Official Title of Study:

A Phase 2, Multicenter, Open-label, Study to Determine the Safety and Efficacy for the Combination of Durvalumab (DURVA) and Daratumumab (DARA) (D2) in Subjects With Relapsed and Refractory Multiple Myeloma (RRMM) (FUSION MM-003)

PROTOCOL MEDI4736-MM-003

NCT Number: NCT02807454

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A PHASE 2, MULTICENTER, OPEN-LABEL, STUDY TO DETERMINE THE SAFETY AND EFFICACY FOR THE COMBINATION OF DURVALUMAB (DURVA) AND DARATUMUMAB (DARA) (D^2) IN SUBJECTS WITH RELAPSED AND REFRACTORY MULTIPLE MYELOMA (RRMM) (FUSION MM-003)

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CELGENE THERAPEUTIC AREA HEAD SIGNATURE PAGE

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
[redacted]
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

{See appended electronic signature page}
Signature of Celgene Therapeutic Area Head **dd mmm yyyy**
Printed Name of Celgene Therapeutic Area Head and Title
By my signature, I indicate I have reviewed this protocol and find its content to be acceptable.

SITE PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Site Principal Investigator	**dd mmm yyyy**
Printed Name of Site Principal Investigator **Institution Name:**_____ By my signature, I agree to personally supervise the conduct of this study at my study site and to ensure its conduct is in compliance with the protocol, informed consent, Institutional Review Board (IRB)/Ethics Committee (EC) procedures, instructions from Celgene representatives, the Declaration of Helsinki, International Council for Harmonisation (ICH) Good Clinical Practices Guidelines, and local regulations governing the conduct of clinical studies.	

COORDINATING PRINCIPAL INVESTIGATOR SIGNATURE PAGE

Signature of Coordinating Principal Investigator	**dd mmm yyyy**
Printed Name of Coordinating Principal Investigator **Institution Name:**_____ By my signature, I agree the protocol has been written to comply with ICH Good Clinical Practices guidelines and agree to offer guidance throughout the study as needed.	

PROTOCOL SUMMARY

On 05 Sep 2017, a Partial Clinical Hold was placed on this study by the United States (US) Food and Drug Administration (FDA). The decision by the FDA was based on data related to risks of anti-programmed cell death-1 (PD-1) antibody, pembrolizumab, in combination with immunomodulatory drugs (IMiDs®) in patients with multiple myeloma. As a result, enrollment into this study has been discontinued. Subjects who are receiving clinical benefit, based on the discretion of the investigator, may remain on study treatment after being reconsented.

Study Title

A Phase 2, Multicenter, Open-label, Study to Determine the Safety and Efficacy for the Combination of Durvalumab (DURVA) and Daratumumab (DARA) (D^2) in Subjects with Relapsed and Refractory Multiple Myeloma (RRMM)

Indication

Multiple myeloma with at least 3 prior therapies including a proteasome inhibitor (PI) and an immunomodulatory agent or double-refractory to a PI and an immunomodulatory agent.

Objectives

Primary: To determine the safety and efficacy of D^2 in subjects with RRMM

Secondary:

- Evaluate additional measures of efficacy (time-to-response, duration of response, progressive-free survival) of D^2 in subjects with RRMM
- Evaluate the pharmacokinetics (PK) of DURVA and DARA in subjects with RRMM

[redacted]

Study Design

This is an open-label, multicenter, Phase 2 study preceded by a run-in phase to evaluate the safety of the proposed dose. The safety run-in cohort will use a 3+3 design to confirm the tolerability for D^2. The Phase 2 portion of the study will use a Simon 2-stage design to determine

the efficacy and safety of D^2. [redacted]

Safety Run-in Phase

A 3+3 design will be used to confirm the tolerability of the proposed doses for D^2. The recommended phase 2 doses (RP2D) of each agent will be tested in the first cohort. Only if this dose level is not tolerable will dose reductions be evaluated. The dose by cohort is as follows:

Cohort	IV DURVA Cycle 1: Day 2 / 28-day cycle Cycles ≥ 2: Day 1 or 2 / 28-day cycle	IV DARA Cycles 1-2: Day 1, 8, 15, 22 /28-day cycle Cycle3-6: Day 1, 15 /28-day cycle Cycle ≥ 7: Day 1 /28-day cycle
1[a]	1500 mg	16 mg/kg[b]
-1	750 mg	16 mg/kg[b, c]

DARA = daratumumab; DURVA = durvalumab; IV = intravenous; MPD = maximum planned dose.
[a] The Cohort 1 dose level is the Maximum Planned Dose (MPD).
[b] DARA infusion rate reduction, per the Darzalex™ Prescribing Information, will be implemented to mitigate toxicities as required.
[c] If DARA infusion rate reduction does not mitigate the toxicities, additional subjects may be enrolled using a reduced infusion rate starting with the first dose of DARA.

Subsequent enrollment beyond 3 to 6 subjects will not occur until the Dose Review Team (DRT) has reviewed the safety data through Cycle 1 of each cohort. The DRT consists of the Celgene medical monitor, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives, as appropriate, study-specific consultant(s) (MD/PhD), as required, and site investigator and/or designees who have enrolled subjects to the study.

Phase 2 Portion

The Phase 2 portion of the study will use a Simon 2-stage design to determine the efficacy and safety of D^2 (Simon, 1989).

Stage 1

Once the RP2D is confirmed, a cohort of 32 subjects (including subjects enrolled in the safety run-in portion) will be enrolled at the RP2D to determine the safety and preliminary efficacy of D^2.

Stage 2

If the threshold for minimum overall response rate are met in Stage 1, an additional 68 subjects will be enrolled to further confirm the safety and efficacy of D^2 at the RP2D.

For all subjects enrolled in the study, upon confirmed progressive disease (PD), for subjects who have had at least 2 cycles of D^2, pomalidomide (POM) + dexamethasone (dex) may be added to the D^2 regimen at the investigator's discretion.

[redacted]

[redacted]

Study Population

The study population will consist of subjects with multiple myeloma who have received at least 3 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.

Length of Study

The study will consist of the following consecutive phases: Screening, Treatment, and Follow-up. The screening period 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. For subjects who have had at least 2 cycles of D^2, upon PD, at the investigator's discretion, POM + dex may be added to the D^2 regimen. 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, and then, all subjects who received POM as part of study treatment, will be followed for second primary malignancies (SPMs) every 6 months until the end of the trial (once last subject completes the 90 day posttreatment follow-up visit).

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 [redacted] analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

For subjects receiving D^2 regimen:

- Intravenous DARA at the assigned dose level (16 mg/kg) for Cycles 1 to 2 Day 1, 8, 15, 22/28-day cycle, Cycle 3 to 6 Day 1, 15 /28-day cycle, Cycle ≥ 7 Day 1/28-day cycle
- Intravenous DURVA at the assigned dose level (1500 or 750 mg) on Cycle 1 Day 2/28-day cycle then Cycle ≥ 2 on Day 1 or 2/28-day cycle

Overview of Key Efficacy Assessments

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

Overview of Key Safety Assessments

- Complete physical examination including vital signs
- Clinical laboratory evaluations
- Pregnancy testing/counseling
- Electrocardiogram (ECG)
- Concomitant medications and procedures
- Adverse events (AEs)
- Second primary malignancies

Pharmacokinetic

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

[redacted]

Other

[redacted]

- Eastern Cooperative Oncology Group (ECOG) Performance Status

Statistical Methods

Simon's 2-stage design (Simon, 1989) will be used. The null hypothesis that the true overall response rate (ORR) is < 30% will be tested against a one-sided alternative. In the first stage, 32 subjects will be accrued. If there are 11 or fewer responses in these 32 subjects (11/32 = 34.4%), the study will be stopped. Otherwise, 68 additional subjects will be accrued to a total of 100. The null hypothesis will be rejected if 39 or more responses are observed in 100 subjects (39/100 = 39%). This design yields a Type I error rate of 0.05 and power of 80% when the true overall response rate is 45%. All analyses will use descriptive statistics. No formal statistical comparison/testing will be performed.

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[redacted]

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1. INTRODUCTION

On 05 Sep 2017, a Partial Clinical Hold was placed on this study by the United States (US) Food and Drug Administration (FDA). The decision by the FDA was based on data related to risks of anti-programmed cell death-1 (PD-1) antibody, pembrolizumab, in combination with immunomodulatory drugs (IMiDs®) in patients with multiple myeloma. As a result, enrollment into this study has been discontinued. Subjects who are receiving clinical benefit, based on the discretion of the investigator, may remain on study treatment after being reconsented.

1.1. Disease Background

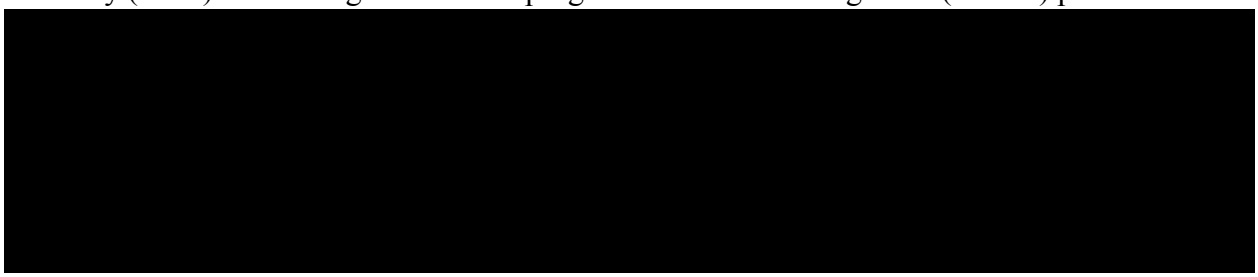
Multiple myeloma (MM) is a rare and incurable progressive neoplastic disease that accounts for 10% of all hematological malignancies. It has been estimated that 62,469 new cases and 43,091 deaths from MM occurred globally in 2012 (Ferlay, 2013).

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 45% (Howlader, 2014). New therapies are needed to treat RRMM patients.

1.2. Compound Background

1.2.1. Durvalumab (MEDI4736)

Durvalumab (MEDI4736) (DURVA) is a human immunoglobulin G (IgG)1 kappa monoclonal antibody (mAb) directed against human programmed cell death ligand 1 (PD-L1) protein.



Refer to the durvalumab 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$_\kappa$ monoclonal antibody (mAb) that binds with high affinity to a unique epitope on CD38. [redacted] DARA was approved under the accelerated approval regulations in the United States (US) on 16 Nov 2015 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. In the European Union (EU) DARA received conditional approval on 20 May 2016 as monotherapy for the treatment of adult patients with RRMM, whose prior therapy included a PI and an immunomodulatory agent and who have demonstrated disease progression on the last therapy.

[redacted]

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]) and Summary of Product Characteristics [SmPC] for the EU.

1.2.3. Pomalidomide

Pomalidomide (POM) is a novel drug in the class of immunomodulatory drugs known as IMiDs® compounds, and is structurally similar to thalidomide. [redacted]

Refer to the POM IB for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and AE profile of the IP; as well as the current label (Pomalyst® PI; Imnovid™ Summary of Product Characteristics [SmPC]).

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).

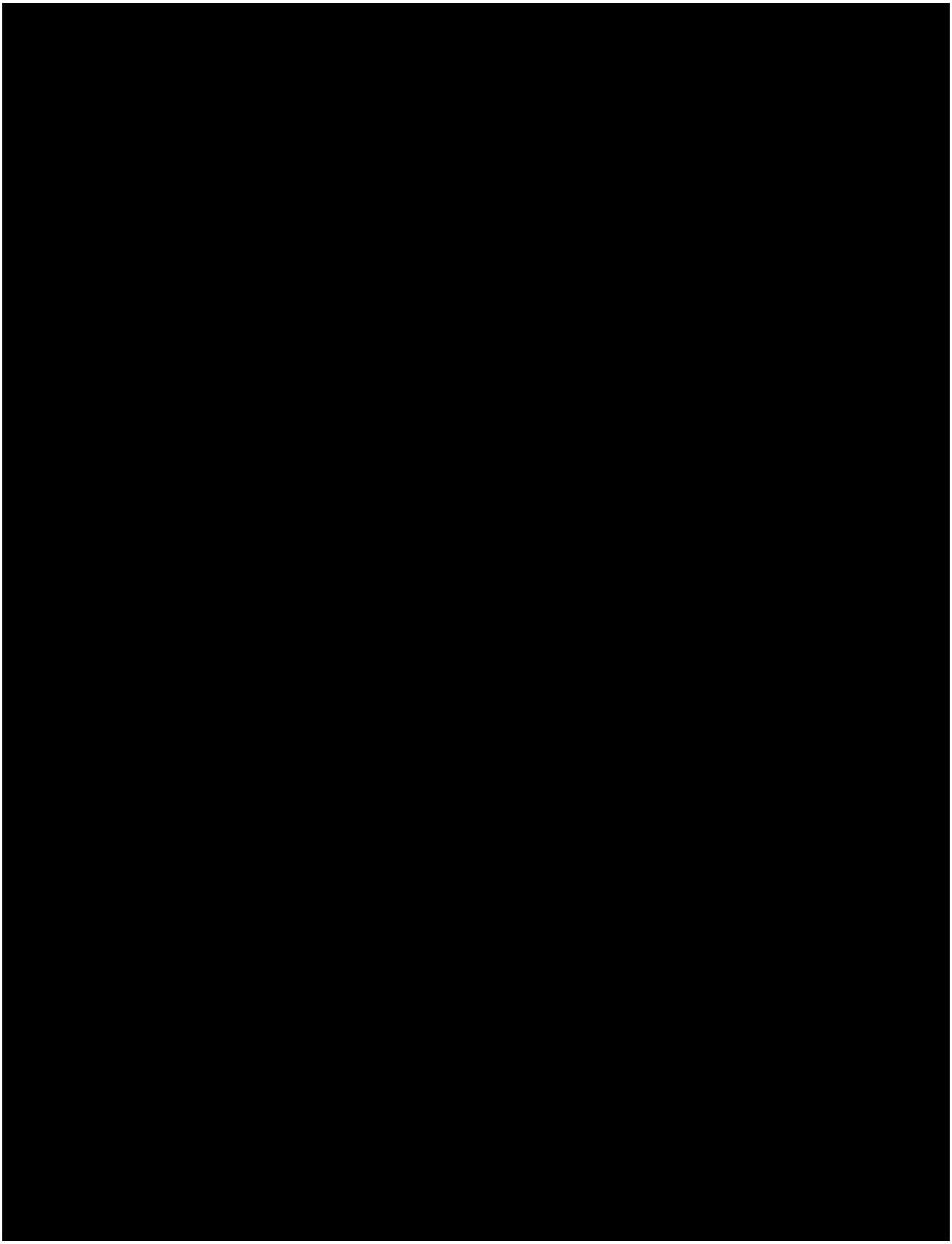
Targeted immunotherapy based on monoclonal antibodies against relevant tumor antigens has not only shown to be feasible, but also an effective approach in treating hematological malignancies. In 2015, DARA was approved under the accelerated approval regulations in the US for the treatment of patients with MM who have received at least three prior lines of therapy including a PI and an immunomodulatory agent or who are double-refractory to a PI and an immunomodulatory agent. In the EU DARA received conditional approval in 2016 as monotherapy for the treatment of adult patients with RRMM, whose prior therapy included a PI and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. 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 (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 durvalumab, 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.

Furthermore, the combination of immunostimulatory antibodies with backbone therapy has shown promising activity in RRMM. Elotuzumab (in combination with LEN and dexamethasone [dex]) is approved for the treatment of for the treatment of patients with MM who have received 1 to 3 prior therapies (Empliciti™ Prescribing Information [PI]). In addition, promising therapeutic activity has been seen with pembrolizumab (anti PD-1 antibody) in combination with POM + dex and LEN + dex and also DARA in combination with LEN+ dex in heavily treated RRMM patients (San Miguel, 2015; Badros, 2015; Plesner, 2015). 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.

1.3.2. Rationale for the Study Design

The study will consist of a safety run-in phase to determine the tolerability of the proposed doses of the DARA + DURVA (D^2) regimen using a 3+3 design. If the doses are tolerable, the Phase 2 portion of the study will be initiated using a Simon 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.

[redacted]



1.3.4. Rationale for Choice of Combination Compounds

Daratumumab is a novel human IgG k monoclonal antibody that targets CD38, a protein that is highly expressed on MM cells. Daratumumab is approved under the accelerated approval regulations in the US 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. In the EU Daratumumab received conditional approval on 20 May 2016 as monotherapy for the treatment of adult patients with relapsed and refractory multiple myeloma, whose prior therapy included a proteasome inhibitor and an immunomodulatory agent and who have demonstrated disease progression on the last therapy. Daratumumab acts through multiple immune effector-mediated mechanisms, including complement-dependent cytotoxicity, antibody-dependent cell-mediated cytotoxicity, and antibody-dependent cellular phagocytosis. In addition to direct targeting of CD38+ myeloma cells, recently published data suggests an immune stimulating/modulatory role for 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).

Durvalumab (MEDI4736) is a human immunoglobulin G (IgG)1 kappa monoclonal antibody (mAb) directed against the human PD-L1 protein. Durvalumab selectively binds human PD-L1 with high affinity and blocks its ability to bind to the PD-1 protein and cluster of differentiation (CD)80. Programmed cell death protein 1 is highly expressed on MM patient T cells and Natural

Killer (NK) cells; and both plasmacytoid dendritic cells (pDCs) and MM cells express PD-1 ligand PD-L1. It has been shown that pDCs allow T-cell and NK-cell immune suppression in the MM bone marrow (BM) milieu by engaging immune checkpoints via 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 lymphocytes activity, as well as enhances NK-cell-mediated MM cell cytolytic activity.

As PD-L1-expressing pDCs are increased in MM BM and localize with PD-L1-positive MM cells (Chauhan, 2009), PD-L1 expression may correlate with progression of disease, with highest levels in RRMM. 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, may enhance both host anti-MM immunity and clinical response and warrant further exploration in a relapsed/refractory population being considered in this study.

In addition, based on recent data from the combinations of immunomodulatory agents (POM and LEN) with monoclonal antibodies (elotuzumab, daratumumab, pembrolizumab), exploration of the addition of POM + dex to DARA and DURVA should be considered in this heavily pretreated population with poor overall survival (see Section 1.3.1).

2. STUDY OBJECTIVES AND ENDPOINTS

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to determine the safety and efficacy of D^2 in subjects with RRMM.
Secondary Objectives
The secondary objectives are: • Evaluate additional measures of efficacy of D^2 in subjects with RRMM • Evaluate the pharmacokinetics (PK) of DURVA and DARA in subjects with RRMM
[redacted]

Table 2: Study Endpoints

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

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description
Secondary	Progression-free survival (PFS)	Time from enrollment to the first documentation of PD or death from any cause during study, whichever occurs earlier
Secondary	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)
[redacted]		

3. OVERALL STUDY DESIGN

3.1. Study Design

This is an open-label, multicenter Phase 2 study preceded by a run-in phase to evaluate the safety of the proposed dose. The safety run-in cohort will use a 3+3 design to confirm the tolerability for D^2. Phase 2 portion of the study will use a Simon 2-stage design to determine the efficacy and safety of D^2. See Figure 1 and Figure 2. [redacted]

3.1.1. D^2 Arm

3.1.1.1. D^2 Safety Run-In Phase

A 3+3 design will be used to confirm the tolerability of the proposed doses for D^2. The recommended phase 2 doses (RP2D) of each agent will be tested in the first cohort. Only if this dose level is not tolerable will dose reductions be evaluated. The dose by cohort will be per Table 3.

Table 3: Dose Levels by Cohort

Cohort	IV DURVA Cycle 1: Day 2 / 28-day cycle Cycle ≥ 2: Day 1 or 2/ 28-day cycle	IV DARA Cycles 1-2: Day 1, 8, 15, 22 /28-day cycle Cycle3-6: Day 1, 15 /28-day cycle Cycle ≥ 7: Day 1 /28-day cycle
1[a]	1500 mg	16 mg/kg[b]
-1	750 mg	16 mg/kg[b, c]

DARA = daratumumab; DURVA = durvalumab; IV = intravenous; MPD = maximum planned dose.
[a] The Cohort 1 dose level is the Maximum Planned Dose (MPD).
[b] DARA infusion rate reduction, per the Darzalex PI and SmPC, will be implemented to mitigate toxicities as required.
[c] If DARA infusion rate reduction does not mitigate the toxicities, additional subjects may be enrolled using a reduced infusion rate starting with the first dose of DARA.

The following dose escalation rules will be applied in determining if the proposed doses are tolerable:

- Initially, 3 subjects will be enrolled into Cohort 1. The dose-limiting toxicity (DLT) evaluation period will be the first treatment cycle.
- If ≤ 1 of the 3 initial subjects experiences a DLT within the first cycle, then 3 additional subjects will be enrolled at the Cohort 1 dose level.
  - If 2 or more of the 6 subjects experience a DLT within the first cycle, then de-escalation to the Cohort -1 dose level may be initiated following review of safety of the initial 6 subjects by the Dose Review Team (DRT)
  - If ≤ 1 of the 6 subjects experiences a DLT within the first cycle, then Phase 2 Simon Stage 1 at the Cohort 1 dose level may be initiated following review of safety of the initial 6 subjects by the DRT.

- If 2 or 3 of the 3 initial subjects in Cohort 1 experience a DLT within the first cycle, then de-escalation to the Cohort -1 dose level may be initiated following review of safety of the initial 3 subjects by the DRT. If de-escalation is agreed upon by DRT, the same rules as above will apply to Cohort -1.

3.1.1.2. D^2 Phase 2 Portion

The Phase 2 will use a Simon 2-stage design to determine the efficacy and safety of D^2 (Simon, 1989).

D^2 Simon Stage 1

Once the RP2D is confirmed, a cohort of 32 subjects (including subject enrolled in the safety run-in portion) will be enrolled at the RP2D to determine the safety and preliminary efficacy of D^2.

D^2 Simon Stage 2

If the threshold for minimum overall response rate (ORR) is met in Stage 1, an additional 68 subjects will be enrolled to further confirm the safety and efficacy of D^2 at the RP2D.

3.1.1.3. Addition of Pomalidomide Plus Dexamethasone to Daratumumab Plus Durvalumab Upon Progressive Disease

For all subjects enrolled into D^2Arm, upon confirmed PD, for subjects who have had at least 2 cycles of D^2, POM + dex may be added to the D^2 regimen at the investigator's discretion.

3.1.3. Dose Review Team

The DRT consists of the Celgene medical monitor, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives, as appropriate, study-specific consultant(s) (MD/PhD), as required, and site investigator and/or designees who have enrolled subjects to the study.

The DRT members are responsible for all dosing decisions for the study. Dosing decisions may include de-escalation to a lower dose; continuation, delay, or termination of dosing, and repetition of or expansion of a cohort. All available safety and, if applicable,

Pharmacokinetic [redacted] (PK[redacted]), [redacted] and preliminary efficacy data will be reviewed and can be considered in the DRT's decisions.

Dose Review Team meetings will be held to review all data, monitor safety, and make dosing and expansion decisions.

3.1.4. Dose-limiting Toxicity

Dose-limiting toxicities will be evaluated during the DLT evaluation period for subjects in the D^2 safety run-in phase [redacted] The DLT evaluation period for the D^2 [redacted] Arms 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 within an assigned treatment arm and experience a DLT

[redacted]

- Receive at least 1 dose of study treatments and experience a DLT after POM + dex added

  OR

- Receive 1 dose of DURVA and all DARA doses as per relevant treatment cycle, ≥ 16 doses of POM and ≥ 3 doses of dex and complete the safety follow-up through the end of the DLT evaluation period.

Nonevaluable subjects will be replaced.

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.

Nonhematologic 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.

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

Figure 1: Overall Study Design

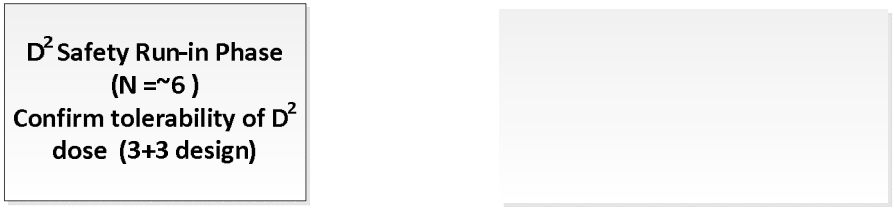


Figure 2: Study Schematic

3.2. Study Duration for Subjects

The study will consist of the following consecutive phases: Screening, Treatment, and Follow-up. The screening period 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. For subjects who have had at least 2 cycles of D^2, upon PD, at the investigator's discretion, POM + dex may be added to the D^2 regimen. 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, and then, all subjects who received POM as part of study treatment, will be followed for second primary malignancies (SPMs) every 6 months until the end of the trial (once last subject completes the 90-day post-treatment follow-up visit).

On 05 Sep 2017, a Partial Clinical Hold was placed on this study by the US FDA. The decision by the FDA was based on data related to risks of anti-PD-1antibody, pembrolizumab, in combination with IMiDs in patients with multiple myeloma. As a result, enrollment into this study has been discontinued. Subjects who are receiving clinical benefit, based on the discretion of the investigator, may remain on study treatment after being reconsented.

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 [redacted] analysis, as pre-specified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

Up to approximately 144 subjects with RRMM will be enrolled worldwide.

- D^2 Cohort: Run-in cohort up to 18; Simon Stage 1 up to 26; Simon Stage 2 up to 68

[redacted]

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 an immunomodulatory agent their disease must be refractory to the most recent immunomodulatory agent containing regimen.*
2. 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
3. Subject achieved a response (MR or better) to at least 1 prior treatment regimen
4. Subject has evidence of PD on or within 60 days of the most recent prior treatment regimen
5. Subject received an alkylating agent alone or in combination with other myeloma treatment
6. Subject has an Eastern Cooperative Oncology Group performance-status score of 2 or less
7. Subject's toxicities resulting from previous therapy (including peripheral neuropathy) have resolved or stabilized to ≤ Grade 1.
8. Subject is at least 18 years of age at the time of signing the informed consent form (ICF).

9. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted.
10. Subject is willing and able to adhere to the study visit schedule and other protocol requirements.
11. Females of childbearing potential (FCBP[1]) must:
    a. Have 2 negative pregnancy tests as verified by the investigator prior to starting study treatment. She must agree to ongoing pregnancy testing during the course of the study, and after end of study treatment. This applies even if the subject practices true abstinence from heterosexual contact.
    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, 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. Refrain from egg cell donation for at least 90 days after the final dose of DURVA or DARA, whichever is later.
12. 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.

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, cell-based therapies (eg, CAR-T cells), or cancer vaccines
2. Subject received DARA or other CD38 antibodies therapies previously
3. 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

[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. Subject received prior treatment with a monoclonal antibody within 5 half-lives of initiating study treatment
5. Subject used any investigational agents within 28 days or 5 half-lives (whichever is longer) of initiating study treatment
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. History of organ or allogeneic stem cell transplantation
8. Subject has received autologous stem cell transplantation (ASCT) within 12 weeks before the date of randomization.
9. 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
    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
10. Subject has clinical evidence of central nervous system (CNS) or pulmonary leukostasis, disseminated intravascular coagulation, or CNS MM
11. Subject has known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) 50% of predicted normal. Note that FEV1 testing is required for subjects suspected of having COPD and subjects must be excluded if FEV1 is < 50% of predicted normal.
12. 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.
13. Subject has plasma cell leukemia, Waldenstrom's macroglobulinemia, POEMS syndrome (polyneuropathy, organomegaly, endocrinopathy, monoclonal protein, and skin changes), or amyloidosis
14. Subject has nonsecretory MM
15. Subject has known allergy or hypersensitivity to study drug formulations
16. 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 syndrome) stable on hormone replacement.
c. Psoriasis not requiring systemic treatment.

17. Subject has history of primary immunodeficiency
18. Subject is positive for human immunodeficiency virus (HIV), chronic or active hepatitis B or active hepatitis A or C.
19. 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 30 days after the last dose of DURVA)
20. 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, 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, CT scan premedication).

21. Subject has any one of the following:

    a. Clinically significant abnormal electrocardiogram (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

22. Subject has prior history of malignancies, other than MM, unless the subject has been free of the disease for $\geq$ 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

23. Subject is a female who is pregnant, nursing, or breastfeeding, or who intends to become pregnant during the participation in the study.
24. Subject has significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study

25. Subject has a condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
26. Subject has a condition that confounds the ability to interpret data from the study

5. TABLE OF EVENTS

Table 4: Table of Events

	Screening Period	Treatment Period									Follow-up Period		
Events		**C 1-2 (±3 days)**					**C 3-6 (±3 days)**		**≥ C7 (±3 days)**				
	-28 to -1	**D 1[b]**	**D 2[g]**	**D 8**	**D 15**	**D 22**	**D 1**	**D 15**	**D 1**	**EOT (≤7 days from trt discon decision)**	**28 days (+3) after EOT**	**90 days (+3) after last DURVA/ DARA dose**	**SPM follow-up every 6 months (±2 weeks) after 90 day follow-up visit[a]**
STUDY ENTRY AND GENERAL ASSESSMENTS													
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 screening)	Continuous, until 90 days after last dose of DURVA or DARA, whichever is later											-

Table 4: Table of Events (Continued)

	Screening Period	Treatment Period									Follow-up Period		
Events		**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**	**SPM follow-up every 6 months (±2 weeks) after 90 day follow-up visit[a]**
	-28 to -1	**D 1[b]**	**D 2[g]**	**D 8**	**D 15**	**D 22**	**D 1**	**D 15**	**D 1**				
Blood Type, Rh, and IAT	-	X	-	-	-	-	-	-	-	-	-	-	-
SAFETY ASSESSMENTS													
Prior/concomitant procedures evaluation	X (-28 days from screening)	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												-
Monitoring for SPMs ***only for subjects receiving POM as part of study treatment***	-	Continuous from first dose of POM to the end of trial (once last subject completes the 90-day follow-up visit)											
Physical examination	X	X	-	-	-	-	X	-	X	X	-	-	-
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 testing	X	-	-	-	-	-	-	-	-	-	-	-	-
Hematology[h]	X	X	X	X	X	X	X	X	X	X	X	X	-

Table 4: Table of Events (Continued)

	Screening Period	Treatment Period									Follow-up Period		
Events		**C 1-2 (±3 days)**					**C 3-6 (±3 days)**		**≥ C7 (±3 days)**				
	-28 to -1	**D 1[b]**	**D 2[g]**	**D 8**	**D 15**	**D 22**	**D 1**	**D 15**	**D 1**	**EOT (≤7 days from trt discon decision)**	**28 days (+3) after EOT**	**90 days (+3) after last DURVA /DARA dose**	**SPM follow-up every 6 months (±2 weeks) after 90 day follow-up visit[a]**
Coagulation parameters	X	X	-	-	X	-	X	-	X	X	-	-	-
Chemistry	X	X	X	X	X	X	X	X	X	X	X	X	-
Thyroid Function Tests	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 test (minimum sensitivity 25 mIU/mL) for FCBP with regular or no menstrual cycles	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 28 days									X	X	X	-
Pregnancy test (minimum sensitivity 25 mIU/mL) for FCBP with irregular menstrual cycles	-10 to -14 days and -24 hours prior to first dose weekly for 28 days after first dose, then every 14 days									X	14 and 28 days after last dose	X	-
Pregnancy counseling for all subjects on POM as part of study treatment	X	X	-	-	-	-	X	-	X	X	X	X	-
Antiviral prophylaxis	-	Initiate within 1 week of starting DARA and continue for 3 months following last dose of DARA.											-
TE prophylaxis for all subjects on POM as part of study treatment	-	Continuous during POM treatment									-	-	-

Table 4: Table of Events (Continued)

	Screening Period	Treatment Period									Follow-up Period		
Events		**C 1-2 (±3 days)**					**C 3-6 (±3 days)**		**≥ C7 (±3 days)**				
	-28 to -1	**D 1[b]**	**D 2[g]**	**D 8**	**D 15**	**D 22**	**D 1**	**D 15**	**D 1**	**EOT (≤7 days from trt discon decision)**	**28 days (+3) after EOT**	**90 days (+3) after last DURVA /DARA dose**	**SPM follow-up every 6 months (±2 weeks) after 90 day follow-up visit[a]**
EFFICACY AND OTHER ASSESSMENTS													
ECOG Performance status	X	X	-	-	-	-	X	-	X	X	-	-	-
Assessment of response (IMWG Uniform Response Criteria)[c]	-	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											-

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)				
	-28 to -1	D 1[b]	D 2[g]	D 8	D 15	D 22	D 1	D 15	D 1	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DURVA /DARA dose	SPM follow-up every 6 months (±2 weeks) after 90 day follow-up visit[a]
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											-
Bone marrow aspirate and/or biopsy sampling for cytogenetics, % plasma cells[redacted]	X BMA and BMB cytogenetics, % plasma cells	[redacted] - BMA and BMB at time of CR confirmation for % plasma cells [redacted]											-
Beta2-microglobulin	X	X	-	-	-	-	X	-	X	X	-	-	-
STUDY TREATMENT (DURVA, DARA, POM, dex)													
Pre- and post-DARA[d] infusion medications	-	X		X	X	X	X	X	X	-	-	-	-
DARA IV administration	-	X[e]		X[e]	X[e]	X[e]	X[e]	X[e]	X[e]	-	-	-	-
DURVA IV administration	-	C1D2[f] C2D1			-	-	X[f]	-	X[f]	-	-	-	-
Oral POM (if applicable)	-	Days 1-21/28-day cycle								-	-	-	-
Oral/IV dex (if applicable)	-	Days 1, 8, 15, 22/28-day cycle								-	-	-	-
Study treatment (DURVA, DARA POM, dex) accountability/compliance	-	X	X	X	X	X	X	X	X	X	-	-	-

Table 4: Table of Events (Continued)

	Screening Period	Treatment Period									Follow-up Period		
Events		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	SPM follow-up every 6 months (±2 weeks) after 90 day follow-up visit[a]
	-28 to -1	D 1[b]	D 2[g]	D 8	D 15	D 22	D 1	D 15	D 1				
Blood sample for DURVA PK (only for subjects in the D[2] Simon Stage 1)	-	C2	C1	C1	C1	C1	C4,C6	-	C10, C14	-	-	-	-
Blood sample for DARA PK (only for subjects in the D[2] Simon Stage 1)		C1		C1	C1	C1	-	-	-	X	X	X	-
[redacted]													

AE = adverse event; BMA = bone marrow aspirate; BMB = bone marrow biopsy; C = Cycle; CrCl = creatinine clearance; dex = dexamethasone; D= Day; DARA = daratumumab; DURVA= durvalumab; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EMP = extramedullary plasmacytomas; EOI = End of Infusion; EOT = End of Treatment; FCBP = female of child-bearing potential; h = hours; HIV = human immunodeficiency virus; IAT = Indirect Antiglobulin Test; IMWG = International Myeloma Working Group; IRT= integrated response technology; IV = intravenous; min = minutes; PD = progressive disease; PK = pharmacokinetics POM = pomalidomide; PR = partial response; SD = stable disease; SPM = second primary malignancy; trt discon = treatment discontinuation.

a Only required for subjects who received POM as part of study treatment

b On Cycle 1 Day 1 (C1D1), safety laboratory assessments must be performed locally 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.

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

d Preinfusion medications to be given before all daratumumab infusions (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); postinfusion medications to be given on the first and second days following all daratumumab infusions.

e Every effort should be made to keep subjects on the planned dosing schedule. 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 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 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.

f 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 [i.e., 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 BP 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 hours window is allowed and may be implement 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 CRF page.

g Only applicable on Cycle 1.

h For subjects who have POM + dex added to the D^2 regimen upon PD, hematology should be monitored (centrally and/or locally) weekly for the first 8 weeks following addition of POM regardless of the cycle at which POM is added. If these assessments are only done locally or if the local results are used in making any treatment-related decision or AE reporting, these local results must be entered as an unscheduled visit into the eCRF.

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 and urinalysis, all safety-related laboratory assessments will be performed centrally; however, tests that may result in dose interruption and/or modification should also be performed locally to allow for treatment related decisions during subject visits. 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
- 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 screening, except for those taken for disease)
- Prior and concomitant procedures evaluation (including all procedures occurring ≤ 28 days before screening)
- Adverse events
- Physical examination, including assessment for potential venous thromboembolism events (VTEs) (can be source documented only),
- Forced expiratory volume test (subjects with 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
- 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 (MCV)
- Coagulation parameters (prothrombin time/international normalized ratio, activated partial thromboplastin time, fibrinogen)
- Chemistry panel including sodium, potassium, calcium, corrected serum calcium, 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 glutamyltransferase (GGT), uric acid, triglycerides, cholesterol, phosphorus 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 T_4, free T_3)
- 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 (local laboratory).
- Urinalysis (color, appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin)
- Females of childbearing potential must have two negative pregnancy tests (sensitivity of at least 25 mIU/mL) prior to starting study treatment. The first pregnancy test must be performed within 10 to 14 days prior to the start of study treatment and the second pregnancy test must be performed within 24 hours prior to the start of study treatment. The subject may not receive study treatment until the study doctor has verified that the results of these pregnancy tests are negative
- Counseling about pregnancy precautions and the potential risks of fetal exposure
- Eastern Cooperative Oncology Group (ECOG) Performance Status (see Appendix C)
- Efficacy assessments / tumor evaluations (see Section 6.4).
- Beta-2 microglobulin test

[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. Day 2 assessments should only be performed during Cycle 1.

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

- Interactive Response Technology (IRT) Registration:
  - Subject may be randomized in the IRT up to 3 days prior to initiating study treatment on Cycle 1 Day 1 (C1D1)
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Adverse event (continuously)
- Second primary malignancy (SPM) monitoring for subjects receiving POM as part of study treatment
- 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 IAT should be done before the first dose of daratumumab. Subject RBC phenotyping (standard or extended) or genotyping is an alternative option to the IAT test, if locally required. Either method must be completed prior to first daratumumab infusion. Subjects will receive a patient identification wallet card for the study that includes the blood profile (ABO, Rh, and IAT or phenotyping) determined before the first infusion of daratumumab along with information on the IAT interference for healthcare providers/blood banks. See Section 6.8 for additional details.
- Hematology panel
  - For subjects who have POM + dex added to the D^2 regimen upon PD, the weekly hematology assessments for the first 8 weeks following addition of POM may be done centrally and/or locally. If these assessments are only done locally or if the local results are used in making any treatment-related decision or AE reporting, these local results should be entered as an unscheduled visit into the eCRF.

- Coagulation parameters
- Chemistry panel
- Thyroid function tests:
  - Cycles 1 to 4: TSH, free T_4, free T_3
  - Cycle 5 onward: TSH, if TSH is abnormal, then reflex testing for free T4 and free T_3
- Renal function (CrCl)
- Urinalysis (only if clinically indicated)
- Urine (or serum) pregnancy test for FCBP (negative results required for study treatment [DURVA, DARA, POM, or dex] administration)
- Counseling about pregnancy precautions and the potential risks of fetal exposure for subjects receiving POM
- Continuous thromboembolism prophylaxis treatment for subjects receiving POM as a part of study treatment
- ECOG Performance status
- Efficacy assessments (see Section 6.4)
- Beta-2 microglobulin test on Day 1 of each cycle

[redacted]

- Blood sampling for PK assessments (see Section 6.5)

[redacted]

- Study treatment (durvalumab, daratumumab, POM, or dex) 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)

- SPM monitoring for subjects who received POM as part of study treatment (monitored until the last subject completes the 90 day follow-up visit)
- 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 T_4, free T_3)
- Renal function (CrCl)
- Urinalysis
- Urine (or serum) pregnancy test for FCBP
- Counseling about pregnancy precautions and the potential risks of fetal exposure for subjects receiving POM
- ECOG Performance Status
- Efficacy assessments 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.
- Beta-2 microglobulin test

[redacted]

- Blood sampling for PK assessments (see Section 6.5)

[redacted]

- Study treatment (durvalumab, daratumumab, POM, or dex) 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 (AESI), reporting, as well as serious adverse events (SAEs) made known to the investigator at any time thereafter that are suspected of being related to study treatment (DURVA, DARA, POM, or dex), 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 durvalumab 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)
- SPM monitoring for subjects who received POM as part of study treatment (monitored until the last subject completes the 90 day follow-up visit)
- Vital signs
- Weight
- Hematology panel
- Chemistry panel
- Thyroid function tests (TSH, free T_4, free T_3)
- Renal function (CrCl)
- Urinalysis
- Urine (or serum) pregnancy test for FCBP
- Counseling about pregnancy precautions and the potential risks of fetal exposure for subjects receiving POM.

6.3.2. Second Primary Malignancy Follow-up

After the 90 days post last dose of DURVA or DARA follow-up visit, all subjects who received POM as part of study treatment will be continue to be followed for SPMs every 6 months until the end of the trial (once last subject completes the 90 day post treatment follow-up visit).

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 sub-type (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 [redacted] assessments
- During treatment:

  [redacted]

  – BMA and BMB at the time of complete response (CR) confirmation for percent plasma cells [redacted]

  [redacted]

The analysis of bone marrow for percentage of plasma cells will be performed locally. The bone marrow samples for cytogenetics [redacted] will be submitted to a central laboratory.

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 assessments (EMPs) 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.

6.4.5. Assessment of Response

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.

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 Phase 2 Stage 1 (including subjects enrolled in the D^2 safety run-in phase) will participate in the Durvalumab PK sample collections at the following time points:

- C1D2: predose (-30 to -5 minutes prior to dose), end of infusion (EOI) (+30 minutes),
- C1D8
- C1D15
- C1D22
- Additional Durvalumab PK samples to be collected to match [redacted] predose (-30 to -5 minutes prior to dose) on C2D1, C4D1, C6D1, C10D1, C14D1 and EOT.

6.5.2. Pharmacokinetics of Daratumumab

All subjects enrolled in Phase 2 Stage 1 (including subjects enrolled in the D2 safety run-in phase) will participate in the Daratumumab PK sample collections at the following time points:

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

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

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

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

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

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 DTT-treated reagent RBCs

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

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

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Products

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) and Pomalidomide will be supplied by Celgene and labeled appropriately as investigational material. Labels will bear Celgene's name 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) and dexamethasone will not be supplied by Celgene; instead it will be obtained by the sites according to local clinical study agreement and in accordance with local guidelines. Additional information may be included on the label as needed or applicable.

Canada:

Durvalumab (MEDI4736), Daratumumab (Darzalex), and Pomalidomide will be supplied by Celgene and labeled appropriately as investigational material. Labels will bear Celgene's name 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.

Dexamethasone will not be supplied by Celgene; instead it will be obtained by the sites 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 and Canada:

Durvalumab (MEDI4736), Daratumumab (Darzalex), Pomalidomide, and dexamethasone will be supplied by Celgene and labeled appropriately as investigational material. Labels will bear Celgene's name 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)

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

Sites 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 MEDI4736 with other IV medications and solutions, other than normal saline, is not known, the MEDI4736 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 (except in the US) in single use vials in single count cartons. Daratumumab is a colorless to pale yellow, preservative-free solution and will be supplied in 20mL vials (20 mg/mL) and/or 5mL vials (20 mg/mL).

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

7.1.3. Pomalidomide (POM)

Pomalidomide will be supplied by Celgene in appropriate strengths for oral administration. Investigational product will contain a 21 day supply of POM. Pomalidomide should be stored in accordance with the product label.

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

7.1.4. Dexamethasone (Dex)

For sites outside the US and Canada, Celgene will provide commercial supplies of Dexamethasone 2 mg and 4 mg tablets for oral administration and 20 mg for IV administration. Dexamethasone should be stored in accordance with the product label.

For additional information 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 and/or POM and/or dex) 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.

On days when DARA, DURVA and POM are dosed on the same day, the DARA infusion should be administered first, followed by the DURVA infusion, then POM administration.

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 durvalumab dose preparation and administration please refer to the pharmacy manual.

7.2.1.1.2. Monitoring During/After Durvalumab Infusion

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 [i.e., 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 BP and pulse measurements should follow the principles as described above or be taken more frequently if clinically indicated.

Subsequent DURVA infusions

For the subsequent DURVA infusion, 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 CRF 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)

Refer to the full prescribing information for daratumumab (Darzalex PI) and Summary of Product Characteristics [SmPC] for the EU.

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

Guidance on preinfusion and postinfusion medications for infusion reaction prophylaxis in relation to DARA dosing is given in Table 6 and can be used in conjunction with site's standard of care for DARA infusions.

Table 6: Daratumumab Preinfusion and Postinfusion Medications

Time point	Medication	Subjects NOT receiving dex as part of study regimen	Subjects receiving dex as part of study regimen
Preinfusion (~1 hr prior to every DARA administration)	Oral montelukast (if approved and available)	per investigator discretion prior to first infusion	per investigator discretion prior to first infusion
	IV corticosteroid	methylprednisolone 100 mg or equivalent dose of an intermediate-acting or long-acting corticosteroid. Following the second infusion, the dose of corticosteroid may be reduced (methylprednisolone 60 mg intravenously.	not applicable[a]
	oral antipyretics	acetaminophen 650 to 1000 mg[b]	acetaminophen 650 to 1000 mg
	oral or IV antihistamine	diphenhydramine 25 to 50 mg or equivalent[b]	diphenhydramine 25 to 50 mg or equivalent
Postinfusion Medication (1st and 2nd day after every DARA administration)	oral corticosteroid[c]	20 mg methylprednisolone or equivalent dose of a corticosteroid in accordance with local standards	Not applicable[a,d]

[a] Not applicable since dexamethasone is already given as part of the study treatment see Section 7.2.2.1.1

[b] 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

[c] 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.

[d] For subjects receiving dexamethasone ≤ 20 mg/week (> 75 years or with dex dose reduced) and given as pre-infusion medication, may receive low-dose methylprednisolone (≤20 mg) PO (or equivalent in accordance with local standards) for the prevention of delayed infusion-related reactions, as clinically indicated.

7.2.1.3. Pomalidomide

Refer to the POM IB for details on dosing and method of administration for POM.

7.2.1.4. Dexamethasone

Refer to the full prescribing information and labeling for dexamethasone contained in the respective current PI, SmPC, or equivalent document for the specific region/country.

7.2.2. Treatment Schedule

7.2.2.1. Daratumumab Plus Durvalumab Treatment Schedule

Initial dosing will begin with Cohort 1. See section 3.1 for dosing rules.

- Intravenous DARA at the dose depending on the assigned cohort: Cycles 1 to 2 on Days 1, 8, 15, 22, Cycle 3 to 6 on Days 1 and 15, then on Day 1 for Cycle 7 onward of a 28-day cycle
  - Cohort 1: 16 mg/kg
  - Cohort -1: 16 mg/kg
- Intravenous DURVA at the dose depending on the assigned cohort on Day 2 of Cycle 1, then Day 1 of Cycle ≥ 2 of a 28-day cycle. For all DURVA infusion 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).
  - Cohort 1: 1500 mg
  - Cohort -1: 750 mg

[redacted]

[redacted]

7.2.3. Overdose

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

- For oral, any amount over the protocol-specified dose
- 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 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, POM, and dex dosing may be continued.
- If POM dosing is withheld or permanently discontinued, then DURVA, DARA, and dex dosing may be continued.
- If dex dosing is withheld or permanently discontinued, then DURVA, DARA, and POM 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).

7.2.4.3. Dose Modification Instructions for Pomalidomide

Guidelines for POM dose interruptions and reductions are provided in Table 7 and Table 8 outlines the dose reduction steps for POM. Refer to the POM IB for additional details.

Table 7: Dose Modification Instructions for Pomalidomide

Toxicity	Dose Modification
Neutropenia Absolute neutrophil count (ANC) < 500/μL or febrile neutropenia	Interrupt pomalidomide treatment for remainder of cycle. Add granulocyte-colony stimulating factor (G-CSF) (at the discretion of the treating physician) When ANC value returns to ≥ 500/μL, resume pomalidomide at 1 dose level lower
Thrombocytopenia Platelet count < 25,000/μL	Interrupt pomalidomide treatment for remainder of cycle. When platelet count returns to ≥ 50,000/μL, resume pomalidomide at 1 dose level lower
Grade 2-3 skin rash	Pomalidomide interruption or discontinuation should be considered at the physician's discretion
Angioedema, Grade 4 rash, exfoliative or bullous rash	Permanently discontinue pomalidomide
For other Grade 3/4 toxicities judged to be related to pomalidomide	Interrupt pomalidomide treatment and restart treatment at 1 mg less than the previous dose when toxicity has resolved to ≤ Grade 2 at the physician's discretion.

ANC = absolute neutrophil count; G-CSF = granulocyte-colony stimulating factor

To initiate a new cycle of pomalidomide following a dose interruption, the neutrophil count must be ≥ 500/μL, the platelet count must be ≥ 50,000/μL, and nonhematologic AEs must be resolved or improved as outlined in Table 7.

Table 8: Pomalidomide Dose Reduction Steps

Dose Level	Oral pomalidomide Dose
Starting Dose	4 mg
Dose Level -1	3 mg
Dose Level -2	2 mg
Dose Level -3	1 mg

The minimum permitted dose level for pomalidomide is 1 mg. No dose re-escalation is permitted for POM.

7.2.4.4. Dose Modification Instructions for Low-dose Dexamethasone

Guideline for low-dose dex dose interruptions and reductions are outlined in Table 9 and Table 10. For the full prescribing information refer to the respective current Prescribing Information, SmPC, or equivalent document for the specific region/country for dex.

Table 9: Dose Modifications for Low-dose Dexamethasone Related Toxicities

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

If recovery from toxicities is prolonged beyond 14 days, then the dose of dexamethasone will be decreased by 1 dose level when dose is restarted.

Table 10: Low-Dose Dexamethasone Dose Reduction Steps

Dose Level	≤ 75 years old Dose	> 75 years old Dose
Starting Dose	40 mg	20 mg
Dose Level -1	20 mg	12 mg
Dose Level -2	10 mg	8 mg

Dexamethasone should be discontinued if subject is unable to tolerate the lowest dose level. No dose re-escalation is permitted for dexamethasone.

7.3. Method of Treatment Assignment

Assignment of subjects will be based on current open cohorts and available slots. Slots will be assigned on a first come-first serve basis and will be valid for 48 hours following assignment. Unconfirmed eligibility following 48 hours from slot assignment may result in forfeiture and subsequent reassignment of the slot.

If [redacted] the D^2 [redacted] Arms are open, the randomization will follow a 1:1 ratio to D^2 [redacted] Arms. However, subjects who do not meet the additional eligibility requirement for receiving POM will be enrolled into the D^2 Arm even when both arms are open.

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

An IRT will be used to track subject assignments to the treatment arms and dose levels.

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, DARA, POM, and dex) 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, DARA, POM, and dex) 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. However, prophylactic use of transfusions or hematopoietic growth factors to prevent a potential DLT should be avoided unless deemed medically necessary by the treating physician for subject safety.

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 considered exclusionary during the study. The sponsor must be notified if a subject receives any of these during the study.

1. The prophylactic use of hematopoietic growth factors or platelet/RBC transfusions will not be allowed during the first cycle (DLT evaluation period); however, it is permitted at the Investigator's discretion after a subject completes the first cycle or within the first cycle if a hematological DLT has already been declared for that subject. Subjects who fail absolute neutrophil count, 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. Pre- and post-infusion medication for infusion reaction prophylaxis as outlined in Table 6 is permitted. Use of

immunosuppressive medications for the management of IP-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled, topical, intranasal corticosteroids or local steroid injections (eg, intra-articular injection) is permitted. Temporary uses of corticosteroids for concurrent illnesses (eg, food allergies, CT scan contrast hypersensitivity, moderate to severe infusion-related reactions, etc) 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 durvalumab.
6. Herbal and natural remedies are to be avoided.
7. Strong inhibitors of CYP1A2 (eg, ciprofloxacin, enoxacin, and fluvoxamine) should be avoided for subjects receiving POM.

8.3. Required Concomitant Medications and Procedures

- **Infusion reaction prophylaxis:** Guidance on preinfusion and postinfusion medications for infusion reaction prophylaxis in relation to DARA dosing is 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.
- **Thromboembolism prophylaxis:** low-dose aspirin, low molecular weight heparin, or other equivalent antithrombotic or anticoagulant will be given to all subjects who receive POM as a part of study treatment.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

All analyses will use descriptive statistics. The analyses will be done by cohorts and arms. Subjects treated with the recommended dose in the Phase 2 portion of D^2 will be combined with the corresponding dose cohort in the safety run-in phase as one single dose cohort for efficacy and safety analysis. Safety and efficacy data for subjects after addition of POM + dex following confirmed PD will be analyzed separately.

9.2. Study Population Definitions

The following 5 populations will be used for analysis:

- Safety Population: all enrolled subjects who take at least 1 dose of any study treatment. All safety analyses will be based on this population
- Dose-limiting Toxicity Evaluable Population: all subjects from the Safety Population who meet the minimum exposure criterion and have sufficient safety evaluations, or experience a DLT during the first treatment cycle.
- Full Analysis Population: all subjects who are enrolled in this study.
- Efficacy Evaluable (EE) Population: all enrolled subjects who take at least 1 dose of study treatment and who have measurable disease at baseline and at least one postbaseline efficacy assessment.
- Pharmacokinetic Population: includes all subjects who receive at least 1 dose of study treatment and have at least 1 measureable plasma exposure. If any subjects are found to be noncompliant with respect to dosing, have incomplete data, or encounter other circumstances that would affect the evaluation of the PK, a decision will be made on a case-by-case basis as to the inclusion of his PK data in the statistical analysis.

9.3. Sample Size and Power Considerations

Sample size for D^2 arm is calculated based on Simon's 2-stage design (Simon, 1989). The null hypothesis that the true overall response rate (ORR) is < 30% will be tested against a one-sided alternative. In the first stage, 32 subjects will be accrued. If there are 11 or fewer responses in these 32 subjects (11/32 = 34.4%), the study will be stopped. Otherwise, 68 additional subjects will be accrued to a total of 100. The null hypothesis will be rejected if 39 or more responses are observed in 100 subjects (39/100 = 39%). This design yields a Type I error rate of 0.05 and power of 80% when the true overall response rate is 45%.

[redacted]

Number of observed responses in 32 subjects	80% Confidence Interval
10/32	31.3% (20.4%, 44.0%)
11/32	34.4% (23.1%, 47.2%)
12/32	37.5% (25.9%, 50.4%)
13/32	40.6% (28.7%, 53.5%)
14/32	43.8% 31.6%, 56.6%)
15/32	46.9% (34.6%, 59.6%)
16/32	50.0% (37.4%, 62.6%)
17/32	53.1% (40.4%, 65.5%)
18/32	56.3% (43.4%, 68.4%)
19/32	59.4% (46.5%, 71.3%)
20/32	62.5% (49.6%, 74.1%)

9.4. Background and Demographic Characteristics

Summaries for the demographics and baseline characteristics will be carried out for each dose cohort and overall for the full analysis population. Age, height, weight, and other continuous baseline disease characteristics will be summarized using descriptive statistics, while gender, race, and other categorical variables will be provided using frequency tabulations.

9.5. Medical History

Medical history data will be summarized for full analysis population using frequency tabulations by the Medical Dictionary for Regulatory Activities (MedDRA) Version 18 or higher system organ class and preferred term.

9.6. Concomitant Medications and Procedures

All concomitant medications and procedures documented during the study will be summarized for full analysis population using frequency tabulations. The Anatomical Therapeutic Chemical (ATC) coding scheme of the World Health Organization (WHO) will be used to group medications into relevant categories for these tabulations.

9.7. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized for full analysis population using frequency and percent by treatment arm and dose cohort and follow-up phases. A summary of subjects enrolled by site will be provided. Protocol deviations will be summarized using frequency tabulations.

9.8. Efficacy Analysis

9.8.1. Response (International Myeloma Working Group Criteria)

Tumor response, including PD, will be assessed by the investigators using the International Myeloma Working Group Criteria (IMWG) criteria.

The ORR will be calculated as the percent of responders (count of subjects with at least a PR, divided by the number of subjects in the EE Population). The ORR together with the proportions in each response category based on the IMWG criteria (ie, CR, Very Good Partial Response [VGPR], PR, Stable Disease [SD], and Progressive Disease [PD]) will be tabulated by dose cohort and arm. A 95% confidence interval of the ORR of D^2 for all subjects treated with the RP2D [redacted].

All response related analysis will be carried out for the efficacy evaluable population

9.8.2. Time-to-Response

Time-to-response (for responders only, per IMWG criteria) is calculated as the time from the first date of dosing of study treatment to the first date of documented response (PR or better).

Time-to-response will be summarized using descriptive statistics or listed by dose cohort and arm.

9.8.3. Duration of Response

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 earliest date when disease progression was confirmed. Duration of response will be summarized using Kaplan Meier statistics as appropriate or listed by dose cohort and arm.

9.8.4. Progression-free survival (PFS)

Progression-free survival will be calculated as the time between the enrollment and PD, as determined by the investigator using the IMWG criteria, or death, whichever occurred earlier. Subjects who do not have a PFS event will be censored on the last adequate response assessment date. Progression-free survival will be summarized for full analysis population using Kaplan-Meier statistics as appropriate or listed by dose cohort and arm.

9.9. Safety Analysis

All safety analyses will be conducted using the Safety Population. All analyses will be presented by dose cohort and arm.

Adverse events will be coded according to the MedDRA Version 18 or higher. The intensity of AEs will be graded according to the NCI CTCAE Version 4.03 or higher.

Treatment-emergent AEs are defined as AE occurring or worsening on or after the first treatment of the study treatment and within 90 days after last dose of durvalumab. Treatment-emergent AEs, AEs leading to study treatment discontinuation, AEs leading to dose reduction/interruption, AEs related to study treatment, SAEs, and AEs leading to death will be summarized by system organ class, and preferred term for each treatment arm and dose cohort. A summary of AEs with

NCI CTCAE Grade 3 or higher, as well as the most frequent preferred terms, and AESIs will be provided. A summary of AEs by dosing cycle based on onset date will also be provided.

If a subject experiences the same preferred term multiple times then, the event will be counted only once and by greatest severity.

All deaths and reasons for death will be summarized. Deaths within 90 days after the last dose of durvalumab will be summarized separately.

Clinical laboratory values will be graded according to NCI CTCAE Version 4.03 or higher for applicable tests. Baseline grade and worst grade during treatment for selected laboratory results will be summarized. Shift from baseline to the worst grade observed during the treatment for selected laboratory results will also be provided.

For vital signs, shift from baseline to worst during the treatment in below, within, and above the normal ranges will be displayed in cross–tabulations. Summary statistics (N, Mean, Standard Deviation, Median, Minimum, and Maximum) of observed and change from baseline values will be presented.

The overall ECG interpretation will be summarized by presenting the number and percentage of subjects with “Normal”, “Abnormal, not clinically significant, and “Abnormal, clinically significant”. Shifts from baseline to worst during the treatment in the overall ECG interpretation will be displayed in cross–tabulations.

The number of subjects who develop anti-drug antibody against durvalumab and/or daratumumab will be summarized.

Graphical displays will be provided where useful to assist in the interpretation of results.

9.10. Interim Analysis

The Phase 2 portion of this study uses the Simon's 2-stage design (Simon, 1989). Once the RP2D is confirmed after the safety run-in portion, a cohort of 32 subjects (including subject enrolled in the safety run-in portion) will be enrolled at the RP2D to determine the safety and preliminary efficacy of D^2. If there are 11 or fewer responses in these 32 subjects (11/32=34.4%), the study will be stopped. Otherwise, 68 additional subjects will be accrued for a total of 100.

9.11. Other Topics

9.11.1. Pharmacokinetic Analysis

Noncompartmental PK parameters such as T_{max}, C_{max}, and AUC will be estimated from the serum DURVA and DARA concentration-time profiles. All concentration data and PK parameters will be summarized for PK population descriptively. The relationship between exposure and response (eg, toxicity [redacted]) may be explored if appropriate.

[redacted]

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 (CRF) rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose CRF (See Section 7.2 for the definition of overdose). Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE on the AE CRF. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and on the AE CRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and CRF but should not be reported as an SAE itself.

In the event of overdose, the subject should be monitored as appropriate and should receive supportive measures as necessary. There is no known specific antidote for DURVA, DARA, POM or dex 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 (durvalumab, daratumumab, POM, dex). 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
- Grade4 =Life-threatening– extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade5 =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, POM, dex) and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected:	A causal relationship of the adverse event to IPs (daratumumab, durvalumab, POM, dex) 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 (daratumumab, durvalumab, POM, dex) caused the adverse

event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

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

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

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 (daratumumab, durvalumab, POM, dex) 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:

aresults in discontinuation from the study; or

- requires treatment, modification/ interruption of IPs (daratumumab, durvalumab, POM, dex) 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 a serious adverse event.

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

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

10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated β-subunit of 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 or 28 days after last dose of POM 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, POM, or dex) 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, POM, or dex) becomes pregnant, the male subject taking IPs (DARA, DURVA, POM, or dex) 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 is accurate and consistent. This requirement applies to all SAEs (regardless of relationship to IPs [DARA, DURVA, POM, or dex]) 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 SAE made known to the Investigator at anytime thereafter that are suspected of being related to IPs (DARA, DURVA, POM, or dex). 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, DARA and POM, based on the IB.

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, suspected unexpected serious adverse reactions (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 investigational products for human use (ENTR/CT3) and also in accordance with country-specific requirements.

For the purpose of regulatory reporting in the EEA, Celgene Drug Safety will determine the expectedness of events suspected of being related to the other IP (dexamethasone) based on the EU SmPC. 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 adverse events 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, POM, or dex) 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 durvalumab (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-mediated adverse event (imAE) is defined as an adverse event 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 imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the Investigator has any questions in regards to an adverse event (AE) being an imAE, 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 durvalumab Investigator Brochure (Section 5.5.2 Summary of Risks).

10.7.1. Second Primary Malignancies

Second primary malignancies (SPMs) will be monitored as events of interest and must be reported as SAEs for subjects receiving POM (see Section 10.5). This includes any second primary malignancy, regardless of causal relationship to study treatment (DARA, DURVA,

POM, or dex), occurring at any time for the duration of the study, from the time of signing the ICF until the until the end of the trial (once the last subject completes the 90 day post treatment follow-up visit), as well as, those SPMs made known to the investigator at any time thereafter that are suspected of being related to study treatment (DARA, DURVA, POM, dex). Events of second primary malignancy are to be reported using the SAE report form and must be considered "Important Medical Events" if no other serious criteria apply; these events must also be documented in the appropriate page(s) of the CRF (ie, AE and SPM CRF) and subject's source documents. Documentation on the diagnosis of the SPM must be provided at the time of reporting as a SAE (eg, any confirmatory histology or cytology results, x-rays, CT scans).

11. DISCONTINUATIONS

11.1. Treatment Discontinuation

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

- Progressive Disease
- Adverse Event
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (including pregnancy, to be specified on the eCRF).

The reason for discontinuation of treatment should be recorded in the eCRF 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:

- Completion of Study
- Screen failure
- Withdrawal by subject
- Death
- Lost to follow-up
- Other (to be specified on the eCRF).

The reason for study discontinuation should be recorded in the eCRF 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, IP 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 for 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 reconsented 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.

Any substantial amendment to the protocol will be submitted to Competent Regulatory Authority in each country and will not be implemented until it has been approved.

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.

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

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

14.2. Data Management

Data will be collected via CRF and entered into the clinical database per Celgene standard operating procedures (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 subinvestigators and other appropriately qualified persons to whom the Investigator has delegated significant study-related duties, together with their roles in the study, curriculum vitae, and their signatures;
- Copies of CRFs (if paper) and of documentation of corrections for all subjects;
- IP accountability records;
- Record of any body fluids or tissue samples retained;
- All other source documents (subject records, hospital records, laboratory records, etc.);

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

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

All study documents should be made available if required by relevant health authorities. Investigator 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, Food and Drug Administration [FDA], European Medicines Agency [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

Abbreviation or Specialist Term	Explanation
[redacted]	
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
β-hCG	β-subunit of human chorionic gonadotropin
BM	Bone marrow
BMA	Bone marrow aspirate
BMB	Bone marrow biopsy
BUN	Blood urea nitrogen
CBC	Complete blood count
CD	Cluster of differentiation
C_{max}	Maximum plasma concentration of drug
CNS	Central nervous system
COPD	chronic obstructive pulmonary disease
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T-lymphocyte-associated antigen 4
D^2	Durvalumab + daratumumab
DARA	Daratumumab
dex	Dexamethasone
DLT	Dose-limiting toxicity

Abbreviation or Specialist Term	Explanation
DRT	Dose Review Team
DURVA	Durvalumab
EC	Ethics Committee
eCRF	electronic case report form
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EE	Efficacy Evaluable (population)
EEA	European Economic Area
EMA	European Medicines Agency
EMP	Extramedullary plasmacytoma
EOI	End of infusion
EOT	End of Treatment
EU	European Union
Fc	Fragment crystallizable
FCBP	Female of child-bearing potential
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIV	Human immunodeficiency virus
IAT	Indirect Antiglobulin Test
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council for Harmonisation
IgA	immunoglobulin A
IgD	immunoglobulin D
IgE	immunoglobulin E
IgG	immunoglobulin G
IgM	immunoglobulin M
IMiDs®	immunomodulatory drugs
IMWG	International Myeloma Working Group
IND	Investigational New Drug

Abbreviation or Specialist Term	Explanation
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IV	Intravenous
LEN	lenalidomide
mAb	Monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MR	Minimal response
[redacted]	
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NK	Natural Killer
NOAEL	No observed adverse effect level
ORR	Overall response rate
[redacted]	
PCP	Pneumocystis carinii pneumonia
[redacted]	
PD	Progressive disease
[redacted]	
PD-1	Programmed cell ceath-1
pDCs	Plasmacytoid dendritic cells
PD-L1	Programmed cell death ligand 1
PD-L2	Programmed cell death ligand 2
PFS	Progression-free survival
PI	Prescribing Information; proteasome inhibitor
PK	Pharmacokinetics
POM	Pomalidomide

Abbreviation or Specialist Term	Explanation
PR	Partial response
Q4W	Every four weeks
RBC	Red blood cell count
RP2D	recommended phase 2 doses
RRMM	Relapsed and refractory multiple myeloma
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SD	Stable Disease
SmPC	Summary of product characteristics
SOP	Standard operating procedure
sPEP	Serum protein electrophoresis
SPM	Second primary malignancy
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal elimination half-life
TNF	Tumor necrosis factor
Tregs	regulatory T cells
TSH	Thyroid stimulating hormone
ULN	Upper limit of normal
uPEP	Urine protein electrophoresis
US/USA	United States/United States of America
VGPR	Very Good Partial Response
VTE	Venous thromboembolism

Appendix B: International Myeloma Working Group Uniform Response Criteria

Response Category[a]	Response Criteria
Stringent Complete Response (sCR)	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 PD

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 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.

Source: Rajkumar, 2011

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, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Source: Oken,1982

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, E-3, and E-4 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-mediated Adverse Events

Immune-mediated Reactions
These guidelines are provided as a recommendation to support investigators in the management of potential immune-mediated adverse events (imAEs). Immune-mediated events can occur in nearly any organ or tissue, therefore, these guidelines may not include all the possible immune-mediated reactions. Investigators are advised to take into consideration the appropriate practice guidelines and other society guidelines (e.g., NCCN, ESMO) in the management of these events. Refer to the section of the table titled "Other -Immune-Mediated Reactions" for general guidance on imAEs not noted in the "Specific Immune-Mediated Reactions" section. Early identification and management of immune-mediated adverse events (imAEs) are essential to ensure safe use of the study drug. Monitor patients closely for symptoms and signs that may be clinical manifestations of underlying immune-mediated adverse events. Patients with suspected imAEs should be thoroughly evaluated to rule out any alternative etiologies (e.g., disease progression, concomitant medications, infections). In the absence of a clear alternative etiology, all such events should be managed as if they were immune-mediated. Institute medical management promptly, including specialty consultation as appropriate. In general, withhold study drug/study regimen for severe (Grade 3) imAEs. Permanently discontinue study drug/study regimen for life-threatening (Grade 4) imAEs, recurrent severe (Grade 3) imAEs that require systemic immunosuppressive treatment, or an inability to reduce corticosteroid dose to 10 mg or less of prednisone or equivalent per day within 12 weeks of initiating corticosteroids. Based on the severity of the imAE, durvalumab should be withheld and corticosteroids administered. Upon improvement to Grade $\leq$ 1, corticosteroid should be tapered over $\geq$ 28 days. More potent immunosuppressive agents such as TNF inhibitors (e.g., infliximab) should be considered for events not responding to systemic steroids. Alternative immunosuppressive agents not listed in this guideline may be considered at the discretion of the investigator based on clinical practice and relevant guidelines. With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. Dose modifications of study drug/study regimen should be based on severity of treatment-emergent toxicities graded per NCI CTCAE version in the applicable study protocol.
AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; ESMO European Society for Medical Oncology

Immune-mediated Reactions			
Pneumonitis/ Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Monitor subjects 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 – Suspected pneumonitis should be confirmed with radiographic imaging and other infectious and disease-related aetiologies excluded, and managed 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. – Consider Pulmonary and Infectious Diseases consults.
	Grade 1	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** – 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
	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 • 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	**For Grade 2** – Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day PO or IV equivalent) – Reimaging as clinically indicated consider chess CT with contrast and repeat in 3-4 weeks – If no improvement within 2 to 3 days, additional

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		steroid taper.	workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started – If no improvement within 2 to 3 days despite IV methylprednisolone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab – Consider as necessary discussing with study physician
	Grade 3 or 4	Permanently discontinue study drug/study regimen	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain Pulmonary and Infectious Disease Consults; consider discussing with study physician, as needed. – Hospitalize the patient – Supportive Care (e.g., oxygen, etc.) – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab

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Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – 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) – **When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF INTESTINAL PERFORATION** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., 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, including intestinal perforation – Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1	No dose modification	**For Grade 1:** – Close monitoring for worsening symptoms – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association

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			colitis diet), loperamide, and other supportive care measures. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2 below. If negative and no infection, continue Grade 1 management.
	Grade 2	Hold study drug/study regimen until resolution to ≤ Grade 1 • 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	**For Grade 2:** – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., 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 2 to 3 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, consult a GI specialist for consideration of further workup, such as imaging and/or colonoscopy to confirm colitis and rule out perforation. – If still no improvement within 2 to 3 days despite 1 to 2mg/kg IV methylprednisolone, promptly start immunosuppressive agents, such as infliximab at 5mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider. [a]**Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Consider, as necessary, discussing with study physician if no resolution to ≤ Grade 1 in 3-4 days

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	Grade 3 or 4	**Grade 3** • For patients treated with PDL-1 inhibitors, hold study drug/study regimen until resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper. Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days. • Permanently discontinue study drug for 1) Grade 3 colitis in patients treated with CTLA-4 inhibitors or 2) Any grade of intestinal perforation in any patient treated with ICI. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 1 to 2 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 2 days, promptly add further immunosuppressants (e.g., infliximab at 5mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). **Caution**: Ensure a GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – **If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.**
Hepatitis (Elevated LFTs)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade** – Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications)
	Grade 1	– No dose modification. If it worsens,	**For Grade 1:**

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Infliximab should not be used for management of Immune Related Hepatitis **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**		treat as Grade 2	- Continue LFT monitoring per protocol
	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. • If toxicity improves to Grade ≤1 or baseline, resume study drug/study regimen after completion of steroid taper. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.[b]	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1-2 days) until LFT elevations improve or resolve. – If no resolution to Grade ≤1 in 1-2 days, consider discussing with study physician, as needed. – If event is persistent (> 2-3 days) or worsens, promptly start prednisone 1-2mg/kg/day PO or IV equivalent.

	Grade 3 or 4	**For Grade 3** 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 to Grade ≤1 or baseline within 14 days, and after completion of steroid taper Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN discontinue study drug/study regimen. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** - Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent - If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an immunosuppressant therapy (i.e., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** - Perform Hepatology Consult, abdominal workup, and imaging as appropriate.

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Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in hepatocellular carcinoma (HCC) subjects** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any elevations in AST, ALT, or TB as described below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ subjects: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ subjects: evaluate quantitative HCV viral load – Consider consulting Hepatologiy or Infectious Diseases specialists regarding changing or starting antiviral HBV if HBV viral load is >2000 IU/ml – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold – For HCV+ with HBcAb+: Evaluate for both HBV and HCV as above
	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline)	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. • For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either	

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		increasing bilirubin or signs of DILI/liver decompensation	
	(Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline) (Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>2-3 days) or worsens, and investigator suspects toxicity to be an AE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressant agents (i.e., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline)	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound,

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	(Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)	completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days	including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider discussing with study physician, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an immunosuppressive therapy (mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatologist). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.**
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	• Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): - **Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise** - **For example manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)** - For the third and fourth level of transaminase rises, **permanently discontinue study drug/study regimen**			

Immune-mediated Reactions			
Nephritis or Renal Dysfunction (elevated serum creatinine)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consult a Nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (e.g., 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 (e.g., disease progression, infections, recent IV contrast, medications, fluid status) – Consider using steroids in the absence of a clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade events
	Grade 1	No dose modification	**For Grade 1:** - 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	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4	**For Grade 2:** – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3

Immune-mediated Reactions			
		• If toxicity improves to ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper	days and as clinically warranted. – Consult Nephrologist and consider renal biopsy if clinically indicated. – If event is persistent beyond 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, consider additional workup. – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4	Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** – 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, consider additional workup and prompt treatment with an immunosuppressant in consultation with a nephrologist
Rash or Dermatitis (including Pemphigoid)	**Any grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of	**General Guidance**	**For any grade:** – Monitor for signs and symptoms of dermatitis (rash and pruritus) – **HOLD STUDY DRUG IF STEVENS-JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED**

Immune-mediated Reactions			
	skin rash)		– **PERMANENTLY DISCONTINUE STUDY DRUG IF SJS, TEN, OR SCAR IS CONFIRMED**
	Grade 1	No dose modification	**For Grade 1:** – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard)
	Grade 2	For persistent (> 1 week) Grade 2 events, hold scheduled study drug/study regimen 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 drug/study regimen after completion of steroid taper	**For Grade 2:** – Obtain Dermatology consult – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with study physician, as needed, and promptly start systemic steroids such as prednisone 1-2 mg/kg/day PO or IV equivalent – Consider skin biopsy if the event persistent for >1 week or recurs
	Grade 3	**For Grade 3:** Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline.	**For Grade 3 or 4:** – Consult Dermatology – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent

Immune-mediated Reactions			
		• If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper. • If toxicity worsens, then treat as Grade 4.	– Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible – Consider, as necessary, discussing with Study Physician
	Grade 4	**For Grade 4:** Permanently discontinue study drug/study regimen	
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, type 1 diabetes mellitus, hypophysitis, hypopituitarism, adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an Endocrinologist for endocrine events – Consider discussing with study physician, as needed – Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c).

Immune-mediated Reactions			
			– If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their primary care physicians or endocrinologists about further monitoring and treatment after completion of the study
	Grade 1	No dose modification	**For Grade 1** – Monitor patient with appropriate endocrine function tests – For suspected hypophysitis/hypopituitarism, consider consulting an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T_4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include free T_4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.

Immune-mediated Reactions			
	Grade 2, 3, or 4	• For Grade 2-4 endocrinopathies other than hypothyroidism and type 1 diabetes mellitus, consider holding study drug/study regimen dose until acute symptoms resolve • Study drug/study regimen can be resumed once the patient stabilizes and after completion of steroid taper • Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen if the patient is clinically stable as per Investigator or treating physician's clinical judgement • If toxicity worsens, then treat based on severity	**For Grade 2, 3 or 4** – Consult Endocrinologist to guide evaluation of endocrine function, and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan – For subjects with abnormal endocrine work up, except for those with isolated hypothyroidism or type 1 diabetes mellitus (DM), and as guided by an endocrinologist consider short-term, corticosteroids (e.g., 1-2mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g. hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated type 1 DM may be treated with appropriate diabetic therapy, and without corticosteroids. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis.** – For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.
Amylase/Lipase increased	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC	**General Guidance**	**For Any Grade:** – For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – Assess for signs/symptoms of pancreatitis

Immune-mediated Reactions			
	grade/severity)		– Consider appropriate diagnostic testing (e.g., abdominal CT with contrast, MRCP if clinical suspicion of pancreatitis and no radiologic evidence on CT) – If isolated elevation of enzymes without evidence of pancreatitis, continue immunotherapy. Consider other causes of elevated amylase/lipase – If evidence of pancreatitis, manage according to pancreatitis recommendations
	Grade 1	No dose modification	
	Grade 2, 3, or 4	**For Grade 2, 3, or 4** In consultation with relevant pancreatic specialist consider continuing study drug/study regimen if no clinical/radiologic evidence of pancreatitis ± improvement in amylase/lipase.	
Acute Pancreatitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider Gastroenterology referral
	Grade 1	No dose modification	**For Grade 1:** - IV hydration - Manage as per amylase/lipase increased (asymptomatic)
	Grade 2, 3, or 4	**For Grade 2** Hold study drug/study regimen dose until resolution to Grade ≤1. **For Grade 3 or 4**	**For Grade 2, 3, or 4** – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – IV hydration

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		Permanently discontinue study drug/study regimen.	
Neurotoxicity (to include but not limited to non-infectious meningitis, non-infective encephalitis, and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (Depending on the type of neurotoxicity, refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications) – Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations) – Perform symptomatic treatment with neurological consult as appropriate – **FOR TRANSVERSE MYELITIS, PERMANENTLY DISCONTINUE FOR ANY GRADE.**
	Grade 1	No dose modifications	**For Grade 1:** 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. • Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤1 within 30 days. If toxicity worsens	**For Grade 2:** – Consider, as necessary, discussing with the study physician – Obtain Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine) – Promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent – If no improvement within 2 to 3 days despite 1-2 mg/kg/day prednisone PO or IV equivalent;

Immune-mediated Reactions			
		then treat as Grade 3 or Grade 4	consider additional workup and promptly treat with an additional immunosuppressive therapy (e.g. IV IG or other immunosuppressant depending on the specific imAE)
	Grade 3 or 4	**For Grade 3 or 4:** • Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** – Consider, as necessary, discussing with study physician – Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IV IG or other immunosuppressant depending on the specific imAE) – Once stable, gradually taper steroids over ≥ 28 days
Peripheral neuromotor syndromes (such as Guillain-Barre and Myasthenia Gravis)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects 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

Immune-mediated Reactions			
			instability – Subjects should be evaluated to rule out any alternative etiology (e.g., 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 subjects 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 Neurology consult – Neurophysiologic diagnostic testing (e.g., 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 – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG
	Grade 1	No dose modification	**For Grade 1:** – Consider discussing with the study physician, as needed. – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation

Immune-mediated Reactions			
			as described above – Consult a neurologist
	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	**For Grade 2:** – Consider discussing with the study physician, as needed – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above – Consult a neurologist – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., 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 Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. 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

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			the diagnosis. o Avoid medications that can worsen myasthenia gravis. *GUILLAIN-BARRE:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Subjects requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.

	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue Study drug/study regimen if Grade 3 imAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability **For Grade 4:** Permanently discontinue study drug/study regimen	**For Grade 3 or 4** – Consider discussing with study physician, as needed – Recommend hospitalization – Monitor symptoms and consult a neurologist *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting Neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. 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. o Subjects requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG o Avoid medications that can worsen myasthenia gravis.

Immune-mediated Reactions			
Myocarditis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** - The prompt diagnosis of immune-mediated myocarditis is important, particularly in subjects with baseline cardiopulmonary disease and reduced cardiac function. - Consider discussing with the study physician, as needed. - Monitor subjects for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). Consult a Cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. - Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If	**For Grade 1:** • Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG,

Immune-mediated Reactions			
		study drug/study regimen is held, resume after complete resolution to Grade 0.	ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. • Consider using steroids if clinical suspicion is high.
	Grade 2, 3, or 4	If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. **Infliximab is contraindicated for patients who have heart failure.**
Myositis/Polymyositis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly.

Immune-mediated Reactions			
			Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium

Immune-mediated Reactions			
			swallow for evaluation of dysphagia or dysphonia. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).
	Grade 1	No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
	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.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is not rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 2 to 3 days, continue additional work up and start treatment with

Immune-mediated Reactions			
			IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult. – Consider discussing with the study physician, as needed. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider starting another immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis.

AChE = acetylcholine esterase; ACTH = adrenocorticotropic hormone; ADL = activities of daily living; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; ASCO = American Society of Clinical Oncology; AST = aspartate aminotransferase; BNP = brain natriuretic peptide; BUN = blood urea nitrogen; CT = computed tomography; CTCAE = Common Terminology Criteria for Adverse Events; ECG = electrocardiogram; FDA = Food and Drug Administration, GI = gastrointestinal; HgA1c = hemoglobin A1c; IG = immunoglobulin; ILD = interstitial lung disease; imAE = immune-mediated adverse event; IV = intravenous; LDH = lactate dehydrogenase; LFT = liver function test; LLN = lower limit of normal; MRI = magnetic resonance imaging; NCI = National Cancer Institute; NCCN = National Comprehensive Cancer Network; PJP = *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO = by mouth; T_3 = triiodothyronine; T_4 = thyroxine; TB = total bilirubin; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD.
[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.
[c] NCCN Clinical Practice Guidelines in Oncology "Management of Immunotherapy-Related Toxicities" Version 1.2020 – December 2019

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

Infusion-Related Reactions		
Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**Dose Modifications**	**Toxicity Management**
Any Grade	General Guidance	**For Any Grade**: – Management per institutional standard at the discretion of investigator – Monitor subjects for signs and symptoms of infusion-related reactions (e.g., 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 (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia)
Grade 1 or 2	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event 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	**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 3/4	Permanently discontinue study drug/study regimen	**For Grade 3 or 4:** Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and famotidine, and IV glucocorticoid)

CTCAE = Common Terminology Criteria for Adverse Events; IM = Intramuscular; IV = Intravenous; NCI = National Cancer Institute.

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"**		
CTC Grade/Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**Dose Modification**	**Toxicity Management**
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
Grade 1	No dose adjustment	Treat accordingly as per institutional standard
Grade 2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
Grade 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
Grade 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; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; imAE = immune-mediated adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

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."

Appendix E-4: Durvalumab Treatment Modification and Toxicity Management Guidelines for Other–immune-mediated Reactions

Other-immune-mediated Reactions		
Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**Dose Modification**	**Toxicity Management**
Any Grade	Note: It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them are not noted specifically in these guidelines (e.g. immune thrombocytopenia, haemolytic anaemia, uveitis, vasculitis).	– The study physician may be contacted for immune-mediated reactions not listed in the "specific immune-mediated reactions" section – Thorough evaluation to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) – Consultation with relevant specialist – Treat accordingly, as per institutional standard.
Grade 1	No dose adjustment	Monitor as clinically indicated
Grade 2	• Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. • Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper	**For Grade 2, 3, or 4** Treat accordingly, as per institutional standard, appropriate clinical practice guidelines, and other society guidelines (e.g., NCCN, ESMO)

Other-immune-mediated Reactions		
Severity Grade of the Event (Refer to NCI CTCAE applicable version in study protocol for defining the CTC grade/severity)	**Dose Modification**	**Toxicity Management**
Grade 3	Hold study drug/study regimen	
Grade 4	Permanently discontinue study drug/study regimen	

AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.
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."

Appendix F: Guideline for Asthma Eligibility Criteria

<table>
<tr><th colspan="2" rowspan="4">Components of Severity</th><th colspan="12">Classification of Asthma Severity</th></tr>
<tr><th colspan="3" rowspan="2">Intermittent</th><th colspan="9">Persistent</th></tr>
<tr><th colspan="3">Mild</th><th colspan="3">Moderate</th><th colspan="3">Severe</th></tr>
<tr><th>0-4 yrs</th><th>5-11 yrs</th><th>12 + yrs</th><th>0-4 yrs</th><th>5-11 yrs</th><th>12 + yrs</th><th>0-4 yrs</th><th>5-11 yrs</th><th>12 + yrs</th><th>0-4 yrs</th><th>5-11 yrs</th><th>12 + yrs</th></tr>
<tr><td rowspan="5">Impairment

Normal FEV_1/FVC :
8-19 yr 85%
20-39 yr 80%
40-59 yr 75%
60-80 yr 70%</td><td>Symptoms</td><td colspan="3">≤ 2 days/week</td><td colspan="3">≤ 2 days/week but not daily</td><td colspan="3">Daily</td><td colspan="3">Throughout the day</td></tr>
<tr><td>Nighttime awakenings</td><td>0</td><td colspan="2">≤ 2x/month</td><td>1-2x/ month</td><td colspan="2">3-4x/month</td><td>3-4x/ month</td><td colspan="2">> 1x/week but not nightly</td><td>> 1x/ month</td><td colspan="2">Often 7x/week</td></tr>
<tr><td>SABA use for symptom control (not prevention of EIB)</td><td colspan="3">≤ 2 days/week</td><td colspan="2">≤ 2 days/week but not daily</td><td>>2 days/ week but not daily, and not more than 1x on any day</td><td colspan="3">Daily</td><td colspan="3">Several time per day</td></tr>
<tr><td>Interference with normal activity</td><td colspan="3">None</td><td colspan="3">Minor limitation</td><td colspan="3">Some limitation</td><td colspan="3">Extremely limited</td></tr>
<tr><td>Lung function
FEV_1
FEV_1/FVC</td><td>N/A</td><td>Normal FEV_1 between exacerbations
> 80%
> 85%</td><td>Normal FEV_1 between exacerbations
> 80%
Normal</td><td>N/A</td><td>> 80%
> 80%</td><td>> 80%
Normal</td><td>N/A</td><td>60-80%
75-80%</td><td>60-80%
Reduced 5%</td><td>N/A</td><td>< 60%
< 75%</td><td>< 60%
Reduced 5%</td></tr>
<tr><td rowspan="2">Risk</td><td rowspan="2">Exacerbations requiring oral systemic corticosteroids</td><td colspan="3">0-1/year</td><td>≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma</td><td>≥ 2/year
Relative annual risk may be related to FEV_1.</td><td>≥ 2/year
Relative annual risk may be related to FEV_1.</td><td>≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma</td><td>≥ 2/year
Relative annual risk may be related to FEV_1.</td><td>≥ 2/year
Relative annual risk may be related to FEV_1.</td><td>≥ 2 exacerbations in 6 months requiring oral steroids or >4 wheezing episodes/1 year lasting >1 day and risk factors for persistent asthma</td><td>≥ 2/year
Relative annual risk may be related to FEV_1.</td><td>≥ 2/year
Relative annual risk may be related to FEV_1.</td></tr>
<tr><td colspan="12">← Consider severity and interval since last exacerbation. Frequency and severity may fluctuate over time for patients in any severity category. →</td></tr>
<tr><td colspan="2" rowspan="2">Recommended Step for Initiating Treatment</td><td colspan="3">Step 1</td><td colspan="3">Step 2</td><td>Step 3 and consider short course of oral steroids</td><td>Step 3: medium dose ICS and consider short course of oral steroids</td><td>Step 3 and consider short course of oral steroids</td><td>Step 3 and consider short course of oral steroids</td><td>Step 3: medium dose ICS OR Step 4 and consider short course of oral steroids</td><td>Step 4 or 5 and consider short course of oral steroids</td></tr>
<tr><td colspan="12">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.</td></tr>
</table>

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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 • **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 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

Celgene Signing Page

This is a representation of an electronic record that was signed electronically in Livelink. This page is the manifestation of the electronic signature(s) used in compliance with the organizations electronic signature policies and procedures.

UserName: [redacted]
Title: [redacted]
Date: Monday, 11 January 2021, 10:09 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
==========

1. JUSTIFICATION FOR AMENDMENT

The primary purpose of Protocol Amendment 4.0 is to update the Durvalumab Treatment Modification and Toxicity Management Guidelines to reflect consistency with the Durvalumab Toxicity Management Guidelines, Version 17 Nov 2020.

Title Page (updated)

1. Contact Information updated.

Appendix E-1 (updated)

2. Appendix E-1: Durvalumab Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events, was updated to reflect consistency with Durvalumab Toxicity Management Guidelines, Version 17 Nov 2020.

Appendix E-2 (updated)

3. Appendix E-2: Durvalumab Treatment Modification and Toxicity Management Guidelines for Infusion-related Reactions, was updated to reflect consistency with Durvalumab Toxicity Management Guidelines, Version 17 Nov 2020.

Appendix E-3 (updated)

4. Appendix E-3: Durvalumab Treatment Modification and Toxicity Management Guidelines for Non-immune-mediated Reactions, was updated to reflect consistency with Durvalumab Toxicity Management Guidelines, Version 17 Nov 2020.

Appendix E-4 (created)

5. Appendix E-4: Durvalumab Treatment Modification and Toxicity Management Guidelines for Other-immune-mediated Reactions, was created to reflect consistency with Durvalumab Toxicity Management Guidelines, Version 17 Nov 2020.

1. JUSTIFICATION FOR AMENDMENT

The primary purpose of this Protocol Amendment 3.0 is to update the Toxicity Management Guidelines (TMGs).

Durvalumab IB Version 15 dated 08 Oct 2019 and Durvalumab Toxicity Management Guidelines, Version 4.03, dated 17 Oct 2019, necessitated the update to Appendix E-1 of this Protocol.

Title Page (updated)

1. Contact Information updated.

Appendix E (updated)

2. Appendix E-1: Durvalumab Treatment Modification and Toxicity Management Guidelines for Immune-mediated Adverse Events, was updated to match Durvalumab Toxicity Management Guidelines, Version 4.03, dated 17 Oct 2019 and Durvalumab IB Version 15 dated 08 Oct 2019.

1. JUSTIFICATION FOR AMENDMENT

Protocol Amendment 2 is written to update the Toxicity Management Guidelines (TMGs) and to reflect that on 05 Sep 2017 the United States (US) Food and Drug Administration (FDA) placed a Partial Clinical Hold on this study. The decision by the FDA was based on risks identified in other trials for an anti-programmed cell death-1 (PD-1) antibody, pembrolizumab, in patients with multiple myeloma in combination with immunomodulatory agents.

Significant changes included in this amendment are summarized below:

Discontinuation of enrollment of new subjects

- Only those subjects already enrolled and treated who are receiving clinical benefit, based on the discretion of the investigator, can remain on treatment after being informed and reconsented on the safety concerns with the combination of a programmed cell death-1 (PD-1) pathway inhibitor and an immunomodulatory agent.
- Changes to the protocol have been made in the Protocol Summary, Section 1 and Section 3.2 to reflect discontinuation of enrollment.

Updates to the Toxicity Management Guidelines (TMGs)

- Updates have been made to the general dose modification and TMGs in Appendix E-1 to include revised Durvalumab Toxicity Management Guidelines.

Other changes:

- Correction of typographical errors and updated tables and table footnotes with revised text throughout the document.

1. JUSTIFICATION FOR AMENDMENT

Protocol Amendment 1.0 was written to [redacted] correct the dosing of daratumumab (DARA) in the protocol summary to correspond with Sections 7.2.2.1 and 7.2.2.1.1 of the protocol (the protocol summary incorrectly stated a dose level of DARA 8 mg/kg).

The amendment also includes several other updates, minor clarifications and corrections:

- Updated status of DARA regulatory approvals to include the European Union (Sections 1.2.2, 1.3.1, 1.3.4 and 7.2.1.2)

[redacted]

- Dose Review Team composition to include study specific consultants, as required (Protocol summary and Section 3.1.3)
- Includes a minimum number of doses of POM and dexamethasone (dex) for the dose limiting toxicity evaluation for subjects who receive POM + dex as part of their regimen. This is to ensure alignment with the other MEDI4736 protocols (Section 3.1.4).
- Minor updates to safety laboratory assessments; added End of Treatment (EOT) visit to urinalysis timepoints (Table 4) and phosphorus to the biochemistry panel (Section 6.1)
- Clarifies that Day 2 assessments are only required during Cycle 1 (Table 4, Section 6.2)
- Updated protocol to require weekly hematology assessments for eight weeks when POM is added to study treatment upon disease progression on the durvalumab (DURVA) + DARA (D^2) regimen (Table 4, Section 6.2)
- Clarification on alternative options to the Indirect Antiglobulin Test (IAT) test (Sections 6.2 and 6.8)
- The pharmacokinetic (PK) window of assessments was updated to logistically facilitate PK collection (Section 6.5.1 and 6.5.2). Updates to PK [redacted] assessments to include an EOT (End of Treatment) assessment (Sections 6.5.1 and 6.6.1).
- Clarification with regards to pre- and post- DARA infusion medications (Protocol summary, Sections 7.2.1.2 and 7.2.2.1.1)

- Update to Durvalumab Treatment Modification and Toxicity Management Guidelines 19 Aug 2016 Version (Appendix E).
- Correction of minor spelling/grammatical errors