	X	C1	-	-	-	-	C6	-	-	X	-	-
Hepatitis and HIV-1 antibody testing	X	-	-	-	-	-	-	-	-	-	-	-
Hematology	X	X	X	X	X	X	X	X	X	X	X	X
Coagulation parameters	X	X	-	-	X	-	X	-	X	X	-	-
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X
Thyroid Function Tests (TSH and free T3/T4 at Screening and Cycles 1-4; TSH for Cycle 5 onwards; reflex testing for free T3/T4 only if TSH is abnormal)	X	X	-	-	-	-	X	-	X	X	-	X
Renal Function (CrCl)	X	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	if clinically indicated								X	X	X
Pregnancy Testing (FCBP only) Refer to Section 6.1	X	X	-				X	-	X	X	X	X

Table 4: Table of Events (Continued)

Events	Screening Period	Treatment Period									Follow-up Period	
		C 1-2 (±3 days)					C 3-6 (±3 days)		≥ C7 (±3 days)	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DURVA/ DARA dose
	-28 to -1	D1[a]	D 2	D8	D 15	D 22	D 1	D 15	D 1			
Antiviral prophylaxis	-	Initiate within 1 week of starting DARA and continue for 3 months following last dose of DARA.										
EFFICACY AND OTHER ASSESSMENTS												
ECOG Performance status	X	X	-	-	-	-	X	-	X	X	-	-
Assessment of response (IMWG Uniform Response Criteria)[b]	-	C2	-	-	-	-	X	-	X	X	-	-
Serum and urine protein electrophoresis	X	X	-	-	-	-	X	-	X	X	-	-
Serum and urine immunofixation	X	X	-	-	-	-	X	-	X	X	-	-
Serum free light chains assay	X	X	-	-	-	-	X	-	X	X	-	-
Quantitative serum immunoglobulin	X	X	-	-	-	-	X	-	X	X	-	-
EMP clinical assessment	X	X	-	-	-	-	X	-	X	X	-	-
EMP radiological assessment (only required if history of or clinical indication of EMPs only assessable radiographically)	X	Day 1 starting at C3, then every 3 cycles thereafter								X	-	
Skeletal Survey for bone lesions	X (within 60 days prior to first dose is acceptable)	Repeated during treatment if clinically indicated to confirm response or PD									-	

Table 4: Table of Events (Continued)

Events	Screening Period	Treatment Period									Follow-up Period	
		C 1-2 (±3 days)					C 3-6 (±3 days)		≥ C7 (±3 days)	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DURVA/ DARA dose
	-28 to -1	D1[a]	D 2	D8	D 15	D 22	D 1	D 15	D 1			
Bone marrow aspirate and/or biopsy sampling for cytogenetics, % plasma cells, CCI	X BMA and BMB cytogenetics, % plasma cells, CCI	CCI - BMA and BMB at time of CR confirmation for % plasma cells CCI								CCI		
β2-microglobulin	X	X	-	-	-	-	X	-	X	X	-	-
Pre- and post-DARA infusion medications[c] (Refer to Section 7.2.1.2)	-	X	-	X	X	X	X	X	X	-	-	-
DARA IV administration (QW, Q2W, or Q4W) Refer to Section 7.2.2	-	X[d]	-	X[d]	X[d]	X[d]	X[d]	X[d]	X[d]	-	-	-
DURVA IV administration	-	C1D2 C2D1[e]		-	-	-	X[e]	-	X[e]	-	-	-
Study treatment (DURVA, DARA) accountability/compliance	-	X	X	X	X	X	X	X	X	X	-	-
Blood sample for DURVA PK (Refer to Section 6.5.1)	-	C2	C1	C1	C1	C1	C4,C6	-	C10, C14	-	-	-
Blood sample for DARA PK (Refer to Section 6.5.2)	-	C1	-	C1	C1	C1	-	-	-	X	X	X

Table 4: Table of Events (Continued)

Events	Screening Period	Treatment Period									Follow-up Period	
		C 1-2 (±3 days)					C 3-6 (±3 days)		≥ C7 (±3 days)	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DURVA/ DARA dose
	-28 to -1	D1[a]	D 2	D8	D 15	D 22	D 1	D 15	D 1			
CCI												

AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; C = Cycle; COPD = chronic obstructive pulmonary disease; CR = complete response; CrCl = creatinine clearance; D= Day; DARA = daratumumab; DURVA= durvalumab; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; eCRF= electronic case report form; EMP = extramedullary plasmacytomas; EOT = End of Treatment; FCBP = female of childbearing potential; HIV = human immunodeficiency virus; IAT = indirect antiglobulin test; IMWG = International Myeloma Working Group; IRT= Interactive Response Technology; IV = intravenous; PD = disease progression; PK = pharmacokinetics; QW = weekly; Q2W = every 2 weeks; Q4W = every 4 weeks; TSH= thyroid stimulating hormone; trt discon = treatment discontinuation.

[a] On Cycle 1 Day 1 (C1D1), safety laboratory assessments must be performed locally (central confirmation is not required) to confirm subject continues to meet the required safety laboratory values prior to initiating study treatment. However, if screening assessments were performed within 72 hours of C1D1, safety laboratory and physical examinations need not be repeated at C1D1.

[b] Per IMWG Uniform Response Criteria all response categories and progressive disease require 2 consecutive assessments.

[c] Pre infusion medications to be given before all daratumumab infusions (if necessary, oral pre infusion medications may be administered at the subject's home on the day of the infusion, provided they are given within 3 hours prior to the infusion); post infusion medications to be given on the first and second days following all daratumumab infusions.

[d] Every effort should be made to keep subjects on the planned dosing schedule (QW, Q2W, or Q4W) as detailed in Section 7.2.2. However, doses given within 3 days of the scheduled dose are permitted, as long as the interval between doses is at least 5 days. Blood pressure is to be measured at the following time points on C1D1 and C1D8: immediately before the start of the infusion; at approximately 30 minutes, 1 hour, 90 minutes, 2 hours, and 3 hours 30 minutes after the start of the infusion; at the end of the infusion; and 30 minutes and 1 hour (+/- 5 minutes) after the end of the infusion. For all other DARA infusions, blood pressure will be measured immediately before the infusion start and at the end of the infusion.

[e] **First DURVA infusion:** blood pressure and pulse will be monitored, as follows (based on a 60-minute infusion): Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion]); approximately 30 minutes during the infusion (halfway through infusion); at the end of the infusion (approximately 60 minutes ±5 minutes). If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated. For DURVA infusions on C2D1 onward, a +24 hour window is allowed and may be implemented per

investigator discretion.

Subsequent DURVA infusions: vital signs will be measured prior to the start of the infusion. Subjects should be carefully monitored and blood pressure and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs eCRF page.

6. PROCEDURES

Any questions regarding the protocol should be directed to the Celgene Medical Monitor or designee.

6.1. Screening Period

The Screening Phase begins when the ICF is signed. Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 28 days of first dosing unless noted otherwise below.

Waivers to the protocol will not be granted during the conduct of this trial, under any circumstances.

Except for pregnancy tests, ECGs and urinalysis, all safety-related laboratory assessments will be performed centrally; however, tests that may result in dose interruption and/or modification may also be performed locally to allow for treatment-related decisions during subject visits. All results from local laboratories used in treatment decisions or AE reporting must be entered as an unscheduled visit into the electronic case report form (eCRF).

The following will be performed at screening as specified in Table 4 after informed consent has been obtained:

- Interactive Response Technology (IRT) registration
  - *Note: Subject may be enrolled in the IRT up to 3 days prior to initiating study treatment on Cycle 1 Day 1 (C1D1)*
- Complete medical history (all relevant medical conditions diagnosed/occurring prior to screening should also be included)
- Demographics (age, sex, race, and if allowed by local regulations, ethnicity, and date of birth, will be collected in the eCRF and/or IRT system)
- Prior disease history (if available the date of initial diagnosis, staging at time of diagnosis [Appendix D], cytogenetics at diagnosis to be collected)
- Prior disease therapies (including surgery, radiation, systemic or any other therapy for the subject's disease)
- Prior and concomitant medication evaluation (including those taken ≤ 28 days before the date that the ICF was signed, except for those taken for disease)
- Prior and concomitant procedures evaluation (including all procedures occurring ≤ 28 days before the date that the ICF was signed)
- Adverse events
- Physical examination, including assessment for potential venous thromboembolism events (VTEs) (can be source documented only)
- Forced expiratory volume test (subjects with or suspected to have chronic obstructive pulmonary disease [COPD])

- Vital signs (including blood pressure, temperature, and heart rate)
- Height and weight
- 12-lead ECG (performed and reviewed locally)
- Hepatitis panel
- HIV-1 antibody test
- Hematology panel including complete blood count (CBC) with differential, including red blood cell (RBC) count, hemoglobin, hematocrit, white blood cell (WBC) count (with differential), platelet count, mean corpuscular volume
- Coagulation parameters (prothrombin time/international normalized ratio, activated partial thromboplastin time, fibrinogen)
- Chemistry panel including sodium, potassium, calcium, corrected serum calcium (refer to Section 6.4.1), chloride, blood urea nitrogen (BUN), creatinine, glucose, albumin, total protein, alkaline phosphatase (ALP), bilirubin (total, direct, and indirect), AST, ALT, lactate dehydrogenase (LDH), magnesium, bicarbonate, lipase, gamma-glutamyl transferase (GGT), uric acid, triglycerides, cholesterol, and amylase. **(NOTE: Tests for AST, ALT, ALP, direct bilirubin, indirect bilirubin, and total bilirubin must be conducted and assessed concurrently)**
- Thyroid function tests (thyroid-stimulating hormone [TSH], free T4, free T3)
- Estimation of renal function will be assessed using the CrCl calculated based on the Cockcroft-Gault formula or the CrCl directly calculated from the 24-hour urine collection method. Cockcroft-Gault formula: CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dl]); for females, the formula is multiplied by 0.85.
- Urinalysis (color, appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin)
- Females of childbearing potential (FCBP) should have two negative medically supervised pregnancy tests assessed locally during screening. The subject may not receive any study treatment until the investigator has verified that the results of these pregnancy tests are negative.
    - The investigator will appraise a female subject as a FCBP according to the following definition (justification must be recorded in the eCRF and the source document):
        - FCBP is defined as a sexually mature woman who has not undergone a hysterectomy or bilateral oopherectomy or has not been naturally menopausal for at least 24 consecutive months (ie has had menses at any time in the preceeding 24 consecutive months). Amenorrhea following cancer therapy does not rule out childbearing potential.
    - Negative serum pregnancy test (minimum sensitivity of 25mIU/ml) at screening
    - Negative serum or urine pregnancy test (investigator's discretion) within 72 hours prior to the start of study treatment (C1D1)

  - Note: Pregnancy testing does not need to be repeated prior to C1D1 if the screening assessment (serum pregnancy test) was performed within 72 hours of the first dose of study treatment
  - Note: Pregnancy testing is not required for non-FCBP subjects.
- Eastern Cooperative Oncology Group (ECOG) Performance Status (see Appendix C)
- Efficacy assessments / tumor evaluations per the IMWG criteria (See Section 6.4).
- β2 microglobulin test
- Bone marrow aspiration/biopsy (for cytogenetics, percent plasma cells, CCI [redacted]
- [redacted]

6.2. Treatment Period

The subject will begin the treatment period upon confirmation of eligibility. The subject must start treatment within 28 days of signing the ICF. For all visits an administrative window of ± 3 days is permitted. Safety laboratory testing at a local laboratory may be performed up to 3 days before the study treatment administration day. Results of these laboratory tests must be evaluated before each study treatment administration.

Treatment cycles are 28 days in duration, the treatment and schedule will be as described in Section 7.2.

The following evaluations will be performed at the frequency specified in Table 4. The evaluations should be should be performed prior to dosing on the visit day, unless otherwise specified.

- Interactive Response Technology (IRT) registration
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Adverse event (continuously)
- Physical examination, including assessment for potential VTEs (can be source documented only)
- Vital signs
- Weight
- 12-lead ECG (C1D1 and C6D1 immediately after DARA infusion)
- Blood Type, Rh, and indirect antiglobulin test (IAT) should be done before the first dose of DARA. See Section 6.8 for additional details.
- Hematology panel
- Coagulation parameters
- Chemistry panel

- Thyroid function tests:
  - Cycles 1 to 4: TSH, free T4, free T3
  - Cycle 5 onward: TSH, if TSH is abnormal, then reflex testing for free T4 and free T3
- Renal function (CrCl) based on the Cockcroft-Gault formula or the CrCl directly calculated from the 24 hour urine collection method. Cockcroft-Gault formula: CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dl]); for females, the formula is multiplied by 0.85 (local laboratory).
- Urinalysis (only if clinically indicated)
- Urine (or serum) pregnancy test for FCBP (negative results required for study treatment [DURVA and/or DARA] administration) within 72 hours prior to dosing on D1 of every treatment cycle. The subject may not receive study treatment until the investigator has verified that the result of the pregnancy test is negative.
- ECOG Performance Status
- Antiviral prophylaxis
- Pre and post medication for DARA infusion (see Section 7.2.1.2)
- Efficacy assessments (see Section 6.4)
- β2 microglobulin test on Day 1 of each cycle
- CCI [redacted]
- Blood sampling for PK assessments (see Section 6.5)
- CCI [redacted]
- Study treatment (DARA and DURVA) administration/accountability/compliance.

6.2.1. End of Treatment

An End of Treatment (EOT) evaluation will be performed for subjects who are withdrawn from treatment for any reason within 7 days after the decision to permanently discontinue treatment has been made.

The following evaluations will be performed as specified in Table 4.

- IRT registration
- Concomitant medications evaluation (monitored until 90 days after last dose of DURVA or DARA, whichever is later)
- Concomitant procedures evaluation (monitored until 90 days after last dose of DURVA or DARA, whichever is later)
- Adverse event evaluation (monitored until 90 days after last dose of DURVA or DARA, whichever is later)

- Physical examination, including assessment for potential VTEs (can be source documented only)
- Vital signs
- Weight
- 12-lead ECG
- Hematology panel
- Coagulation parameters
- Chemistry panel
- Thyroid function tests (TSH, free T4, free T3)
- Renal function (CrCl) based on the Cockcroft-Gault formula or the CrCl directly calculated from the 24 hour urine collection method. Cockcroft-Gault formula: CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dl]); for females, the formula is multiplied by 0.85.
- Urinalysis
- Urine (or serum) pregnancy test for FCBP
- ECOG Performance Status
- Antiviral prophylaxis
- Efficacy assessments per the IMWG criteria will be performed according to the schedule defined in the Table of Events and do not need to be performed specifically for the EOT visit except as specified in Section 6.4.
- β2 microglobulin test
- CCI [redacted]
- Blood sampling for DARA PK assessments (see Section 6.5)
- CCI [redacted]
- Study treatment (DARA and DURVA) accountability/compliance.

6.3. Follow-up Period

6.3.1. Safety Follow-up

All subjects will be followed for 90 days after the last dose of DURVA or DARA, whichever is later, for AEs, including adverse events of special interest (AESIs), reporting, as well as serious adverse events (SAEs) that had occurred within that time frame but were made known to the investigator at any time thereafter that are suspected of being related to study treatment (DURVA, DARA), as described in Section 10.1.

Subjects are to return to the study site 28 (+3) days after the EOT visit and 90 (+3) days after the last dose of DARA or DURVA, whichever is later, for safety follow-up visits procedures as specified in Table 4.

- Concomitant medications evaluation (monitored until 90 days after last dose of DURVA or DARA, whichever is later)
- Concomitant procedures evaluation (monitored until 90 days after last dose of DURVA or DARA, whichever is later)
- Adverse event (including AESIs) evaluation (monitored until 90 days after last dose of DURVA or DARA, whichever is later)
- Vital signs
- Weight
- Hematology panel
- Chemistry panel
- Thyroid function tests (TSH, free T4, free T3)
- Renal function (CrCl) based on the Cockcroft-Gault formula or the CrCl directly calculated from the 24 hour urine collection method. Cockcroft-Gault formula: CrCl (mL/min) = (140 – age) (weight [kg]) / 72 (serum creatinine [mg/dl]); for females, the formula is multiplied by 0.85 (local laboratory).
- Urinalysis
- Urine (or serum) pregnancy test for FCBP
- Antiviral prophylaxis
- Blood sampling for DARA PK assessments (see Section 6.5)
- CCI [redacted]

6.4. Efficacy Assessments

6.4.1. Laboratory Assessments for Efficacy Parameters

All laboratory assessments for efficacy will be performed centrally.

If screening assessments are performed within 3 days of C1D1, efficacy laboratory assessments need not be repeated at C1D1:

- Serum protein electrophoresis (sPEP) and urine protein electrophoresis (uPEP) tests (performed on 24-hour urine collection) are required at screening, on Day 1 of each cycle, and at the EOT Visit.
- Serum and urine immunofixation tests are required at screening, on Day 1 of each cycle, and at the EOT Visit.

- Quantitative serum immunoglobulin assessment includes IgG, IgA, and IgM for all subjects, and IgE or IgD only for subjects with the respective MM subtype (IgE or IgD) and is required at screening, on Day 1 of each cycle, and at the EOT Visit.
- Serum free light chains assay is required at screening, on Day 1 of each cycle, and at the EOT Visit.
- Corrected serum calcium will be assessed as part of the safety serum chemistry assessments performed at screening, on Day 1 of each cycle, and at the EOT Visit.

6.4.2. Bone Marrow Aspiration and/or Biopsy

A bone marrow aspirate (BMA) and biopsy (BMB) is mandatory at the following time points:

- At screening, BMA and BMB for percent plasma cells, cytogenetics, CCI [redacted]
- During treatment:
  - CCI [redacted]
  - BMA and BMB at the time of complete response (CR) confirmation for percent plasma cells CCI [redacted]
  - CCI [redacted]

The analysis of bone marrow for percentage of plasma cells will be performed locally and at a central laboratory. CCI [redacted]

6.4.3. Bone Lesion Assessment

Bone lesion assessment by x-ray (skeletal survey) or CT Scan will be performed at screening and when clinically indicated to confirm response or PD. The same method (x-ray or CT Scan) should be used throughout the study. All films will be analyzed locally by the site investigator/radiologist. If a bone lesion assessment by x-ray or CT Scan was performed within 60 days prior to the start of Cycle 1, it may be used for the screening assessment.

If assessment is done by x-ray, the following are the minimum plain radiological films required for the skeletal (bone) survey:

- Lateral skull
- Anteroposterior (AP) and lateral cervical spine
- AP and lateral thoracic spine
- AP and lateral lumbar spine
- Posteroanterior 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.

6.4.4. Extramedullary Plasmacytoma Assessments

Clinical assessment for extramedullary plasmacytoma (EMP) assessments will be performed at screening, on Day 1 of every cycle, and at the EOT Visit.

For EMPs that are only assessable radiographically (by x-ray and/or conventional [spiral] CT/magnetic resonance imaging [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 the EOT Visit, and when clinically indicated to confirm a response (≥ PR) or PD. The radiographic modality used at screening (eg, x-ray) will be repeated at each assessment time point throughout the study. All scans will be reviewed locally only. Celgene may request redacted copies of reports.

6.4.5. Assessment of Response

6.4.5.1. Investigator Assessment

Starting from Cycle 2, response will be assessed by the investigators using the International Myeloma Working Group (IMWG) Uniform Response Criteria (Rajkumar, 2011) (Appendix B) at every cycle on Day 1 and at the EOT Visit. Response must be based on the central laboratory data to ensure consistency across investigative sites. All treatment discontinuation decisions due to disease progression will be made by treating physicians based on response as assessed using results from central laboratories by the IMWG criteria, except for new or increase in bone lesions or soft tissue plasmacytomas.

6.4.5.2. Independent Response Adjudication Committee Assessment

An IRAC will be formed by a group of experts in the MM disease area to review efficacy data. For each subject, the IRAC will determine tumor response at scheduled or unscheduled visits, and the time of PD (if disease progressed). In addition, the IRAC will determine the best overall response of each subject up to time of the data cut off for interim and final analyses.

The IRAC will adjudicate efficacy data incrementally according to IRAC Charter during the study. The IRAC adjudicated response data will be used for efficacy analysis in all interim and final analyses. Primary efficacy analyses will be conducted in tumor response data, including progressive disease (PD) that are assessed by the IRAC according to the IMWG Uniform Response Criteria (Appendix B).

NOTE: Per IMWG Uniform Response Criteria all response categories and progressive disease require 2 consecutive assessments except for radiographic or bone marrow assessments

6.5. Pharmacokinetics

Serum samples will be collected to assay concentrations of DURVA and DARA. On PK sampling days, dosing and sample collection information including dosing date, dosing time (24 hour clock), and actual PK blood sampling time (24 hour clock) should be accurately documented on the appropriate eCRF pages.

6.5.1. Pharmacokinetics of Durvalumab

All subjects enrolled in Part 1 Stage 1 will participate in the DURVA PK sample collections at the following time points:

- C1D2: pre dose (-30 to -5 minutes prior to dose), end of infusion (EOI) (+5 minutes),
- C1D8: 144 hours post C1D2 dose (± 1 hour)
- C1D15: 312 hours post C1D2 dose (± 1 hour),
- C1D22: 480 hours post C1D2 dose (± 1 hour).
- Additional DURVA PK samples to be collected CCI [redacted] on C2D1, C4D1, C6D1, C10D1, and C14D1.

6.5.2. Pharmacokinetics of Daratumumab

DARA PK sample collections will occur at the following time points for subjects enrolled in Part 1 Stage 1:

- C1D1: predose (-30 to -5 minutes prior to dose), and EOI (+5 minutes)
- C1D8: predose (-30 to -5 minutes prior to dose), and EOI (+5 minutes)
- C1D15: predose (-30 to -5 minutes prior to dose), and EOI (+5 minutes)
- C1D22: predose (-30 to -5 minutes prior to dose), and EOI (+5 minutes)
- EOT
- 28 days after EOT,
- 90 days after last DARA or DURVA dose

CCI [redacted]

CCI

6.8. Blood Type, Rh and Indirect Antiglobulin Test (IAT)

Blood type, Rh, and IAT should be done before the first dose of DARA for the reasons detailed below. Subject RBC phenotyping (standard or extended) is an alternative option to the IAT test, if locally required. Either method must be completed prior to first DARA infusion.

DARA interferes with the indirect antiglobulin test (IAT), which is a routine pre-transfusion test performed to identify a patient's antibodies to minor antigens so that suitable donor blood can be given for transfusion. DARA does not interfere with ABO/RhD typing. CD38 is expressed at very low levels on erythrocytes. DARA 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 DARA 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 DARA 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 DARA 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 DARA include:

a. Providing ABO/RhD compatible, phenotypically (standard or extended phenotyping) or genotypically matched units
b. Providing ABO/RhD compatible, K-negative units after ruling out or identifying alloantibodies using dithiothreital-treated reagent RBCs

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

Despite DARA binding to CD38 on erythrocytes, no indication of clinically significant hemolysis has been observed in DARA studies. For additional details, refer to the DARA IB.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Product(s)

Investigational product supply will be managed by IRT. All IP must be stored in accordance with the product label in a secured area to prevent unauthorized access.

United States:

Durvalumab (MEDI4736) will be supplied by Celgene and labeled appropriately as investigational material. Labels will bear Celgene's name, telephone number and address, the protocol number, product name, dosage form and strength, medication identification kit/number, lot number, expiry date, dosing instructions, storage conditions, the quantity of IP contained, and required caution statements and/or regulatory statement as applicable.

Daratumumab (Darzalex) will not be supplied by Celgene; instead it will be obtained according to local clinical study agreement and in accordance with local guidelines. Additional information may be included on the label as needed or applicable.

Outside the United States:

Durvalumab (MEDI4736), and Daratumumab (Darzalex) will be supplied by Celgene and labeled appropriately as investigational material. Labels will bear Celgene's name, telephone number and address, the protocol number, product name, dosage form and strength, medication identification kit/number, lot number, expiry date, dosing instructions, storage conditions, the quantity of IP contained, and required caution statements and/or regulatory statement as applicable.

7.1.1. Durvalumab (MEDI4736)

DURVA will be supplied by Celgene in single-use vials in single count cartons. Each 10 ml vial will be supplied as a vialed liquid solution containing 500 mg (nominal) of IP at a concentration of 50 mg/mL. DURVA should be stored in accordance with the product label.

Sites are to supply the following:

- IV infusion bags of normal saline (0.9% [w/v] sodium chloride injection, 250 mL size). Saline bags must be latex-free and can be made of polypropylene, polyethylene, polyolefin copolymers, or polyvinyl chloride. Infusion lines should contain a 0.2-µm in-line filter.
- Since the compatibility of DURVA with other IV medications and solutions, other than normal saline, is not known, the DURVA solution should not be infused through an IV line in which other solutions or medications are being administered.

For additional information on preparation and storage please refer to the pharmacy manual.

7.1.2. Daratumumab (Darzalex)

Daratumumab (Darzalex™) will be supplied by Celgene in single-use vials in single count cartons. Daratumumab is a colorless to pale yellow, preservative-free solution and will be supplied in 20 mL vials (20 m/mL) and/or 5 mL vials (20 mg/mL).

- Since the compatibility of DARA with other IV medications and solutions, other than normal saline, is not known, the DARA solution should not be infused through an IV line in which other solutions or medications are being administered.

For additional information on preparation and storage please refer to the pharmacy manual.

7.2. Treatment Administration and Schedule

The first day of study treatment dosing (DARA and/or DURVA) is considered Day 1 of a cycle.

7.2.1. Treatment Administration

On days when DARA and DURVA are dosed on the same day, the DARA infusion should be administered first, followed by the DURVA infusion. Simultaneous infusion of DARA and DURVA is prohibited.

- Since the compatibility of DARA or DURVA with other IV medications and solutions, other than normal saline, is not known, the DARA or DURVA solution should not be infused through an IV line in which other solutions or medications are being administered.
- If DARA and DURVA will be infused through the same port, the port must be flushed with saline prior to attaching dedicated DARA IV line.

7.2.1.1. Durvalumab (MEDI4736)

7.2.1.1.1. Durvalumab Product Dose Preparation/Administration

The IV infusion for subjects will be approximately 1 hour in duration.

For detailed information on DURVA dose preparation and administration please refer to the pharmacy manual.

7.2.1.1.2. Monitoring During/After Durvalumab Infusion

7.2.1.1.2.1. First DURVA infusion

For the first DURVA infusion (C1D2), blood pressure and pulse will be monitored, as follows (based on a 60-minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [ie, the beginning of the infusion])
- Approximately 30 minutes during the infusion (halfway through infusion)
- At the end of the infusion (approximately 60 minutes ±5 minutes)

If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated.

7.2.1.1.2.2. Subsequent DURVA infusions

For the subsequent DURVA infusions, vital signs will be measured prior to the start of the infusion. Subjects should be carefully monitored and blood pressure and other vital signs should be measured during and post infusion as per institution standard and as clinically indicated. Any clinically significant changes in vital signs should be entered onto an unscheduled vital signs electronic case report form (eCRF) page.

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and reinitiated at 50% of the initial rate until completion of the infusion. For patients with a ≤ Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen/paracetamol and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is ≥ Grade 3 or higher in severity, study drug will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

7.2.1.2. Daratumumab (Darzalex)

Subjects should be carefully observed during DARA infusions. Refer to the full prescribing information for DARA (Darzalex PI).

Pre-infusion and post infusion medications for infusion reaction prophylaxis will be given as detailed in Table 6 for all subjects.

7.2.1.2.1. Infusion-related Reactions of Grade 1 or Grade 2

If the investigator assesses an adverse event to be related to the infusion, then the infusion should be paused. When the subject's condition is stable, the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption. Subsequently, the infusion rate may be increased at the investigator's discretion.

If the subject experiences a Grade 2 or higher event of laryngeal edema, or a Grade 2 or higher event of bronchospasm that does not respond to systemic therapy and does not resolve within 6 hours from onset, then the subject must be withdrawn from daratumumab treatment.

7.2.1.2.2. Infusion-related Reactions of Grade 3 or Higher

For infusion-related adverse events that are Grade 4, the infusion should be stopped and the subject withdrawn from DARA treatment.

For infusion-related adverse events that are Grade 3, the infusion must be stopped and the subject must be observed carefully until resolution of the adverse event or until the intensity of the event decreases to Grade 1, at which point the infusion may be restarted at the investigator's discretion. Upon restart, the infusion rate should be half of that employed before the interruption.

Subsequently, the infusion rate may be increased at the investigator's discretion. If the intensity of the adverse event returns to Grade 3 after restart of the infusion, then the procedure described in this section should be repeated, or the subject may be withdrawn from treatment. Should the intensity of the adverse event increase to Grade 3 for a third time, then the subject must be withdrawn from DARA treatment.

Table 6: Daratumumab Pre Infusion and Post Infusion Medications

Time point	Medication	All Subjects
Pre infusion (~1 hr prior to every daratumumab (DARA) administration)	Oral montelukast (if approved and available)	per investigator discretion prior to first infusion
	Intravenous (IV) corticosteroid	methylprednisolone 100 mg or equivalent dose of an intermediate-acting or long-acting corticosteroid (Refer to Table 7 for conversion table). Following the second infusion, the dose of corticosteroid may be reduced (methylprednisolone 60 mg intravenously)
	oral antipyretics	acetaminophen 650 to 1000 mg[a]
	oral or IV antihistamine	diphenhydramine 25 to 50 mg or equivalent
Post infusion Medication (1^{st} and 2^{nd} day after every DARA administration)	oral corticosteroid[b]	20 mg methylprednisolone or equivalent dose of a corticosteroid in accordance with local standards

[a] If necessary, oral preinfusion medications may be administered at the subject's home on the day of the infusion, provided they are given within 3 hours prior to the infusion

[b] 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.

Table 7: Conversion Table for Glucocorticoid Dose

Generic Name	Oral or Intravenous Dose (mg)
Dexamethasone	0.75
Hydrocortisone	20
Methylprednisolone	4
Prednisolone	5
Prednisone	5

7.2.2. Treatment Schedule

7.2.2.1. Daratumumab Plus Durvalumab Treatment Schedule

See Section 3.1 for dosing rules.

- Intravenous DARA on the same dosing schedule received on last MM Dara-containing regimen
  - 16 mg/kg starting at the same dosing schedule; QW, Q2W, or Q4W, as their last DARA-containing MM therapy.
  - Dosing schedule should be adjusted as shown below; provided that the patient has a response of stable disease (SD) or better:
    - QW frequency (Days 1, 8, 15 and 22/28-day cycle): Weeks 1 to 8 then Q2W Weeks 9 to 24
    - Q2W frequency(Days 1, 15 of a 28-day cycle): Weeks 1 to 16 then Q4W
    - Q4W frequency (Day 1 of each 28-day cycle):Week 1 onwards until disease progression
- Intravenous DURVA:
  - 1500 mg on Day 2 of Cycle 1, then Day 1 of Cycle ≥ 2 of a 28-day cycle.

    NOTE: For all DURVA infusions after Cycle 1, a +1 day window is allowed (subject may either receive the DURVA infusion on same day as the DARA infusion or on the next day per the investigator's discretion; concomitant administration of DARA and DURVA is prohibited).

7.2.3. Overdose

Overdose, as defined for this protocol, refers to DURVA and DARA dosing only. On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of DURVA and DARA assigned to a given subject, regardless of any associated AEs or sequelae.

- For IV, 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as any amount more frequent than the protocol-required schedule or frequency. On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the eCRF. See Section 10.1 for the reporting of AEs associated with overdose.

7.2.4. Dose Modifications and Interruptions

Subjects will be evaluated for AEs at each visit with the NCI CTCAE Version 4.03 or higher as a guide for the grading of severity.

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

- If DURVA is permanently discontinued, then the subject must be permanently discontinued from all study treatments.
- If DARA is withheld or permanently discontinued, then DURVA dosing may be continued.

7.2.4.1. Dose Modification Instructions for Durvalumab

Refer to Appendix E for detailed instructions for DURVA dose modifications and toxicity management.

7.2.4.2. Dose Modification Instructions for Daratumumab

For dose modification instructions for DARA, refer to the full prescribing information (Darzalex PI).

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 non-hematologic 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,
  - Grade 3 fatigue or asthenia that lasts for <7 days after the last administration of DARA.

DARA treatment should be resumed when the toxicity has resolved to ≤Grade 2. If DARA administration does not commence within the pre-specified window (Table 8) of the scheduled administration date, then the dose will be considered a missed dose.

Administration may resume at the next planned dosing date. A missed dose will not be made up.

Table 8: Daratumumab-related Toxicity Management

Cycles	Dosing Frequency	Dose Miss	Dosing Resumption
1 and 2	Weekly (QW)	>3 days	next planned QW dosing date
3 to 6	Biweekly (Q2W)	>7 days	next planned Q2W dosing date
7+	Every 4 weeks (Q4W)	>21 days	next planned Q4W dosing date

Any dose delay of more than 28 days due to toxicity will result in permanent discontinuation of DARA. Dose delays of more than 28 days for other reasons should be discussed with the Sponsor.

7.2.4.2.1. Interruption or Missed Doses

A dose delay of 3 days or more from the planned date of administration for any reason other than toxicities suspected to be related to DARA should be brought to the attention of the Sponsor at the earliest possible time.

Subjects missing ≥3 consecutive planned doses of DARA for reasons other than toxicity should be withdrawn from treatment, unless, upon consultation with the Sponsor and the review of safety and efficacy, continuation is agreed upon.

7.3. Treatment Assignment

Celgene trial staff will review specific eligibility criteria for all screened subjects prior to initiation of study treatment via the IRT.

An IRT will be used to track subject assignments to the treatment stages and/or parts.

7.4. Packaging and Labeling

The label(s) for IP will include Sponsor name, address and telephone number, the protocol number, IP name, dosage form and strength (where applicable), 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.

7.5. Investigational Product Accountability and Disposal

Celgene (or designee) will review with the Investigator and relevant site personnel the process for investigational product return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.6. Investigational Product Compliance

Accurate recording of all study treatment administration (DURVA and DARA) will be made in the appropriate section of the subject's eCRF and source documents. The investigator or designee is responsible for accounting for all study-specific treatment (DURVA and DARA) either administered or in their custody during the course of the study.

8. CONCOMITANT MEDICATIONS AND PROCEDURES

Over the course of this study, additional medications may be required to manage aspects of the disease state of the subjects, including side effects from trial treatments or disease progression. Supportive care, including but not limited to anti-emetic medications, may be administered at the discretion of the investigator.

See Appendix E for additional details on DURVA toxicity management.

All concomitant treatments, including blood and blood products, used from 28 days prior to first dose of study treatment until 90 days after last dose of DURVA or DARA, whichever is later, must be reported on the eCRF.

For information regarding other drugs that may interact with IP and affect its metabolism, PK, or excretion, please see the IBs and/or local package inserts.

8.1. Permitted Concomitant Medications and Procedures

Subjects with myeloma-associated bone disease may receive bisphosphonate therapy prior to study entry, unless such therapy is contraindicated. The use of bisphosphonates is permitted throughout the study.

Platelet/RBC transfusions and hematopoietic growth factors are also permitted during the study.

Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.

8.2. Prohibited Concomitant Medications and Procedures

The following medications are prohibited (except for the outlined exceptions) during the study. The Sponsor must be notified if a subject receives any of these during the study.

1. Subjects who fail ANC, hemoglobin or platelet eligibility criteria at Screening should not be retested for the study after being treated with growth factors or platelet/RBC transfusion.
2. Any investigational anticancer therapy.
3. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment.
4. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers. The following exceptions apply:
    a. Pre and post infusion medications as outlined in Table 6 and Table 7 for the management of infusion-related reactions.
    b. Use of immunosuppressive medications in subjects with contrast allergies (eg, CT scan contrast hypersensitivity) is acceptable.
    c. Use of inhaled, topical, or intranasal corticosteroids or local steroid injections (eg, intra-articular injection) is permitted.

d. Temporary uses of corticosteroids for concurrent illnesses (eg, food allergies) are acceptable upon discussion and agreement with the Medical Monitor.

5. Live attenuated vaccines during the study through 30 days after the last dose of DURVA.
6. Herbal and natural remedies are to be avoided.
7. Egg cell and sperm donation

8.3. Required Concomitant Medications and Procedures

- **Infusion reaction prophylaxis:** Pre infusion and post infusion medications for infusion reaction prophylaxis will be given as detailed in Table 6.
- **Antiviral prophylaxis:** All subjects must initiate antiviral prophylaxis to prevent herpes zoster reactivation within 1 week of starting DARA and continue for 3 months following last dose of DARA.
  - Acceptable antiviral therapy includes acyclovir (eg, 400 mg given orally 3 times a day, or 800 mg given orally 2 times a day or per institutional standards), famciclovir (eg, 125 mg given orally, twice a day or per institutional standards), or valacyclovir (eg, 500 mg given orally, twice a day or per institutional standards), initiated within 1 week after the start of study drug.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

This is a single-arm, multicenter, Phase 2 study to evaluate the efficacy and safety of the combination regimen of DARA plus DURVA in subjects with RRMM who have progressed while on last MM treatment (DARA-containing regimen)

This section defines the subject populations for the statistical data analyses, the justifications of sample size, and the methodologies that will be used for the efficacy and safety analyses. All statistical analyses specified in the protocol will be conducted using SAS Version 9.2 or higher unless otherwise specified.

9.2. Study Population Definitions

For the purpose of statistical analyses and data presentation, the study populations are defined as follows:

9.2.1. Full Analysis Set Population

The full analysis set population (FAS) will include all enrolled subjects. The primary efficacy analyses will be performed on the FAS population.

9.2.2. Efficacy Evaluable Population

The supportive efficacy analyses will be performed on the efficacy evaluable (EE) population, which will include all enrolled subjects who take at least one dose of D^2 and who have measureable disease at baseline and at least one post-baseline efficacy measurement.

9.2.3. Safety Population

The safety population will include all subjects who take at least one dose of D^2. All safety analyses will be based on this population.

9.2.4. Pharmacokinetic Population

The PK population will include all subjects who received at least one dose of study treatment and who have at least one measureable plasma concentration. For subjects who are determined to be noncompliant with respect to administration of IP, or for subjects with incomplete data, a decision as to their inclusion in the population will be made on a case-by-case basis prior to the analysis.

9.3. Sample Size and Power Considerations

The study consists of 2 parts. In Part 1, a two-stage design with one interim analysis for futility at the end of Stage 1 is used. PASS software, Version 13.03 has been used to calculate the sample sizes. Setting the Type I error rate at 0.05, a total sample size of 50 subjects provides a power of at least 80% to reject the null hypothesis of ORR less than 10% with a target response rate of 25%. In Stage 1, 18 subjects will be enrolled and if there are at least 3 subjects out of 18 who achieved a response (PR or above) by end of cycle 3, the study will continue to Stage 2. If there are 2 or less subjects who achieved a response out of 18 subjects in Stage 1, the study will

be terminated for futility and will not proceed to Stage 2. In Stage 2, an additional 32 subjects will be enrolled. If there are at least 9 subjects who achieved a response out of a total of 50 subjects from Stages 1 and Stage 2, the null hypothesis will be rejected. If it is determined at the end of Part 1 to further evaluate the efficacy and safety of the combination regimen of DARA plus DURVA, then up to an additional 70 subjects will be enrolled in Part 2. This will bring the total number of subjects treated during the study up to approximately 120. The additional subjects will add to the certainty about the efficacy and safety of this combination therapy. Table 9 shows the exact 95% CIs around the response rates observed based on different scenarios. For example, if the observed ORR is 25%, the lower limit of the 95% CI will be 17.5%. If the observed ORR is 30%, the lower limit of the 95% CI will be 22.0%.

Table 9: Estimated Overall Response Rate and 95% Confidence Interval Out of 120 Subjects

Number of Responders in 120 Subjects	ORR	95% Confidence Interval
30	25.0 %	17.5, 33.7
31	25.8 %	18.3, 34.6
32	26.7 %	19.0, 35.5
33	27.5 %	19.7, 36.4
34	28.3 %	20.5, 37.3
35	29.2 %	21.2, 38.2
36	30.0 %	22.0, 39.0
37	30.8 %	22.7, 39.9
38	31.7 %	23.5, 40.8
39	32.5 %	24.2, 41.7
40	33.3 %	25.0, 42.5

ORR=overall response rate

9.4. Background and Demographic Characteristics

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

9.5. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

9.6. Efficacy Analysis

Primary efficacy analyses will be performed on the FAS population. Supportive efficacy analyses will also be performed using the EE population.

9.6.1. Primary Efficacy Endpoint

The primary efficacy endpoint will be based on the tumor response, including PD, as assessed by an IRAC using the IMWG Uniform Response Criteria.

The overall response rate (ORR) will be calculated as the number of responders (PR or better), divided by the number of subjects in the FAS population. The ORR together with the proportions in each category based on the IMWG criteria (ie, stringent complete response [sCR], complete response [CR], very good partial response [VGPR], partial response [PR], stable disease [SD], and disease progression [PD] will be tabulated, together with the 2-sided exact 95% CI.

This efficacy analysis will be conducted after the 18 subjects from Stage 1 have completed at least 3 cycles of treatment, Stage 2 of the Part 1 study and at the end of Part 2 of the study if the decision has been made to expand the study.

9.6.2. Secondary Efficacy Endpoints

Time-to-response (for responders only, per IMWG Uniform Response Criteria) is calculated as the time from treatment initiation of study treatment to the first date of documented response (PR or better). Time to response will be summarized using descriptive statistics.

Duration of response (for responders only, per IMWG criteria) is defined as time from the earliest date of documented response (PR or better) to the first documentation of PD or death, whichever is earlier. Duration of response will be analyzed using the Kaplan-Meier (KM) method. Median duration of response along with the two-sided CI will be provided.

Progression-free survival is defined as time from treatment initiation to the first date of documented PD or death from any cause during the study, whichever occurs earlier. Subjects who do not have a PFS event will be censored on the last adequate assessment date. PFS will be summarized using the KM method.

Overall survival is defined as time from treatment initiation to death due to any cause. Subjects who are alive or lost to follow-up will be censored on the last-known-alive date. The OS will be analyzed using the KM method. Median OS and the corresponding 95% CI will be provided.

9.7. Safety Analysis

All subjects in the safety population who receive at least 1 dose of DARA plus DURVA, will be included in the safety analyses. Adverse events, vital sign measurements, physical exam findings, clinical laboratory data, ECG interpretations, pregnancy tests for FCBP, concomitant medications and procedures will be tabulated and summarized.

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Adverse event listings will include the verbatim term and the MedDRA preferred tem. Adverse events will be graded according to the CTCAE Version 4.03 criteria.

The frequency of AEs will be tabulated by MedDRA SOC and PT. In the by-subjects analysis, a subject having the same event more than once will be counted only once. Adverse events leading to discontinuation from treatment, leading to dose reduction/interruption/delay, classified as CTCAE Grade 3 or higher, DARA, DURVA-related events, and serious AEs will be tabulated and listed separately. By-subject listings of all AEs, serious AEs, and their attributes will be provided.

Primary cause of death recorded on the eCRF death form will be coded according to MedDRA and summarized by SOC and PT. By-subject listing of death will also be provided.

Clinical laboratory results will be summarized descriptively and will include a display of change from baseline. Laboratory values outside of the normal ranges will be identified. Laboratory data will be graded according to CTCAE Version 4.03 criteria for select analytes unless otherwise specified. The frequencies of the worst severity grade observed during treatment will be displayed in cross-tabulations by screening status.

9.8. Interim Analysis

This study will be conducted in 2 parts. Part 1 and Part 2. Part 1 consists of one pre-planned interim analysis for futility purposes at the completion of Stage 1.

9.9. Other Topics

9.9.1. Pharmacokinetic Analysis

Noncompartmental PK parameters such as time to maximum concentration (T_{max}), maximum observed concentration (C_{max}), area under the curve (AUC), terminal elimination half-life ($t_{1/2}$), clearance (CL/F), and volume of distribution (V_z/F) will be estimated from the plasma concentration-time profile. All concentration data and PK parameters will be summarized descriptively.

CCI [redacted]

[redacted]

9.10. Study Committees

9.10.1. Data Monitoring Committee

An external and independent DMC with multidisciplinary representation will be established to monitor the safety data regularly.

The DMC will review the safety and the efficacy data at the end of Stage 1. If the study is to proceed to Stage 2, the DMC will also review the safety and efficacy data at the end of Stage 2.

The DMC chairman may convene formal DMC meetings if there are any unusual safety/efficacy concerns. The Sponsor can also request a DMC review of the safety data if unexpected safety concerns arise during the conduct of the trial. The DMC responsibilities, authorities, and procedures will be detailed in the DMC charter.

9.10.2. Independent Review Adjudication Committee

An IRAC will be set up for this trial to assess the response data for each subject using the IMWG Uniform Response Criteria. The IRAC will determine the tumor response to therapy and to confirm the time of disease progression (PD) (if disease progressed) at scheduled or unscheduled visits for each subject.

10. ADVERSE EVENTS

10.1. 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 10.3), regardless of etiology. Any worsening (ie, any clinically significant adverse change in the frequency or intensity of a preexisting condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the case report form (eCRF) rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an IP 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 eCRF (see Section 7.2.3 for the definition of overdose). Any sequela of an accidental or intentional overdose of an IP 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 DURVA, or DARA, overdose. Actual treatment should depend on the severity of the clinical situation and the judgment 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 findings from other tests and/or procedures.

All AEs will be recorded by the Investigator from the time the subject signs informed consent until 90 days after the last dose of DURVA or DARA, whichever is later, as well as those SAEs made known to the Investigator at any time thereafter that are suspected of being related to study IPs (DARA, DURVA). Adverse events 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.

10.2. Evaluation of Adverse Events

A qualified Investigator will evaluate all AEs as to:

10.2.1. 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.

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 start of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- an elective treatment of or an elective procedure for a pre-existing condition, unrelated to the studied indication, that has not worsened from baseline.
- 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 the IP, action taken regarding the IP, and outcome.

10.2.2. Severity/Intensity

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

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03 or higher);
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

Adverse events that are not defined in the CTCAE should be evaluated for severity/intensity 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.

10.2.3. Causality

The Investigator must determine the relationship between the administration of the IPs (DARA, DURVA) and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	A causal relationship of the AE to IPs (DARA, DURVA) administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.
Suspected:	There is a **reasonable possibility** that the administration of IPs (DARA, DURVA) caused the AE. '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.

10.2.4. Duration

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

10.2.5. Action Taken

The Investigator will report the action taken with IPs (DARA, DURVA) as a result of an AE or SAE, as applicable (eg, discontinuation, interruption, or dose reduction of IPs, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

The Investigator will report the outcome of the event for both AEs and SAEs.

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

10.3. Abnormal Laboratory Values

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

- results in discontinuation from the study; or
- requires treatment, modification/ interruption of IPs (DARA, DURVA) dose, or any other therapeutic intervention; or
- is judged to be of significant clinical importance, eg, one that indicates a new disease process and/or organ toxicity, or is an exacerbation or worsening of an existing condition.

Regardless of severity grade, only laboratory abnormalities that fulfill a seriousness criterion need to be documented as an SAE.

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. If possible, the laboratory abnormality should be recorded as a medical term and not simply as an abnormal laboratory result (eg, record thrombocytopenia rather than decreased platelets).

10.4. Pregnancy

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

10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated β-subunit human chorionic gonadotropin [β-hCG]) or positive pregnancy test in a female subject of childbearing potential regardless of disease state) occurring while the subject is on study treatment, or within 90 days after last dose of DURVA / DARA, whichever occurs later are considered immediately reportable events. Investigational product is to be discontinued immediately *and the subject instructed to return any unused portion 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 Pregnancy Initial Report Form, or approved equivalent form.

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

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

If the outcome of the pregnancy was abnormal (eg, spontaneous 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 IPs (DARA, DURVA) 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.

10.4.2. Male Subjects

If a female partner of a male subject taking IPs (DARA, DURVA) becomes pregnant, the male subject taking IPs (DARA, DURVA) should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

10.5. 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 (eg, via email), using the SAE Report Form, or approved equivalent form. This instruction pertains to initial SAE reports as well as any follow-up reports.

The Investigator is required to ensure that the data on these forms are accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IPs [DARA, DURVA]) that occur during the study (from the time the subject signs informed consent until 90 days after the last dose of DURVA or DARA, whichever is later) or any SAEs made known to the Investigator at any time thereafter that are suspected of being related to IPs (DARA, DURVA). Serious adverse events occurring prior to treatment (after signing the ICF) will be captured.

The SAE report should provide a detailed description of the SAE and include a concise summary 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 should 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/Ethics Committee (IRB/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.

10.5.1. 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 five (5) business days. Urgent queries (eg, missing causality assessment) may be handled by phone.

10.6. 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 DURVA and DARA based on their respective IBs.

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.

For countries within the European Economic Area (EEA), Celgene or its authorized representative will report in an expedited manner to Regulatory Authorities and Ethics Committees concerned, SUSARs in accordance with Directive 2001/20/EC and the Detailed Guidance on collection, verification and presentation of adverse reaction reports arising from clinical trials on IPs for human use (ENTR/CT3) and also in accordance with country-specific requirements.

Events of 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 AEs and will not be reported as expedited safety reports to regulatory authorities.

Celgene or its authorized representative shall notify the Investigator of the following information:

- Any AE suspected of being related to the use of IPs (DARA, DURVA) in this study or in other studies that is both serious and unexpected (ie, suspected unexpected serious adverse reaction [SUSAR]);
- Any finding from tests in laboratory animals that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity.

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 14.3 for record retention information).

Celgene Drug Safety Contact Information:

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

10.7. Adverse Events of Special Interest

An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of DURVA(MEDI4736) and may require close monitoring and rapid communication by the Investigator to the Sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of durvalumab.

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an AE being an irAE, the Investigator should promptly contact the Medical Monitor.

Further information on these AESIs (eg, presenting symptoms) can be found in the current version of the DURVA IB (Section 5.5.2 Summary of Risks).

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the investigational product(s):

- Adverse event
- Withdrawal by subject
- Pregnancy
- Death
- Lost to follow-up
- Other (to be specified on the CRF)

The reason for discontinuation of treatment should be recorded in the CRF and in the source documents.

The decision to discontinue a subject from treatment 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.

11.2. Study Discontinuation

The following events are considered sufficient reasons for discontinuing a subject from the study:

- Screen failure
- Adverse event
- Withdrawal by subject
- Pregnancy
- Death
- Lost to follow-up
- Other (to be specified on the CRF)

The reason for study discontinuation should be recorded in the CRF and in the source documents.

12. EMERGENCY PROCEDURES

12.1. 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/contract research organization 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.

12.2. Emergency Identification of Investigational Products

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

13. REGULATORY CONSIDERATIONS

13.1. 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 Council 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.

13.2. 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, including obligations of confidentiality of Celgene information. 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 form (ICF) 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.

The information contained in the protocol and amendments (with the exception of the information provided by Celgene on public registry websites) is considered Celgene confidential information. Only information that is previously disclosed by Celgene on a public registry website may be freely disclosed by the Investigator or its institution, or as outlined in the Clinical Trial Agreement. Celgene protocol, amendment and IB information is not to be made publicly available (for example on the Investigator's or their institution's website) without express written approval from Celgene. Information proposed for posting on the Investigator's or their institution's website must be submitted to Celgene for review and approval, providing at least 5 business days for review.

At the time results of this study are made available to the public, Celgene will provide Investigators with a summary of the results that is written for the lay person. The Investigator is responsible for sharing these results with the subject and/or their caregiver as agreed by the subject.

13.3. 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 ICF 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 ICF 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 ICF. The revised ICF 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.

13.4. 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 ICF, it is the responsibility of the Investigator to obtain such permission in writing from the appropriate individual.

13.5. 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.

13.6. Institutional Review Board/Independent Ethics Committee Review and Approval

Before the start of the study, the study protocol, ICF, 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.

IP can only be supplied to an Investigator by Celgene or its authorized representative after documentation on 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 ICF 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.

13.7. 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 AEs 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.

13.8. Termination of the Study

Celgene reserves the right to terminate this study prematurely 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, etc).

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.

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

The Investigator must ensure that the records and documents pertaining to the conduct of the study and the distribution of the IP 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.

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene SOPs. 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.

14.3. Record Retention

Essential documents must be retained by the Investigator according to the period of time outlined in the clinical trial agreement. 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 ICFs 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. The Investigator or institution should take measures to prevent accidental or premature destruction of these documents.

15. 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 SOPs.

15.1. Study Monitoring and Source Data Verification

Celgene ensures that appropriate monitoring procedures are performed before, during and after the study. All aspects of the study are reviewed with the Investigator and the staff at a study initiation visit and/or at an Investigators' Meeting. 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. During monitoring visits, the facilities, investigational product storage area, CRFs, subject's source documents, and all other study documentation will be inspected/reviewed by the Celgene representative in accordance with the Study Monitoring Plan.

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.

15.2. 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/ECs, regulatory authorities (eg, FDA, EMA, Health Canada) 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.

16. PUBLICATIONS

As described in Section 13.2, all protocol- and amendment-related information, with the exception of the information provided by Celgene on public registry websites, is considered Celgene confidential information and is not to be used in any publications. Celgene protocol-related information proposed for use in a publication must be submitted to Celgene for review and approval, and should not be utilized in a publication without express written approval from Celgene, or as described in the Clinical Trial Agreement.

Celgene will ensure Celgene-sponsored studies are considered for publication in the scientific literature in a peer-reviewed journal, irrespective of the results. At a minimum, this applies to results from all Phase 3 clinical studies, and any other study results of significant medical importance. This also includes results relating to investigational medicines whose development programs have been discontinued.

Study results may also be presented at one or more medical congresses, and may be used for scientific exchange and 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.

Eligibility for external authorship, as well as selection of first authorship, will be based on several considerations, including, but not limited to, contribution to protocol development, study recruitment, data quality, participation in data analysis, participation in study steering committee (when applicable) and contribution to abstract, presentation and/or publication development.

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18. APPENDICES

Appendix A: Table of Abbreviations

Table 10: Abbreviations and Specialist Terms

Abbreviation or Specialist Term	Explanation
ADCC	Antibody-dependent cell-mediated cytotoxicity
ADL	Activity of daily life
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
AUC	Area under the curve
BM	Bone marrow
β-hCG	β-subunit of human chorionic gonadotropin
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BUN	Blood urea nitrogen
C	Cycle
CBC	Complete blood count
CD	Cluster of differentiation
CDC	Complement-dependent cytotoxicity
CIs	Confidence intervals
CIPs	Complementary-inhibitory proteins
CL/F	Clearance
C_{max}	Maximum observed concentration
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
CR	Complete response
CrCl	Creatinine clearance
CT	Computed tomography

Table 10: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
CTCAE	Common Terminology Criteria for Adverse Events
D	Day
D^2	Daratumumab plus durvalumab
DARA	Daratumumab
DURVA	Durvalumab
DLT	Dose-limiting toxicity
DMC	Data Monitoring Committee
DNA	Deoxyribonucleic acid
DOR	Duration of response
DRT	Dose Review Team
EC	Ethics Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
EE	Efficacy evaluable
EEA	European Economic Area
EMP	Extramedullary plasmacytoma
EOI	End of infusion
EOT	End of Treatment
EU	European Union
FAS	Full analysis set
Fc	Fragment crystallizable
FCBP	Females of childbearing potential
FDA	Food and Drug Administration
FEV	Forced expiratory volume
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
IAT	Indirect antiglobulin test
IB	Investigator's Brochure

Table 10: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ICF	Informed consent form
ICH	International Council on Harmonisation
IFNγ	Interferon gamma
Ig	Immunoglobulin
ILD	Interstitial lung disease
IMWG	International Myeloma Working Group
IMiD	Immunomodulatory drug
IND	Investigational New Drug
IP	Investigational product
IRAC	Independent Response Adjudication Committee
irAE	Immune related adverse events
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITT	Intent to treat
IV	Intravenous
KM	Kaplan-Meier
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MR	Minimal response
MRI	Magnetic resonance imaging
CCI	[redacted]
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural killer cells
NOAEL	No observed adverse effect level
ORR	Overall response rate
OS	Overall survival
CCI	[redacted]
PD	Disease progression

Table 10: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
PD-1	Programmed cell death-1
PD-L1	Programmed death-ligand 1
PFS	Progression-free survival
PI	Proteasome inhibitor
PI	Prescribing Information
PK	Pharmacokinetics
PR	Partial response
PT	Preferred term
QW	Weekly
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RBC	Red blood cell
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	Ribonucleic acid
RRMM	Relapsed and refractory multiple myeloma
SAE	Serious adverse event
sCR	Stringent complete response
SD	Stable disease
SmPC	Summary of Product Characteristics
SOC	System organ class
SOP	Standard operating procedure
sPD-L1	Soluble programmed death-ligand 1
sPEP	Serum protein electrophoresis
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal elimination half-life
T_{max}	Time to maximum concentration
TCR	T-cell receptor
TSH	Thyroid stimulating hormone
Tregs	Regulatory t-cells
TTR	Time-to-response

Table 10: Abbreviations and Specialist Terms (Continued)

Abbreviation or Specialist Term	Explanation
ULN	Upper limit of normal
uPEP	Urine protein electrophoresis
USA	United States of America
VGPR	Very good partial response
VTE	Venous thromboembolism
V_z/F	Volume of distribution
WBC	White blood cell

Appendix B: International Myeloma Working Group Uniform Response Criteria

Response Category[a]	Response Criteria
Stringent Complete Response (sCR)	Complete response (CR) as defined below, *plus* Normal serum free light chain (FLC) ratio *and* Absence of clonal plasma cells by immunohistochemistry or 2- to 4-color flow cytometry
Complete Response (CR)	Negative immunofixation of serum and urine *and* Disappearance of any soft tissue plasmacytomas *and* ≤ 5% plasma cells in bone marrow In patients in whom the only measurable disease is by serum FLC levels: CR in such patients indicates a normal FLC ratio of 0.26 to 1.65 in addition to CR criteria listed above.
Very Good Partial Response (VGPR)	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 In patients in whom the only measurable disease is by serum FLC levels: VGPR in such patients requires a > 90% decrease in the difference between involved and uninvolved FLC levels.
Partial Response (PR)	≥ 50% reduction of serum M-Protein and reduction in 24-hour urinary M-protein by ≥ 90% or to < 200 mg per 24 hours If the serum and urine M-protein are not measurable, a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria. If serum and urine M-protein are unmeasurable, and the serum free light chain assay is also unmeasurable, a ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above, if present at baseline a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, or progressive disease (PD)

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

Response Category[a]	Response Criteria
Progressive disease (PD)	**Requires only one of the following:** Increase of 25% from lowest response value in any of the following: • Serum M-component (absolute increase must be ≥ 0.5 g/dL), *and/or* • Urine M-component (absolute increase must be ≥ 200 mg/24 h), *and/or* Only in patients without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels (absolute increase must be ≥ 10 mg/dL) Only in patients without measurable serum and urine M protein levels and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute percentage must be ≥ 10%) Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder
Additional Response Criteria	
Molecular Complete Response	CR plus negative allele-specific oligonucleotide polymerase chain reaction (ASO-PCR), sensitivity 10^{-5}
Immunophenotypic Complete Response	Stringent CR *plus* Absence of phenotypically aberrant plasma cells (clonal) in bone marrow (BM) with a minimum of 1 million total BM cells analyzed by multiparametric flow cytometry (with > 4 colors)
Minimal Response (MR) in patients with relapsed refractory myeloma adopted from the European Group for Blood and Marrow Transplantation (EBMT) criteria	≥ 25% but ≤ 49% reduction of serum M-protein and reduction in 24-hour urine M-protein by 50%-89% In addition to the above criteria, if present at baseline, 25%-49% reduction in the size of soft tissue plasmacytomas is also required No increase in size or number of lytic bone lesions (development of compression fracture does not exclude response)

[a] All response categories (CR, sCR, VGPR, PR, and PD) require 2 consecutive assessments made at any time before the institution of any new therapy; CR, sCR, VGPR, PR, and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable on serum, urine, both, or neither. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For PD, serum M-component increases of more than or equal to 1 g/dL are sufficient to define relapse if the starting M-component is ≥ 5 g/dL.

Appendix C: ECOG Performance Status

Eastern Cooperative Oncology Group (ECOG) Performance Status

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

Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

Appendix D: Staging Systems for Multiple Myeloma

Table 11: Staging Systems for Multiple Myeloma

Stage	Durie-Salmon Criteria[a]	International Staging System (ISS) Criteria[b]
I	*All of the following:* 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 g/dL; IgA value < 3 g/dL Urine light chain M-component on electrophoresis < 4 g/24h	Serum beta-2 microglobulin < 3.5 mg/L Serum albumin ≥ 3.5 g/dL
II	Neither Stage I nor Stage II	Neither Stage I nor Stage II
III	*One or more of the following:* 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 g/dL; IgA value > 5 g/dL Urine light chain M-component on electrophoresis > 12 g/24h	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

[a] Durie, 1975.
[b] Greipp, 2005.

Appendix E: Durvalumab Treatment Modification and Toxicity Management Guidelines

Note: The toxicity management guidelines in Appendix E-1, E-2, and E-3 prepared by the Sponsor are to assist the investigator in the exercise of his/her clinical judgment in treating these types of toxicities and should be applied to management of adverse events related to study treatment and not ANY adverse event.

Appendix E-1: Durvalumab Treatment Modification and Toxicity Management Guidelines for Immune-related Adverse Events

<table>
<tr><th colspan="3">Immune-Mediated Reactions</th></tr>
<tr><th></th><th>Dose Modifications</th><th>Toxicity Management</th></tr>
<tr><td rowspan="2">Immune-related Adverse Events (Overall Management For toxicities not noted below)</td><td>Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03.
In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions:
• Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/regimen
• Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.</td><td rowspan="2">It is recommended that management of irAEs follow the guidelines presented in this table
– Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, infections, etc.)
– In the absence of a clear alternative etiology, all events should be considered potentially immune related.
– Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events
– For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone PO 1-2mg/kg/day PO or IV equivalent
– If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2-4mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper)
– More potent immunosuppressives such as TNF inhibitors (eg, infliximab) – (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic</td></tr>
<tr><td>Grade 1 No dose modification
Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1
• If toxicity worsens then treat as Grade 3 or Grade 4
Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to Grade ≤1 after completion of steroid taper
Patients with endocrinopathies who may require prolonged or continued steroid replacement</td></tr>
</table>

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
		can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10 mg/day or equivalent.	steroids. – Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient
	Grade 3	Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below	
	Grade 4	Permanently discontinue study drug/study regimen	
	Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen		
Pneumonitis/ILD	Grade of Pneumonitis (CTCAE version 4.03)	General Guidance	– Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) – Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated – Consider pulmonary and infectious disease consult

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 then the decision to reinitiate study drug/regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	For Grade 2 (Mild to Moderate New Symptoms) – Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (eg, prednisone 1-2mg/kg/day PO or IV equivalent) – Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started – If still no improvement within 3-5 days despite IV methylprednisone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[a,b] – Consider pulmonary and infectious disease consult – Consider as necessary discussing with study physician
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention	Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain pulmonary and infectious disease consult – Hospitalize the patient – Supportive Care (oxygen, etc.) – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	indicated [eg, tracheostomy or intubation])		additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[a]
Diarrhea/ Enterocolitis	Grade of Diarrhea (CTCAE version 4.03)	General Guidance	– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) – Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event – Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 diarrhea (stool frequency of <4 over baseline per day)	No dose modification	For Grade 1 diarrhea : – Close monitoring for worsening symptoms – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
	Grade 2 diarrhea (stool frequency of	Hold study drug/study regimen until resolution to ≤ Grade 1	For Grade 2 diarrhea: – Consider symptomatic treatment including hydration,

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	4-6 over baseline per day)	• If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 then study drug/study regimen can be resumed after completion of steroid taper	electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5 mg/kg once every 2 weeks[3]). **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Consult study physician if no resolution to ≤ Grade 1 in 3-4 days – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

[3] ASCO Educational Book 2015 Michael Postow MD "Managing Immune Checkpoint Blocking Antibody Side Effects.

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen	For Grade 3 or 4 diarrhea: – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent – Monitor stool frequency and volume and maintain hydration – Urgent GI consult and imaging and/or colonoscopy as appropriate – If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (eg, infliximab at 5 mg/kg once every 2 weeks). – Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis**	Grade of Liver Function Test Elevation (CTCAE version 4.03) Any Grade Grade 1 (AST or ALT > to 3 times ULN and/or TB > to 1.5 times ULN)	No dose modification If it worsens, treat as Grade 2 event	– Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications) For Grade 1 AST or ALT and/or TB elevation – Continue LFT monitoring per protocol

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or TB >1.5-3.0 times ULN)	Hold Study drug/study regimen dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 or baseline resume study drug/study regimen after completion of steroid taper	For Grade 2 AST or ALT and or TB elevation : – Regular and frequent checking of LFTs (eg, every 1-2 days) until elevations of these are improving or resolved. – If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day PO or IV equivalent. – If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone PO or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[4]. Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 (AST or ALT >5-20 times ULN and/or TB > 3.0-10 times ULN	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN -Hold study drug/study regimen dose until resolution to ≤ Grade 1 or baseline -Resume study drug/study regimen if elevations downgrade ≤ Grade 1 or	For Grade 3 or 4 AST or ALT and/or TB elevation: – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent – If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent,

[4] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects", by Michael Postow MD.

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
		baseline within 14 days and after completion with steroid taper. Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue study drug/study regimen Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause[iv]	promptly start treatment with immunosuppressive therapy (mycophenolate mofetil) Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Hepatology consult, abdominal workup, and imaging as appropriate. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 4 (AST or ALT > 20 times ULN and/or TB > 10 times ULN)	Permanently discontinue study drug/study regimen	
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Grade of Elevated Serum Creatinine (CTCAE version 4.03) Any Grade	General Guidance	– Consult with Nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.) – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections etc.) – Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	Grade 1 [Serum Creatinine > 1-1.5 X baseline; > ULN to 1.5 X ULN]	No dose modification	For Grade 1 elevated creatinine: – Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity, treat as Grade 2 or Grade 3 or 4 – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
	Grade 2 [Serum Creatinine>1.5-3.0 X baseline; >1.5 X-3.0 X ULN]	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper.	For Grade 2 elevated creatinine: – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult Nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4mg/kg/day started. – Once improving gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	Grade 3 or 4 (Grade 3: Serum Creatinine > 3.0 X baseline; >3.0-6.0 X ULN Grade 4: Serum Creatinine > 6.0 X ULN)	Permanently discontinue study drug/study regimen	– Carefully monitor serum creatinine on daily basis – Consult Nephrologist and consider renal biopsy if clinically indicated – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]
Rash (excluding Bullous skin formations)	Grade of Skin Rash (Please refer to NCI CTCAE version 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****
	Grade 1	No dose modification	For Grade 1: – Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream)
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen	For Grade 2 : – Obtain dermatology consult

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
		until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves to ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper.	– Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream) – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent – Consider skin biopsy if persistent for >1-2 weeks or recurs
	Grade 3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue Study drug/study regimen	For Grade 3 or 4: – Consult dermatology – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – Discuss with Study Physician
	Grade 4	Permanently discontinue study drug/study regimen	

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)	General Guidance	– Consult Endocrinologist – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, infections, etc.) – Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
	Grade 1 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade 1)	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) – Monitor patient with appropriate endocrine function tests – If TSH < 0.5 X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	Grade 2 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 2)	For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the patient is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10 mg/day or equivalent.	For Grade 2: (including those with symptomatic endocrinopathy) – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids – Initiate hormone replacement as needed for management – Evaluate endocrine function, and as clinically indicated, consider pituitary scan – For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (eg, 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, Levothyroxine, hydrocortisone, or sex hormones). - – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	Grade 3 or 4 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 3 or 4)	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper	For Grade 3 or 4: – Consult endocrinologist – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity – Once improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – Discuss with study physician
Immune mediated Neurotoxicity (to include but not limited to limbic encephalitis. autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Grade of Neurotoxicity Depending on the type of neurotoxicity, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity		
	Any Grade	General Guidance	– Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc.)

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
			– Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations) – Symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	See "Any Grade" recommendations above.
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to ≤ Grade 1 • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1. o If toxicity worsens then treat as Grade 3 or Grade 4 • Study drug/study regimen can be resumed once event improves to ≤ Grade 1 stabilizes after completion of steroid taper	– Discuss with the study physician – Obtain Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) – Promptly start systemic steroids prednisone 1-2mg/kg/day PO or IV equivalent – If no improvement within 3-5 days despite 1-2mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IVIG)
	Grade 3	• Hold Study drug/study regimen dose until resolution to ≤ Grade 1	For Grade 3 or 4: – Discuss with study physician

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
		• Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days.	– Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IVIG) – Once stable, gradually taper steroids over ≥28 days
	Grade 4	• Permanently discontinue study drug/study regimen	
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis		General Guidance	– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG

Immune-Mediated Reactions			
	Dose Modifications		**Toxicity Management**
	Grade 1	No dose modification	– Discuss with the study physician – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a neurology consult unless the symptoms are very minor and stable
	Grade 2	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue study drug/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	Grade 2 – Discuss with the study physician – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above – Obtain a Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) • *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. • *GUILLAIN-BARRE:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.

Immune-Mediated Reactions			
	Dose Modifications		Toxicity Management
	Grade 3	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: – Discuss with study physician – Recommend hospitalization – Monitor symptoms and obtain neurological consult • *MYASTHENIA GRAVIS* ○ Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. ○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. ○ If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. • *GUILLAIN-BARRE*: • Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 4	Permanently discontinue study drug/study regimen	

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b] NCI CTCAE version 4.03.
FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

Appendix E-2: Durvalumab Treatment Modification and Toxicity Management Guidelines for Infusion-related Reactions

Infusion-Related Reactions		
Severity Grade	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance	– Management per institutional standard at the discretion of investigator – Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator – Consider premedication per institutional standard prior to subsequent doses – Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions.
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

Appendix E-3: Durvalumab Treatment Modification and Toxicity Management Guidelines for Non-immune-mediated Reactions

Non-immune Mediated Reactions (Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician"		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modification**	**Toxicity Management**
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (ie, events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the Sponsor)	Treat accordingly as per institutional standard

AChE = acetylcholine esterase; ADA = American Dietetic Association; ADL= activity of daily life; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN= blood urea nitrogen; CT = computed tomography; CTC= common terminology criteria; GI = gastrointestinal; FT4= free T4; ILD = interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; LFT= liver function tests; LLN= lower level normal; MRI=magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TB= total bilirubin; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

Appendix F: Guideline for Asthma Eligibility Criteria

Components of Severity		Classification of Asthma Severity								
		Intermittent			Persistent					
					Mild			Moderate		Severe
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
Impairment	Symptoms	≤ 2 days/week			≤ 2 days/week but not daily			Daily			Throughout the day		
	Nighttime awakenings	0	≤ 2x/month		1-2x/ month	3-4x/month		3-4x/ month	> 1x/week but not nightly		> 1x/ month	Often 7x/week	
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			≤ 2 days/week but not daily		>2 days/ week but not daily, and not more than 1x on any day	Daily			Several time per day		
	Interference with normal activity	None			Minor limitation			Some limitation			Extremely limited		
Normal FEV_1/FVC : 8-19 yr 85% 20-39 yr 80% 40-59 yr 75% 60-80 yr 70%	Lung function FEV_1 FEV_1/FVC	N/A	Normal FEV_1 between exacerbations > 80% > 85%	Normal FEV_1 between exacerbations > 80% Normal	N/A	> 80% > 80%	> 80% Normal	N/A	60-80% 75-80%	60-80% Reduced 5%	N/A	< 60% < 75%	< 60% Reduced 5%
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma	≥ 2/year Relative annual risk may be related to FEV_1.	≥ 2/year Relative annual risk may be related to FEV_1.
		← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →											
Recommended Step for Initiating Treatment		Step 1			Step 2			Step 3 and consider short course of oral steroids	Step 3: medium dose ICS and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3 and consider short course of oral steroids	Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids	Step 4 or 5 and consider short course of oral steroids
		In 2-6 weeks, evaluate level of asthma control that is achieved. 0-4 years: If no clear benefit is observed in 4-6 weeks, stop treatment and consider alternate diagnosis or adjusting therapy. 5-11 and 12+ years: adjust therapy accordingly.											

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Appendix F: Guideline for Asthma Eligibility Criteria (Continued)

Components of Control		Classification of Asthma Control								
		Well Controlled			Not Well Controlled			Very Poorly Controlled		
		0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs	0-4 yrs	5-11 yrs	12 + yrs
	Symptoms	≤ 2 days/week but not more than once on each day		≤ 2 days/ week	> 2 days/week or multiple times on ≤2 days/week		> 2 days/ week	Throughout the day		
Impairment	Nighttime awakenings	≤ 1x/month		≤ 2x/month	> 1x/month	≥ 2x/month	1-3x/week	> 1x/week	≥ 2x/week	≥ 4x/week
	Interference with normal activity	None			Some limitation			Extremely limited		
	SABA use for symptom control (not prevention of EIB)	≤ 2 days/week			> 2 days/week			Several times per day		
	Lung function FEV_1 or peak flow FEV_1/FVC	N/A	> 80% > 80%	> 80%	N/A	60-80% 75-80%	60-80%	N/A	< 60% < 75%	< 60%
	Validated questionnaires ATAQ ACQ ACT			0 ≤ 0.75 ≥ 20			1-2 ≥ 1.5 16-19			3-4 N/A ≤ 15
Risk	Exacerbations requiring oral systemic corticosteroids	0-1/year			≥ 2/year					
		Consider severity and interval since last exacerbation								
	Reduction in lung growth/ Progressive loss of lung function	Evaluation requires long-term follow-up								
Recommended Action for Treatment		• Maintain current step • Regular follow-up every 1-6 months • Consider step down if well controlled for at least 3 months			Step up 1 step • **Before step up:** Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control.** 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.	Step up at least 1 step	• Step up 1 step • Reevaluate in 2-6 weeks • For side effects, consider alternative treatment options	• Consider short course of oral steroids • Step up 1-2 steps • **Before step up:** Review adherence to medication, inhaler technique, and environmental control. If alternative treatment was used, discontinue it and use preferred treatment for that step. • **Reevaluate the level of asthma control in 2-6 weeks to achieve control.** 0-4 years: If no clear benefit is observed in 4-6 weeks, consider alternative diagnoses or adjusting therapy. 5-11 years: Adjust therapy accordingly. • **For side effects**, consider alternative treatment options.		• Consider short course of oral steroids • Step up 1-2 steps • Reevaluate in 2 weeks • For side effects, consider alternative treatment options

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Title: PPD
Date: Monday, 03 October 2016, 03:24 PM Eastern Daylight Time
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