Official Title of Study:

A PHASE 1/2 MULTICENTER, OPEN-LABEL STUDY TO DETERMINE THE RECOMMENDED DOSE AND REGIMEN OF DURVALUMAB (MEDI4736) IN COMBINATION WITH LENALIDOMIDE (LEN) WITH AND WITHOUT DEXAMETHASONE (DEX) IN SUBJECTS WITH NEWLY DIAGNOSED MULTIPLE MYELOMA (NDMM)

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INVESTIGATIONAL PRODUCT (IP):	**Lenalidomide, Dexamethasone and Durvalumab (MEDI4736)**
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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.	

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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.	

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

The study was placed on full clinical hold by the United States (US) Food and Drug Administration (FDA) on 05 Sep 2017. The decision by the FDA was based on data from non-Celgene-sponsored studies related to risks of anti-programmed cell death 1 (PD-1), pembrolizumab, in combination with immunomodulatory agents. As the result, the study was closed for further enrollment, and all subjects were discontinued from all study treatments (durvalumab, lenalidomide and dexamethasone). All subjects are being followed for second primary malignancies (SPMs), every 6 months for 5 years after the last subject has been enrolled as per protocol. After stopping data collection in the clinical database, any SPM events will continue to be recorded in the subject's source documents, and reported to Celgene Drug Safety**.**

Study Title

A Phase 1/2, multicenter, open-label study to determine the recommended dose and regimen of durvalumab (MEDI4736) in combination with lenalidomide (LEN) with and without dexamethasone (dex) in subjects with newly diagnosed multiple myeloma (NDMM).

Indication

Newly diagnosed multiple myeloma (NDMM).

Objectives

Primary Objective:

- To determine the recommended dose of durvalumab in combination with LEN with and without dex in subjects with NDMM

Secondary Objectives:

- To evaluate the safety and preliminary efficacy of durvalumab in combination with LEN with and without dex in subjects with NDMM
- To evaluate the pharmacokinetics of durvalumab and LEN with and without dex in subjects with NDMM

Exploratory Objectives:

- To evaluate additional efficacy of durvalumab in combination with LEN with and without dex in subjects with NDMM.

Study Design

This is a multicenter, open-label, Phase 1/2 study to determine the recommended dose and regimen of durvalumab in combination with LEN with and without dex in subjects with NDMM. The study will consist of a dose-finding phase and a dose-expansion phase to determine the optimal regimen. See Figure 1 and Figure 2.

Dose-finding Phase

The dose-finding phase will determine the recommend dose and regimen of durvalumab in combination with LEN with and without dex in a 28-day treatment cycle.

Three treatment arms (A, B and C) will be enrolled in parallel:

Treatment Cohort A (for high risk transplant non-eligible [TNE] NDMM subjects)

- Intravenous (IV) durvalumab at 1500 mg on Day 1 of a 28-day cycle,
- Oral LEN 25 mg/day (adjust per the creatinine clearance [CrCl] value, see details in Section 7.2.1.2, and Table 4) on Days 1 to 21 of each 28-day treatment cycle,
- Oral dex 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle.

Treatment Cohort B (for ≥ 65 years old TNE NDMM subjects who are not high risk)

- Intravenous durvalumab at 1500 mg on Day 1 of a 28-day cycle,
- Oral LEN 25 mg/day (adjust per the CrCl value, see details in Section 7.2.1.2 and Table 4) on Days 1 to 21 of each 28-day treatment cycle,
- Oral dex 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of each 28-day cycle (for up to 12 cycles),

Treatment Cohort C (for high risk post-transplant NDMM subjects as maintenance)

- Intravenous durvalumab at 1500 mg on Day 1 of a 28-day cycle,
- Oral LEN 10 mg/day on Days 1 to 21 of each 28-day treatment cycle,

All subjects on these 3 treatment Cohorts will continue study treatment until PD or unacceptable toxicity occurs.

See detailed eligibility criteria on Section 4.2 and Section 4.3 for each cohort.

Based on experience with durvalumab in other indications (solid tumors and MDS), the initial dose of durvalumab will be at 1500 mg every treatment cycle for each cohort. In the event of dose limiting toxicities, the dose of durvalumab would be de-escalated to 750 mg level.

The Dose Review Team (DRT) are responsible for dosing decisions. The DRT members will consist of the following: Celgene medical monitor, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives as appropriate, and site investigator and/or designees.

Initially, 6 subjects will be enrolled into each cohort for dose-limiting toxicity (DLT) evaluation and will receive 1500 mg durvalumab. The DLT evaluation period will be the first treatment cycle.

- If ≤ 1 of the 6 initial subjects experience a DLT within the first cycle, then the dose-expansion phase may be initiated with durvalumab 1500 mg as the recommended dose (RD);
- If 2 or more of the 6 initial subjects experience a DLT within the first cycle, then the maximum tolerated dose (MTD) has been exceeded and de-escalation to durvalumab 750 mg level after review of safety and PK/Pd of the initial 6 subjects by the DRT

Any of the cohorts may be removed from the study based on emerging PK, Pd, efficacy or safety data.

Dose de-escalation will only occur after review of safety data (DLT), and possibly PK/Pd data by the DRT.

Dose-expansion Phase

All expansion decisions will be determined by the DRT after review of all safety, and if applicable PK/Pd, and/or biomarker, and/or preliminary efficacy data.

After all 6 subjects enrolled in the Dose-finding phase have completed the Cycle 1 treatment; and all data are obtained and reviewed, additional eligible subjects (See detailed eligibility criteria on Section 4.2 and Section 4.3) for each respective cohort may be enrolled. The total of subjects for each Cohort can be expanded up to 40 (including 6 subjects enrolled in the dose-finding phase and 34 in the expansion phase).

The expansion for each study cohort can be occurred independently.

Study Population

The study population is to include NDMM subjects who have measurable myeloma protein (M-protein) by protein electrophoresis analyses (in serum [SPEP] and/or urine [UPEP]) per International Myeloma Working Group (IMWG) criteria.

See Section 4.2 and Section 4.3 of the protocol for detailed eligibility criteria.

Length of Study

Screening period will be within 28 days prior to start of Cycle 1. Eligible subjects will be treated in 28-day cycles and may continue study treatment until PD or unacceptable toxicity occurs. All subjects will have an End of Treatment visit (EOT) 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 durvalumab for safety follow-up visits. Occurrence of second primary malignancies (SPM) will continue to be monitored at the above required 90 day visit and then every 6 months up to 5 years after the last subject enrolled into the study.

The End of Trial is defined as either the date of the last visit of the last subject to complete the post-treatment follow-up, or the date of receipt of the last data point from the last subject that is required for primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

Study Treatments

Subjects will be assigned into different treatment cohorts based on the eligibility criteria.

For subjects in Cohort C, the study treatment is to be initiated at 100 days (±14 days) after transplant.

The initial dose of durvalumab will be at 1500 mg on Day 1 of a 28-day treatment cycle for all treatment cohorts.

The dose of LEN will be 25 mg (adjustable per the CrCl value, see details in Section 7.2.1.2, Table 4) on Days 1 to 21 of each 28-day treatment cycle for treatment Cohort A and Cohort B. The dose of LEN will be 10 mg on Days 1 to 21 of each 28-day treatment cycle for treatment Cohort C.

The dose of dex will be 40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle for treatment Cohort A and Cohort B (for up to 12 cycles).

Overview of Key Efficacy Assessments

- Myeloma paraprotein
- Serum immunoglobulins
- Serum free light-chain
- Corrected serum calcium
- Response assessment (per IMWG Uniform Response Criteria)
- Bone marrow aspiration/biopsy
- Radiographic assessments of lytic bone lesions
- Extramedullary plasmacytoma (EMP) assessments
- Eastern Cooperative Oncology Group (ECOG) Performance Status
- Cytogenetic findings in malignant myeloma clone
- [redacted] measured by ClonoSIGHT™ next generation sequencing (NGS) assay

Overview of Key Safety Assessments

- Complete physical examination including vital signs
- Clinical laboratory evaluations (hematology, serum chemistry, urinalysis, thyroid function tests)
- Creatinine clearance
- Pregnancy testing / counseling
- Electrocardiogram (ECG)
- Concomitant medications and procedures
- Immunogenicity of durvalumab
- Adverse events, including adverse events of special interest (AESIs for example, second primary malignancies)

Pharmacokinetic

- Serum/plasma samples will be collected to assay concentrations of durvalumab and LEN

[redacted]

Statistical Methods

Up to 138 subjects are planned to be enrolled in the study: up to 36 total in the 3 cohorts for dose finding and up to 102 in the 3 cohorts for expansion. The actual number of subjects will depend on the number of dose level being tested. Data will be reviewed and analyzed on an ongoing basis to allow DRT for making the decisions. Final analyses will be performed after the End of Trial has been reached. All analyses will use descriptive statistics. No formal statistical comparison/testing will be performed.

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1. INTRODUCTION

1.1. Disease Background

Multiple myeloma (MM) is a rare and incurable progressive neoplastic disease that accounts for 12% of all hematological malignancies (Ferlay, 2015). It has been estimated that 24,050 new cases and 11,090 deaths from MM occurred in the United States (US) in 2014 (Howlader, 2014), and that 114,000 new cases and 80,000 deaths from MM occurred globally in 2012 (Ferlay, 2015).

Significant progress has been made in the treatment of MM with various combinations of melphalan, prednisone, dexamethasone, doxorubicin, cyclophosphamide, etoposide, cisplatin, immunomodulatory agents (thalidomide, lenalidomide and pomalidomide), and proteasome inhibitors (eg, bortezomib and carfilzomib) or with autologous stem cell transplant following high-dose chemotherapy (National Comprehensive Cancer Network [NCCN] Guidelines, 2015). Despite the progress in treatment options; such as newer IMiDs® and proteasome inhibitor classes of drugs, MM remains incurable using conventional treatments, with an overall 5-year relative survival of 45% (Howlader, 2014). New treatment options are therefore needed, especially for the high risk newly diagnosed MM patients.

Multiple myeloma (MM) is more recently being recognized as a heterogeneous group of disease with variability in outcomes based on specific clinical and biologic predictors. With the recent increase in treatment armamentarium and the projected further increase in approved therapeutic agents in the coming years, the issue of having some mechanism to dissect this heterogeneity and rationally apply treatment is coming to the fore. Based on a number of robustly validated prognostic markers, MM patients can be broadly categorized into standard, intermediate and high risk for disease relapse, morbidity and mortality. The high-risk features include patient-specific factors such as old age, poor performance status and comorbidities; clinical features such as primary plasma cell leukemia and extramedullary disease; disease-specific biologic features such as deletion 17p, t (4;14) and high-risk gene expression profiling signatures (Chang, 2014; Usmani, 2015). In clinical practice, a better definition of MM subgroups is essential to provide more effective personalized therapies. Using combined the International Staging System (ISS) with chromosomal abnormalities (CA) and serum lactate dehydrogenase (LDH) to evaluate their prognostic value in newly diagnosed MM (NDMM) has improved prognostic power compared with the individual ISS, CA, and LDH parameters (Palumbo, 2015).

1.2. Compound Background

1.2.1. Durvalumab (MEDI4736)

Durvalumab (MEDI4736) is a human immunoglobulin (Ig) G1 kappa monoclonal antibody (mAb) targeted against human programmed cell death ligand 1 (PD-L1). Durvalumab is expressed in Chinese hamster ovary cells and has an overall molecular weight of approximately 149 kDa. Durvalumab selectively binds to human PD-L1 (cluster of differentiation [CD274]) with high affinity and blocks its ability to bind to programmed cell death 1 (PD-1[CD279]) protein and cluster of differentiation (CD80). The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that

reduces binding to the complement component C1q and the Fc gamma receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC) (Oganesyan, 2008).

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

1.2.2. Lenalidomide (LEN)

Lenalidomide (LEN) is a drug in the class of immunomodulatory drugs known as IMiDs® compounds, which are structurally similar to thalidomide. Another IMiD® compound is pomalidomide. All three (thalidomide, lenalidomide, and pomalidomide) are approved for the treatment of MM, and are being evaluated for a number of other hematologic malignancies. The lenalidomide also has been approved for the treatment of relapsed mantle cell lymphoma (MCL) patients and myelodysplastic syndromes (MDS) associated with deletion 5q abnormality patients.

IMiDs® compounds may affect the immune system in several ways, such as inducing immune responses, enhancing activity of immune cells, altering and modulating the induction of pro- and anti-inflammatory cytokines, and inhibiting inflammation. IMiDs®are also anti-angiogenic. Although their precise mechanism of action is currently under investigation, these agents offer promise for their anticancer and anti-inflammatory activities.

Please refer to the lenalidomide Investigator's Brochure for detailed information concerning the available pharmacology, toxicology, drug metabolism, clinical studies, and adverse event profile of the investigational product (IP); as well as the current label of lenalidomide (Revlimid® Prescribing Information, Revlimid Summary of Product Characteristics, Revlimid® Product Monograph).

1.3. Rationale

1.3.1. Study Rationale and Purpose

1.3.1.1. Cancer and Immune Function

The importance of the immune system in cancer development and progression has been recognized during the past thirty years (Pardoll, 2015; Hanahan, 2011). Evidence for tumor immune surveillance, a process whereby the immune system recognizes and eliminates transformed and malignant cells, has been clearly shown in carcinogen-induced murine models of cancer (Shankaran, 2001; Dunn, 2005). These data suggest that the immune system can seek and eliminates tumor cells, but also contribute to phenotypic and genotypic "shaping" of the tumor in a process called immunoediting (Dunn, 2004). Similarly, the tumor and tumor microenvironment can disrupt and alter anti-tumor immune cells through a variety of mechanisms resulting in tumor growth. Once such mechanism is through coercing natural checkpoint pathways that control T cell activation and inhibition. A seminal observation of inhibition of cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) in murine models of cancer provided evidence that manipulation of checkpoint blockade could significantly impact tumor growth and survival (Leach, 1996).

Another such checkpoint pathway involves Programmed cell death-1 (PD-1) and Programmed cell death ligand 1(PD-L1). PD-L1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response (Keir, 2008). In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell (Keir, 2008; Park, 2010). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells, thus providing an additional inhibitory signal and preventing T cells from killing target cancer cells and protecting the tumor from immune elimination (Hirano, 2005). Additional mechanisms for PD-L1-mediated immune suppression have been described, including promoting regulatory T cell (Treg) skewing, effector T cell apoptosis, and inhibiting optimal antigen presentation (Chen, 2015).

PD-L1 is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung (Mu, 2011), renal (Thompson, 2006; Thompson, 2005; Krambeck, 2007), pancreatic (Nomi, 2007; Loos, 2008; Wang, 2010), ovarian cancer (Hamanishi, 2007), and hematologic malignancies (Andorsky, 2011; Brusa, 2013) tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis.

1.3.1.2. Immune-checkpoint Inhibition

Tumor-infiltrating lymphocytes (TILs) have the capacity to control the growth of many types of cancers (Gooden, 2011). Most tumors show infiltration by TILs, but tumors modulate the local microenvironment through expression of inhibitory molecules. In human disease, engagement of TIL cell-surface receptors with these inhibitory ligands, such as CTLA-4, LAG-3, TIM-3, and PD-1, leads to a dysfunctional immune response, causes T-cell exhaustion, and facilitates tumor progression (Baitsch, 2012; Matsuzaki, 2010).

The first successful demonstration of checkpoint blockade utilized a CTLA-4 antibody (Ipilimumab) in metastatic melanoma patients (Hodi, 2010). Blockade of the PD-1, and PD-L1 pathways have shown remarkable clinical activity not only in conventionally immune-responsive tumors such as melanoma (Robert, 2015; Hamid, 2013; Brahmer, 2012; Topalian, 2012) and renal cell carcinoma (Motzer, 2015) but also in non-small cell lung cancer (NSCLC) (Brahmer, 2015; Garon, 2015), MSI^{hi} colorectal cancer (Le Dung, 2015), and Hodgkins disease (Ansell, 2015). The combination of PD-1 and CTLA-4 blockade is being evaluated across multiple solid and hematological disease indications and has proven effective in melanoma (Wolchok, 2013; Larkin, 2015).

Pembrolizumab and nivolumab are both PD-1 blocking antibodies and the first in the anti-PD-1 pathway family of checkpoint inhibitors to gain approval from the US Food and Drug Administration (FDA). For metastatic melanoma, single agent pembrolizumab and nivolumab have been approved in the US, EU, Japan and other countries worldwide. The combination of nivolumab + ipilimumab has been approved in the US for metastatic melanoma. Pembrolizumab has been approved in the US and nivolumab in the US and EU for the treatment of advanced, previously treated squamous and non-squamous NSCLC.

1.3.2. Rationale for the Study Design

Durvalumab has been studied primarily in subjects with solid tumors and a limited number of subjects with MDS but not on multiple myeloma subjects. While PK and safety of durvalumab as monotherapy and in combination have been characterized in more than 500 subjects, the paraprotein present in myeloma may alter the PK and Pd of durvalumab and higher doses may be required. The durvalumab in combination with LEN+/- dex in the newly diagnosed multiple myeloma (NDMM) population has not been previously studied. While the starting dose of 1500 mg is justified based on PK and Pd data and the expectation is that there will not be synergistic toxicity, dose de-escalation may be considered. As dex may interfere with the immune mediated efficacy of durvalumab but has shown efficacy when added with LEN, this study aims to generate PK/Pd, safety and preliminary efficacy data with and without the use of dex.

1.3.3. Rationale for Dose, Schedule, and Regimen Selection

1.3.3.1. Dose/Schedule

1.3.3.1.1. Durvalumab (MEDI4736)

The dose and schedule for durvalumab monotherapy (20 mg/kg every 4 weeks [Q4W]) was selected based on 2 sets of data: (1) the safety analysis of doses (0.1, 0.3, 1.0, 3.0, and 10 mg/kg every 4 weeks [Q2W]) administered in Study CD-ON-MEDI4736-1108 (a Phase 1/2 study to evaluate the safety, tolerability, and PK of IV durvalumab given as monotherapy in subjects with advanced solid tumors; and (2) PK profile simulations for durvalumab administered using 10 mg/kg Q2W and 20 mg/kg Q4W schedules.

Safety and PK characteristics of the studied dose and schedule 10 mg/kg Q2W:

After evaluation of the PK data from subjects enrolled in Study CD-ON-MEDI4736-1108, durvalumab exhibited nonlinear (dose-dependent) PK consistent with target-mediated drug disposition. Linear PK was observed at doses of 3 mg/kg and higher and is consistent with near complete target suppression, as reflected in target trough plasma concentrations of drug >100 ug/mL. This trough concentration is supported by sPD-L1 suppression data. Furthermore, the 10 mg/kg Q2W dose was not associated with any dose-limiting toxicities (DLTs) in the dose escalation phase and was, therefore, selected for further evaluation in the dose-expansion phase of Study CD-ON-MEDI4736-1108. Safety information is presented for 19 patients exposed to 1500 mg dose monotherapy (expressed as 20 mg/kg Q4W), in study CD-ON-MEDI4736-1108/ D4190C00001, and 4 patients exposed in study D4190C00002. There are over 100 patients treated at the 1500 mg (or the equivalent 20 mg/kg Q4W) dose in combination treatment studies.

Extrapolation of dose and schedule of 10 mg/kg Q2W to 20 mg/kg Q4W through population PK modeling:

A population PK model was developed using durvalumab monotherapy data from Phase 1 of Study CD-ON-MEDI4736-1108 (*N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg every 3 weeks [Q3W]; solid tumors*) (Fairman, 2014). This population PK model adequately described monotherapy Pharmacokinetic data and was utilized to predict expected PK exposures following 20 mg/kg Q4W dosing regimens (since none of the monotherapy studies explored Q4W regimens). PK simulations indicate that a similar overall exposure as represented by area under the plasma concentration curves (AUCs) (4 weeks) is expected following both 10 mg/kg Q2W

and 20 mg/kg Q4W regimens. However, median C_{max} at steady state is expected to be higher with 20 mg/kg Q4W (~1.5 fold) and median trough concentration at steady state is expected to be higher with 10 mg/kg Q2W (~1.25 fold).

Justification for fixed dosing over weight-based dosing:

Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similar findings have been reported by others (Ng, 2006; Wang, 2009; Zhang, 2012; Narwal, 2013). Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies (Wang, 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 proteins in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters (Zhang, 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

1.3.3.1.2. Lenalidomide and Dexamethasone

The LEN and dex dose/schedule will be as per the current label for lenalidomide for NDMM (Revlimid® Prescribing Information, Revlimid Summary of Product Characteristics, Revlimid® Product Monograph).

1.3.3.2. Regimen

Durvalumab + LEN with and without dex

The synergistic anti-proliferative activity of IMiDs® and dex has been previously established in both in vitro and in vivo (Revlimid® Prescribing Information, Revlimid Summary of Product Characteristics, Revlimid® Product Monograph; Pomalyst® Prescribing Information; Imnovid™ Summary of Product Characteristics; Gandhi, 2010). However, the immunostimulatory effect of IMiDs® may be inhibited by the anti-inflammatory action of dex (Gandhi, 2010). In order to gain data on the impact of dex on the potential immunostimulatory synergy of durvalumab +LEN with dex will be tested in this study.

1.3.4. Rationale for Choice of Combination Compounds

Durvalumab (MEDI4736) is a human immunoglobulin G1 kappa monoclonal antibody targeted against PD-L1. The proposed mechanism of action for durvalumab involves, immune system

activation leading to T-cell activation and proliferation, inhibition of human tumor growth via a T-cell-dependent mechanism, and immune mediated killing.

It has been observed that lenalidomide, an IMiD®, was capable of down-regulating the expression of PD-L1 on the malignant plasma cells from MM patients and that its in vitro application resulted in an enhancement of the myeloma-targeting activity of an anti-PD-1 antibody (Benson, 2010). Lenalidomide treatment not only results in a decrease in T-cell expression of PD-1 but also down-regulates expression of PD-L1 on malignant plasma cells from patients with MM. When combined, lenalidomide and an anti-PD-L1 antibody demonstrated a synergistic antitumor effect by enhancing the T-cell mediated immune response to MM tumor cells (Görgün, 2015). PD-L1 is highly expressed in BM-stroma cells (BMSC). PD1/PD-L1-blockade abrogates BMSC-induced MM growth, and combined blockade of PD-1/PD-L1 with lenalidomide further inhibits BMSC-induced tumor growth. These effects are associated with induction of intracellular expression of IFNγ and Granzyme-B in effector cells. Lenalidomide with PD-1/PD-L1-blockade inhibits MDSC (myeloid-derived suppressor cells)-mediated immune suppression.

Lenalidomide has shown efficacy in combination with dexamethasone for NDMM patients who are either 65 years of age or older or not candidates for stem cell transplant (Benboubker, 2014), and recently has been approved by both Food and Drug Administration (FDA) and European Medicines Agency (EMA) for this indication. Studies have been conducted in both the induction and maintenance transplant setting using lenalidomide.

The LEN MM-020 Phase 3 is a pivotal study (FIRST Trial) with the largest data set in transplant non eligible (TNE) newly diagnosed multiple myeloma (NDMM) patients. 1623 patients were randomized to lenalidomide–dexamethasone in 28-day cycles until disease progression (535 patients), to the same combination for 72 weeks (18 cycles; 541 patients), or to MPT for 72 weeks (547 patients). The primary end point was progression-free survival with continuous lenalidomide–dexamethasone versus MPT. The median progression-free survival was 25.5 months with continuous lenalidomide–dexamethasone, and 21.2 months with MPT (hazard ratio for the risk of progression or death, 0.72 for continuous lenalidomide–dexamethasone vs. MPT, P<0.001). Continuous lenalidomide–dexamethasone was superior to MPT for all secondary efficacy end points, Overall survival at 4 years was 59% with continuous lenalidomide–dexamethasone, and 51% with MPT.

Cytogenetic abnormalities in MM patients are prognostic importance and can be associated with poor outcomes. In the MM-020 study, a total of 762 of 1623 patients from the intent-to-treat population had validated cytogenetic profile, with 142 patient in the high-risk group (with t(4:14), or/and, t(14;16), or/and 17p13 deletions abnormality) and 620 patient in the non-high-risk group. In the high-risk group, median duration of treatment was 10.0 months with lenalidomide–dexamethasone continuous, and 12.0 months with MPT. The lenalidomide–dexamethasone continuous treatment resulted in a 24% reduced risk of death or progression compared with MPT and an even greater 32% reduced risk in patients without high-risk cytogenetics. In non–high-risk patients, median PFS was 31.1 months with lenalidomide–dexamethasone continuous compared with 24.9 months with MPT, the OS was similar across treatment arms for high-risk patients. The ORRs in all cytogenetic risk groups favored lenalidomide–dexamethasone continuous vs MPT. In patients with high-risk cytogenetics, higher-quality responses were also observed with lenalidomide–dexamethasone continuous vs

MPT treatment; although OS and ORR benefits overall and in patients without high-risk cytogenetics were not as pronounced (Avet-Loiseau, 2015).

Three studies in the transplant setting noted prolonged time to disease progression when used in either the maintenance or induction therapy: Attal reported that the rate of complete or very good partial response was 84% for lenalidomide maintenance therapy and 76% for placebo ($p = 0.009$) (Attal, 2012); McCarthy reported that the median time to progression was 39 months among patients in the lenalidomide group and 21 months among patients in the placebo group ($p < 0.001$) (McCarthy, 2012). The PFS was the primary end point for Palumbo's study, and results showed median of 31 months of PFS for MPR-lenalidomide group compared with median of 14 months for MPR only (hazard ratio, 0.49; $p < 0.001$) (Palumbo, 2012).

Based on the current available information from the PD-L1 inhibition and lenalidomide, the combination of durvalumab + LEN + dex warrants further investigation in NDMM patients.

1.3.5. Rationale for Pharmacodynamics and Potential Predictive Biomarkers

Durvalumab (MEDI4736) binds to human PD-L1 with high affinity and blocks its ability to bind PD-1, thus restoring immune activation with downstream effects on cytokine production, proliferation, cell survival, and transcription factors associated with effector T-cell function. Measurements of pharmacodynamic biomarkers, such as soluble PD-L1 saturation and immune cell activation status, could help our understanding of the pharmacological effect of durvalumab and contribute to decision making in the dose and schedule selection. In addition, a number of recent studies have reported a correlation between several molecular markers, including the expression level of PD-L1 in tumor and immune cells, neoantigen presentation and T-cell clonality, and the clinical activity of immune checkpoint inhibitors (Topalian, 2012; Herbst, 2014).

Experience of MEDI4736 in solid tumors showed that greater responses were observed in subjects with PD-L1-positive, and much lower rate of responses in subjects with PD-L1-negative tumors (Segal, 2014). More recent data indicates that a combination of elevated PD-L1 protein expression and elevated IFNgene expression in pretreatment tumor biopsies may predict the best response to durvalumab monotherapy (Higgs, 2015; Higgs, 2016). Thus, continued evaluation of these biomarkers and a broad exploration of additional biomarkers related to immunological and disease factors are needed to aid the identification of potential predictive biomarkers for this therapy.

A key scientific objective of this clinical trial is to evaluate the dynamic changes in the microenvironment of the tumor. While understanding the immunologic characteristics at baseline may be both predictive and prognostic, it will be extremely critical to understand the changes in the local immune system following treatment with durvalumab and the combination agents. Biomarker analysis of durvalumab in non-small cell lung cancer patients demonstrated a statistically significant increase in $CD8^+$ infiltrating lymphocytes from on-treatment tumor samples compared with pre-treatment biopsies. This data is consistent with the PD effects observed in tumor biopsies from patients treated with Atezolizumab (a PD-L1 inhibitor) and Pembrolizumab (a PD-1 inhibitor). Notably, while pharmacodynamic response to durvalumab and MPDL3280A can also be observed in the periphery, peripheral markers have not been shown to be correlated with response. For pembrolizumab, increase in $CD8^+$ density at tumor or invasive margin after treatment is observed in responders while absent in progressors in

melanoma, indicating that the $CD8^+$ TILs were activated and targeting the tumor (Tumeh, 2014). Serial biopsy analyses for MPDL3280 showed that increases in PD-L1 protein expression and genes indicative of activated T cells (eg, granzyme, interferon [IFN]-gamma) were more frequently observed in patients who respond to the therapy compared with the nonresponders (Herbst, 2014).

Evaluation of post-treatment tumor samples is critical for identifying pharmacodynamic changes that are induced by durvalumab. These biomarker data will facilitate better understanding of the mechanism of action for durvalumab alone or in combination with other agents to facilitate future clinical trial designs. The data may also reveal new targets/additional immune system pathways to improve therapeutic outcomes.

Recent research on the mechanism of action of lenalidomide, pomalidomide, and thalidomide suggest that in tumor cells and T cells, cereblon, a component of E3 ubiquitin ligase complexes, is a target for binding by these compounds. These studies showed that the loss of cereblon or its downstream substrates, such as Ikaros and Aiolos, decreases or eliminates the anti-tumor and immunomodulatory activity of lenalidomide and pomalidomide respectively (Ito, 2010; Zhu, 2011; Lopez-Girona, 2012). In several retrospective analyses, high cereblon levels at baseline have been reported to be associated with better clinical outcomes in subjects treated with regimens containing lenalidomide, pomalidomide, or thalidomide. Thus, further investigation is warranted on whether there is any potential correlation of Cereblon levels to clinical outcomes by measuring baseline and on-treatment Cereblon levels in tumor and T cells.

Since both durvalumab and LEN regulate immune cell activation and functions, we will also quantify subsets of immune cells and assess their functions from peripheral blood and bone marrow samples (at baseline and during treatment) to explore whether and how immune functions are modulated by the individual components and the combinations.

2. STUDY OBJECTIVES AND ENDPOINTS

2.1. Study Objectives and Endpoints

Table 1: Study Objectives

Primary Objective
The primary objective of the study is to determine the recommended dose of durvalumab in combination with LEN +/- dex in subjects with NDMM.
Secondary Objective(s)
The secondary objectives are to • Evaluate the safety and preliminary efficacy of durvalumab in combination with LEN +/- dex in subjects with NDMM • Evaluate the pharmacokinetics of durvalumab and LEN with and without dex in subjects with NDMM.
Exploratory Objective(s)
The exploratory objectives are to: • To evaluate additional efficacy of durvalumab in combination with LEN with and without dex in subjects with NDMM.
[redacted]

Table 2: Study Endpoints

Endpoint	Name	Description
Primary	Recommend Dose	Review safety (including dose-limiting toxicities [DLTs]), and if applicable, PK/Pd, and/or biomarker, and/or preliminary efficacy data by Dose Review Team (DRT)
Secondary	Safety	Type, frequency, seriousness and severity of adverse events (AEs) (included second primary malignancies), and relationship of AEs to study treatment
Secondary	Overall Response Rate (ORR) (for Cohorts A and B)	Tumor response, including progressive disease, based on the investigator assessments according to the International Myeloma Working Group (IMWG) Uniform Response Criteria (Rajkumar, 2011).

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description
Secondary	Response Improvement Rate (RIR) (for Cohort C)	Response improved from the assessment at the Cycle 1 Day 1 (C1D1); (Pre-autologous stem cell transplantation [ASCT] diseases measurement will be used as baseline for response assessment)
Secondary	Time to Response (TTR) (for Cohorts A and B)	Time from C1D1 to the first documentation of response
Secondary	Duration of response (DOR) (for Cohorts A and B)	Time from the first response (partial response [PR] or better) to the first documentation of disease progression or death, whichever is earlier, based on the investigator assessments according to the IMWG Uniform Response Criteria
Secondary	Pharmacokinetic	Typical serum/plasma PK parameters for durvalumab and lenalidomide, 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 (Vz/F)
Secondary	Immunogenicity	Frequency of development of anti-drug antibodies and neutralization
Secondary	Progression-Free Survival (PFS)	Time from C1D1 to the first documentation of disease progression (based on the investigator assessments according to the IMWG Uniform Response Criteria) or death from any cause during study, whichever occurs earlier
Secondary	Overall Survival(OS)	Time from C1D1 to death due to any cause
[redacted]		

Table 2: Study Endpoints (Continued)

Endpoint	Name	Description
[redacted]		

3. OVERALL STUDY DESIGN

3.1. Study Design

This is a multicenter, open-label, Phase 1/2 study to determine the recommended dose and regimen of durvalumab in combination with LEN with and without dex in subjects with NDMM. The study will consist of a dose-finding phase as well as a parallel dose-expansion phase to determine the optimal regimen. See Figure 1 and Figure 2 and Dose-finding Phase.

The dose-finding phase will determine recommended dose (RD) for durvalumab in combination with LEN with and without dex in a 28-day treatment cycle. Three treatment Cohorts (A, B, and C) will be enrolled in parallel:

- Cohort A: durvalumab + LEN +dex on high risk TNE NDMM subjects;
- Cohort B: durvalumab + LEN +dex (for up to 12 cycles) on ≥ 65 years old TNE NDMM subjects who are not high risk;
- Cohort C: durvalumab + LEN as maintenance on post-transplant high risk NDMM subjects;

In the US, two treatment arms (A and B) will be enrolled in parallel. Cohort C will enroll upon completion of at least 4 cycles of follow-up for safety assessment of Cohort A and B. [redacted]

On 05 Sep 2017, US FDA placed this study on full clinical hold. As a result, the study was closed for further enrollment, and all subjects were discontinued from all study treatments (durvalumab, lenalidomide and dexamethasone).

Based on experience with durvalumab for other indications, the initial dose of durvalumab will be 1500 mg for each treatment cohort. The dose of durvalumab might be de-escalated to 750 mg level.

The dose of LEN will be 25 mg (adjustable per the CrCl value, see details in Section 7.2.1.2, Table 4) on Days 1 to 21 of each 28-day treatment cycle for subjects on Cohort A and B. The dose of LEN will be 10 mg on Days 1 to 21 of each 28-day treatment cycle for subjects on Cohort C.

The dose of dex will be 40 mg/day (for subjects ≤ 75 years old) or 20 mg/day (for subjects > 75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle for Cohort A and Cohort B (for up to 12 cycles).

Initially, 6 subjects will be enrolled into each cohort and each will receive 1500 mg durvalumab. The dose-limiting toxicity (DLT) evaluation period will be the first treatment cycle.

- If ≤ 1 of the 6 initial subjects experience a DLT within the first cycle, then the dose-expansion phase may be initiated with durvalumab 1500 mg as the recommended dose (RD);

- If 2 or more of the 6 initial subjects experience a DLT within the first cycle, then the maximum tolerated dose (MTD) has been exceeded and de-escalation to durvalumab 750 mg level after review of safety and PK/Pd of the initial 6 subjects by the DRT

Any of the cohorts may be removed from the study based on emerging PK, Pd, efficacy or safety data.

Dose de-escalation will only occur after review of safety (DLT) and possibly PK/Pd data by the DRT.

3.1.1.1. Dose Review Team (DRT)

The DRT are responsible for dosing decisions. The DRT members will consist of the following: Celgene medical monitor, Celgene lead safety physician, Celgene biostatistician, other Celgene functional area representatives as appropriate and site investigator and/or designees.

Dosing decisions may include de-escalation to a lower dose; continuation, delay or termination of dosing, repetition of a dose level, or expansion of a treatment cohort. All available safety, and if applicable, PK/PD, biomarker, and preliminary efficacy data will be reviewed and can be considered in the DRT's decisions.

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

3.1.1.2. Dose-limiting Toxicity (DLT)

Dose-limiting toxicities will be evaluated during the DLT evaluation period for the subjects in the dose-finding portion of the study. The DLT evaluation period will be defined as the first treatment cycle for each subject. Subjects are considered evaluable for assessment of DLT if they:

- Receive 1 dose of durvalumab;

If the subjects did not complete the first cycle of study treatment due to the reason other than DLT 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 or higher.

The DLT is defined as the occurrence of any toxicity listed below:

Hematologic DLT:

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

Non-Hematologic DLT:

- Any non-hematological toxicity Grade ≥3 except for alopecia and nausea controlled by medical management
- Any treatment interruption greater than 2 weeks due to adverse reactions

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

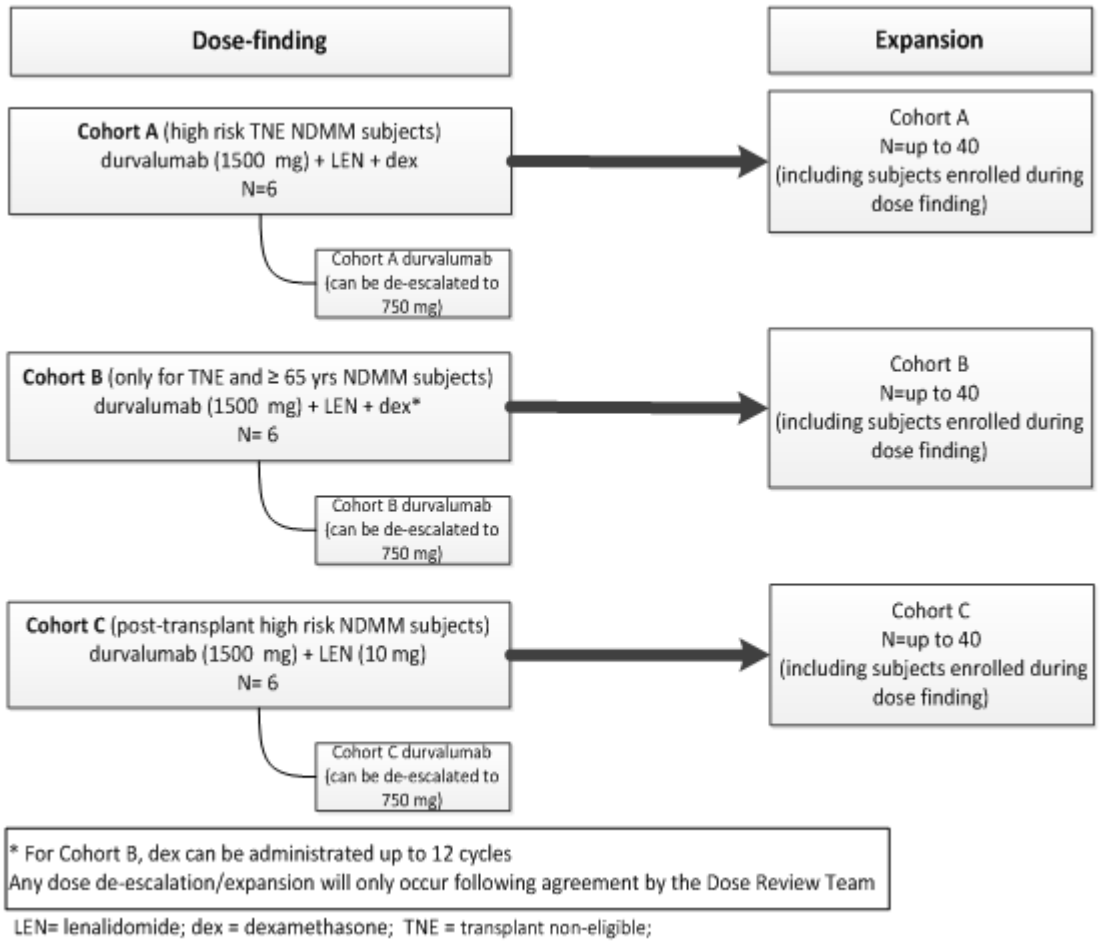
3.1.2. Dose-expansion Phase

All dose expansion decisions will be determined by the DRT after review of safety, and if applicable PK/Pd, biomarker and preliminary efficacy data.

After all 6 subjects enrolled in the Dose-finding phase have completed the Cycle 1 treatment; and all data are obtained and reviewed, additional eligible subjects (see detailed eligibility criteria in Section 4.2 and Section 4.3) for each respective cohort may be enrolled. The total of subjects for each Cohort can be expanded up to 40 (including the subjects enrolled in the Dose-finding Phase).

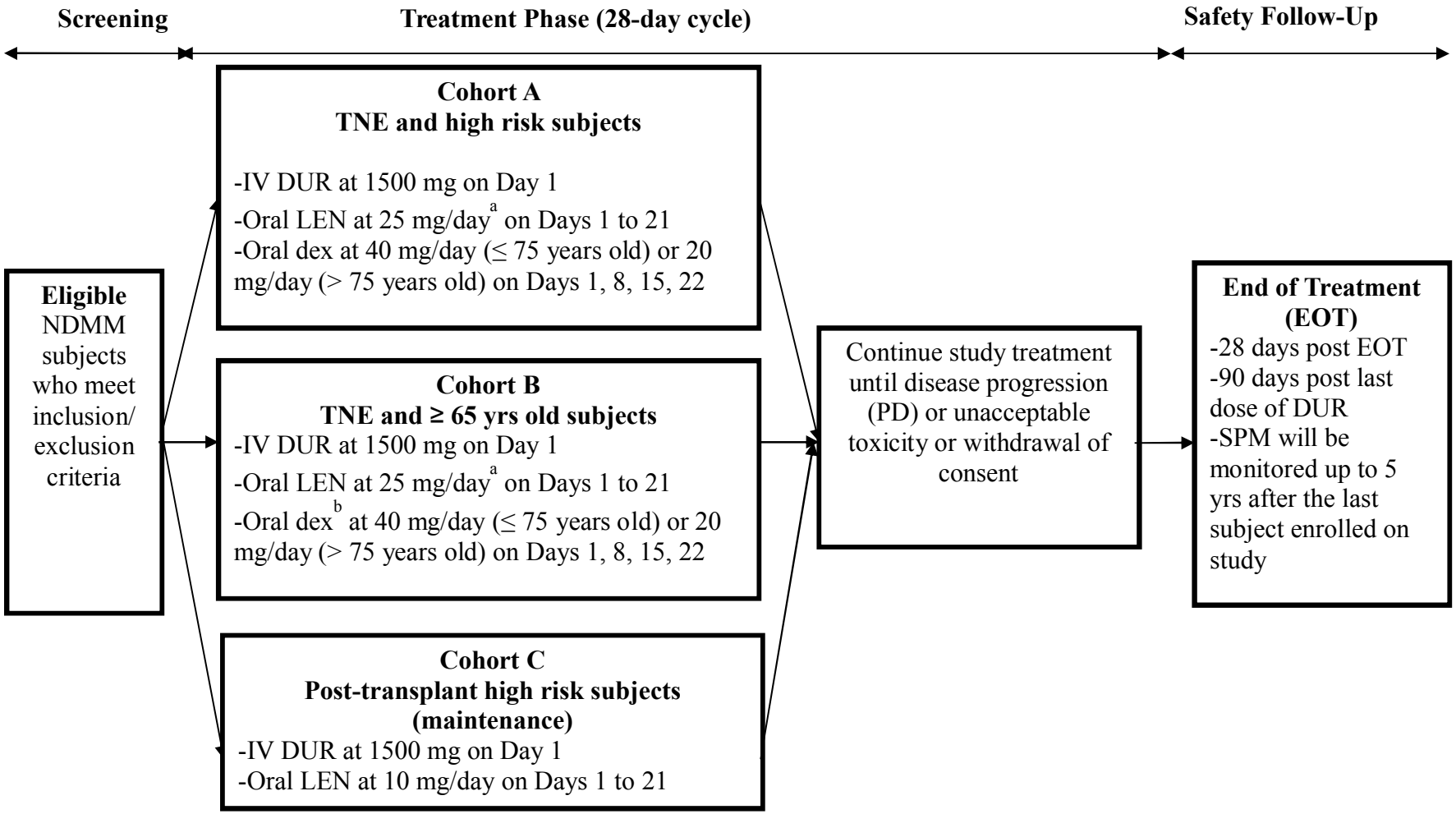
The expansion for each study cohort can occur independently.

Figure 1: Overall Study Design



LEN= lenalidomide; dex = dexamethasone; TNE = transplant non-eligible;

Figure 2: Study Scheme



LEN= lenalidomide; dex = dexamethasone; PD = progressive disease; EOT = end of treatment; IV = intravenous; TNE = transplant non-eligible;

[a] LEN dose is adjusted per the creatinine clearance value, see details in Section 7.2.1.2 and Table 4.

[b] For Cohort B, the dex can be administered up to 12 cycles.

3.2. Study Duration for Subjects

The study will consist of screening, treatment, and follow-up periods. Refer to Figure 2 for the study schema.

3.2.1. Screening Period

Informed consent must be obtained prior to any study-specific procedures being performed. Subjects who meet all eligibility criteria and have completed all screening procedures may be enrolled into the study. Screening assessments must be completed within 28 days prior to the first dose of study treatment, depending on the specific assessment, as outlined in Table 3.

3.2.2. Treatment Period

Eligible subjects will report to the study site to receive study treatment and protocol-specified procedures according to Table 3. The treatment period will consist of continuous 28-day cycles.

For the first 3 subjects of each cohort in the dose-finding portion, there will be at least a 24-hour observation period and 24 to 48 hours after that to communicate safety data (e.g., adverse event [AE], basic laboratory, and vital signs) to the sponsor before the dosing of the next subject occurs.

For subjects on Cohort C, the study treatment is to be initiated at 100 days (±14 days) after transplant.

Dose modifications and interruptions are permitted as detailed in Section 7.2.4.

All subjects may continue to receive study treatment until disease progression or unacceptable toxicity occurs, or withdrawal of consent.

3.2.2.1. End of Treatment Visit

Subjects are to return to the study site for the End of Treatment (EOT) Visit assessment within 7 (± 3) days after discontinuation of all study treatment (Table 3).

3.2.3. Follow-up Period

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 visit procedures as outlined in Table 3. Adverse events and SAEs will be monitored until 90 days after last dose of durvalumab. Adverse events and SAEs that lead to study treatment discontinuation and/or study withdrawal should be followed until resolution, stabilization, or death. The occurrence of SPM will continue to be monitored at the above required 90 days visit and every 6 months up to 5 years after the last subject is enrolled into the study. Data entry into the clinical database will continue until 15 Dec 2019. After this date, the occurrence of SPMs will continue to be monitored, and any events will continue to be recorded in the subject's source documents and report to Celgene Drug Safety.

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 the primary, secondary and/or exploratory analysis, as prespecified in the protocol, whichever is the later date.

4. STUDY POPULATION

4.1. Number of Subjects

Up to 138 subjects with newly diagnosed MM will be enrolled in the United States, Canada, and Europe (including but not limited to France, Germany, Spain, Netherlands, and Italy).

4.2. Inclusion Criteria

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

1. Subject is ≥ 18 years of age at the time of signing the informed consent form (ICF)
2. Subject must understand and voluntarily sign an ICF prior to any study-related assessments/procedures being conducted
3. Subject is willing and able to adhere to the study visit schedule and other protocol requirements
4. Subject must have documented diagnosis with previously untreated (for cohort C, the induction and consolidation treatment along with the first ASCT are allowed), symptomatic MM as defined by the criteria below (Rajkumar, 2014; NCCN-MM, 2015):
    - MM diagnostic criteria (all 3 required);
        - Monoclonal protein present in the serum and/or urine
        - Clonal bone marrow plasma cells ≥10% or biopsy-proven bony or extramedullary plasmacytoma*
        - Any one or more of the following myeloma defining events:
            - one or more of the following Myeloma-related organ dysfunction (at least one of the following);
                - [C] Calcium elevation (serum calcium >11.5 mg/dl)[> 2.65 mmol/L]
                - [R] Renal insufficiency (serum creatinine >2 mg/dl)[177 μmol/L or more] or creatinine clearance < 40 ml/min
                - [A] Anemia (hemoglobin <10 g/dl or >2 g /dL below the lower limit of laboratory normal)
                - [B] Bone lesions (lytic or osteopenic) one or more bone lesions on skeletal radiography, CT, or PET-CT
            - one or more of the following biomarkers of malignancy:
                - Clonal bone marrow plasma cell percentage* ≥60%
                - Abnormal serum free light-chain ratio ≥100 (involved kappa) or < 0.01 (involved lambda)

* Clonality should be established by showing κ/λ-light-chain restriction on flow cytometry, immunohistochemistry, or immunofluorescence. Bone marrow plasma cell percentage should preferably be estimated from a core biopsy specimen; in case of a disparity between the aspirate and core biopsy, the highest value should be used.

- >1 focal lesions detected by functional imaging including PET/CT and/or whole body magnetic resonance imaging (MRI)

AND have measurable disease by protein electrophoresis analyses as defined by the following:

- IgG MM: Serum monoclonal paraprotein (M-protein) level ≥ 1.0 g/dl or urine M-protein level ≥ 200 mg/24 hours
- IgA MM: Serum M-protein level ≥ 0.5 g/dl or urine M-protein level ≥ 200 mg/24 hours
- IgM MM (IgM M-protein plus lytic bone disease documented by skeletal survey plain films): Serum M-protein level ≥ 1.0 g/dl or urine M-protein level ≥ 200 mg/24 hours
- IgD MM: Serum M-protein level ≥ 0.05 g/dl or urine M-protein level ≥ 200 mg/24 hours
- Light chain MM: Serum M-protein level ≥ 1.0 g/dl or urine M-protein level ≥ 200 mg/24 hours

5. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2 (see Appendix C)
6. Females of childbearing potential (FCBP[1]) must:
   a. Have two 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[2] from heterosexual contact.
   b. She must either commit to true abstinence from heterosexual contact (which must be reviewed on a monthly basis and be 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 90 days after discontinuation of study treatment.
   c. Refrain from egg cell and blood donation for 90 days after the final dose of durvalumab.
7. Male subjects must:
   a. 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 FCBP 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.

[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].

b. Refrain from sperm and blood donation for at least 90 days after the final dose of durvalumab

8. For Cohort A subject must be transplant non-eligible (TNE) and meet at least one of the following high risk factors:
   a. Cytogenetic abnormalities finding in malignant myeloma clone with t(4; 14); and / or del(17p); and / or 1q amplification; and / or t(14:16);or
   b. ISS Stage III; or
   c. Serum LDH > 2 x ULN;
9. For Cohort B subject must be ≥ 65 years of age at the time of signing the informed consent form (ICF) and transplant non-eligible (TNE); excluding the subjects who meet the Cohort A criteria
10. For Cohort C subject must be after first autologous stem cell transplantation (ASCT) for NDMM and meet the following criteria:
    a. Have a post-transplant response as PR or better at the time of enrollment to this study;
    b. Have one of the following high risk factors at the time of NDMM diagnosis;
       - Cytogenetic abnormalities finding in malignant myeloma clone with t(4; 14); and / or del(17p); and / or 1q amplification; and / or t(14; 16); or
       - ISS stage III; or
       - Serum LDH > 2 x ULN;
    c. MRD positive (defined as more than 1 malignant cell in 10^5 cells) measured by ClonoSIGHT™ NGS assay of a BMA sample) at the time of enrollment to this study; BMA sample collected at the time of multiple myeloma diagnosis, prior to induction therapy available for central MRD assessment by ClonoSIGHT™ NGS assay

4.3. Exclusion Criteria

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

1. Previous treatment with anti-myeloma therapy (does not include radiotherapy, bisphosphonates, or a single short course of steroid [ie, less than or equal to the equivalent of dexamethasone 40 mg/day for 4 days; such a short course of steroid treatment must not have been given within 14 days of Cycle 1 Day 1], for Cohort C, the induction and consolidation treatment along with the first ASCT are allowed)
2. Any of the following laboratory abnormalities:
   a. Absolute neutrophil count (ANC) < 1,000/μL
   b. Untransfused platelet count < 75,000 cells/μL
   c. Serum aspartate aminotransferase/serum glutamic oxaloacetic transaminase (SGOT/AST) or alanine aminotransferase (SGPT/ALT) > 2.5 × upper limit of normal (ULN)
   d. Serum total bilirubin > 1.5 × ULN or > 3.0 mg/dL for subjects with documented Gilbert's syndrome

e. Corrected serum calcium >13.5 mg/dL (> 3.4 mmol/L)

3. Renal failure requiring hemodialysis or peritoneal dialysis
4. Any serious medical condition that places the subject at an unacceptable risk if he or she participates in this study. Examples of such a medical condition are, but are not limited to, subject with unstable cardiac disease as defined by: cardiac events such as myocardial infarction (MI) within the past 6 months, NYHA (New York Heart Association) heart failure class III-IV, uncontrolled atrial fibrillation or hypertension; subjects with conditions requiring chronic steroid or immunosuppressive treatment, such as rheumatoid arthritis, multiple sclerosis and lupus, that likely need additional steroid or immunosuppressive treatments in addition to the study treatment
5. Peripheral neuropathy ≥ Grade 2
6. Primary AL (immunoglobulin light-chain) amyloidosis and myeloma complicated by amyloidosis
7. Prior history of malignancies, other than MM, unless the subject has been free of the disease for ≥ 5 years with the exception of the following non-invasive 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
8. Subjects is positive for human immunodeficiency virus (HIV); chronic or active hepatitis B or active hepatitis A, or C
9. Subject had prior exposure to immunotherapy, including, but not limited to, other anti-CTLA-4, anti-PD-1, anti-PD-L1 monoclonal antibody or inhibitor, cell-based therapies, or cancer vaccines
10. Subjects has history of organ or allogeneic stem cell transplantation
11. Subjects who have had clinical evidence of central nervous system (CNS) or pulmonary leukostasis, disseminated intravascular coagulation, or CNS multiple myeloma, or plasma cell leukemia
12. Known or suspected hypersensitivity to the excipients contained in the formulation of durvalumab, lenalidomide, or dexamethasone
13. Major surgery (as defined by the investigator) within the 28 days prior to the first dose of study treatment
14. Received prior treatment (for any reason) with a monoclonal antibody within 5 half-lives of initiating study treatment
15. Use of any investigational agents within 28 days or 5 half-lives (whichever is longer) of initiating study treatment

16. Current or prior use of immunosuppressive medication within 14 days prior to the first dose of study treatment. The following are exceptions to this criterion:
    a. Intranasal, inhaled, topical 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, computed tomography [CT] scan premedication);
17. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis with the exception of a prior episode that has resolved or diverticulosis, celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea; systemic lupus erythematosus; Wegener's syndrome [granulomatosis with polyangiitis]; myasthenia gravis; Graves' disease; rheumatoid arthritis; hypophysitis, uveitis) 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; or
    c. Subjects with psoriasis not requiring systemic treatment;
18. History of primary immunodeficiency
19. Subject has incidence of gastrointestinal disease that may significantly alter the absorption of LEN
20. Receipt of live, attenuated vaccine within 30 days prior to the first dose of durvalumab (NOTE: subjects, if enrolled, should not receive live vaccine during the study and for 30 days after the last dose of durvalumab)
21. Unable or unwilling to undergo protocol required thromboembolism prophylaxis (for Cohort C, this will be only for the subjects who have a history of VTE)
22. Females who are pregnant, nursing or breastfeeding, or intend to become pregnant during the participation to the study
23. Any significant medical condition, laboratory abnormality, or psychiatric illness that would prevent the subject from participating in the study
24. Any condition including the presence of laboratory abnormalities, which places the subject at unacceptable risk if he/she were to participate in the study
25. Any condition that confounds the ability to interpret data from the study

5. TABLE OF EVENTS

Table 3: Table of Events

Events	Screening Period	Treatment Period								Safety Follow-up Visits	
		Cycle 1				Cycle 2-4 (±2 days for all visits)		≥ Cycle 5 (±2 days for all visits)	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DUR dose
	-28 to -1	D1[a]	D8	D15	D22	D1	D15	D1			
STUDY ENTRY AND GENERAL ASSESSMENTS											
Informed consent	X	-	-	-	-	-	-	-	-	-	-
Inclusion/exclusion criteria	X	-	-	-	-	-	-		-	-	-
IRT registration	X	X	-	-	-	-	-	-	X	-	-
Complete medical history	X	-	-	-	-	-	-	-	-	-	-
Demographics	X	-	-	-	-	-	-	-	-	-	-
Confirmation of Diagnosis /Stage	X	-	-	-	-	-	-	-	-	-	-
HIV and Hepatitis Screening Panel (A, B & C)	X	-	-	-	-	-	-	-	-	-	-
Cytogenetic data (done by central Lab)	X	-	-	-	-	-	-	-	-	-	-
Prior/ concomitant medication evaluation	X (-28 days from screening)	Continuous, until 90 days after last dose of durvalumab									
Prior/ concomitant procedures evaluation	X (-28 days from screening)	Continuous, until 90 days after last dose of durvalumab									

Table 3: Table of Events (Continued)

Events	Screening Period	Treatment Period								Safety Follow-up Visits	
		Cycle 1				Cycle 2-4 (±2 days for all visits)		≥ Cycle 5 (±2 days for all visits)	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DUR dose
	-28 to -1	D1[a]	D8	D15	D22	D1	D15	D1			
STUDY ENTRY AND GENERAL ASSESSMENTS											
SAFETY ASSESSMENTS											
Adverse event evaluation	Continuous starting after informed consent signature, until 90 days after last dose of durvalumab										
Assessment of Second Primary Malignancy	Continuous starting after informed consent signature, up to 5 years after the last subject enrolled into the study										
Physical examination	X	X	-	-	-	X	-	X	X	-	-
Vital signs	X	X	X	X	X	X	X	X	X	X	X
Weight	X	X	X	X	X	X	X	X	X	X	X
Height	X	-	-	-	-	-	-	-	-	-	-
12-lead electrocardiogram (ECG)	X	Repeated only if clinically indicated							X	-	-
Clinical examination for peripheral neuropathy	X	-	-	-	-	-	-	-	-	-	-
Hematology laboratory (done by central laboratory)	X	X	X	X	X	X	X	X	X	X	X
Coagulation parameters (done by central laboratory)	X	X	-	X	-	X	-	X	X	-	X
Chemistry laboratory (done by central laboratory)	X	X	X	X	X	X	X	X	X	X	X
Thyroid function tests (done by central laboratory)[i]	X	X		X		X	X	C5 then every 2 cycles	X	-	X

Table 3: Table of Events (Continued)

Events	Screening Period	Treatment Period								Safety Follow-up Visits	
		Cycle 1				Cycle 2-4 (±2 days for all visits)		≥ Cycle 5 (±2 days for all visits)	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DUR dose
	-28 to -1	D1[a]	D8	D15	D22	D1	D15	D1			
STUDY ENTRY AND GENERAL ASSESSMENTS											
Renal Function (CrCl using Cockcroft-Gault formula or 24 hour urine collection method)	X	X	X	X	X	X	X	X	X	X	X
Urinalysis	X	repeated during treatment if clinically indicated							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	X	X	-	-	-	X	-	X	X	X	X
Thromboembolism prophylaxis for all subjects on LEN as part of treatment[b]	-	Continuous during LEN treatment								-	-
EFFICACY AND OTHER ASSESSMENTS											
ECOG Performance status	X	X	-	-	-	X	-	X	X	-	-
Assessment of response (IMWG Uniform Response Criteria)[c]	-	X	-	-	-	X	-	X	X	-	-

Table 3: Table of Events (Continued)

Events	Screening Period	Treatment Period								Safety Follow-up Visits	
		Cycle 1				Cycle 2-4 (±2 days for all visits)		≥ Cycle 5 (±2 days for all visits)	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DUR dose
	-28 to -1	D1[a]	D8	D15	D22	D1	D15	D1			
Serum and urine electrophoresis (done by central Lab)	X	X	-	-	-	X	-	X	X	-	-
STUDY ENTRY AND GENERAL ASSESSMENTS											
Serum and urine immunofixation (done by central laboratory)	X	X	-	-	-	X	-	X	X	-	-
Serum free light-chain assay (done by central laboratory)	X	X	-	-	-	X	-	X	X	-	-
Quantitative serum immunoglobulin (done by central laboratory)	X	X	-	-	-	X	-	X	X	-	-
Beta-2 microglobulin (done by central laboratory)	X	X	-	-	-	X	-	X	X	-	-
Extramedullary plasmacytomas (EMP) clinical assessment	X	X	-	-	-	X	-	X	X	-	-
Minimal Residual Disease Assay (Bone Marrow Aspiration) for subjects on Cohort C (done by central laboratory)[d]	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 3: Table of Events (Continued)

Events	Screening Period	Treatment Period								Safety Follow-up Visits	
		Cycle 1				Cycle 2-4 (±2 days for all visits)		≥ Cycle 5 (±2 days for all visits)	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DUR dose
	-28 to -1	D1[a]	D8	D15	D22	D1	D15	D1			
STUDY ENTRY AND GENERAL ASSESSMENTS											
Bone lesions assessment	X (within 60 days prior to first dose acceptable)	repeated during treatment if clinically indicated to confirm response or progression								-	-
Pharmacokinetics	-	**LEN PK sampling for all Cohorts** C1D1: pre-dose, 0.5, 1, 2, 4, and 8 hours post C1D1 LEN dose C1D15: pre-dose, 0.5, 1, 2, 4, and 8 hours post C1D15 LEN dose **DUR PK sampling for all Cohorts:** -C1D1: pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, 168 hours (C1D8), 336 hours (C1D15) and 504 hours (C1D22) after administration of DUR on C1D1 -C2D1: pre-infusion (-60 to -5 minutes prior to dose), end of infusion (EOI), 4 hours, and 336 hours (C1D15) after administration of DUR on C2D1 -C4D1, C6D1, C10D1, and C14D1: pre-infusion (-60 to -5 minutes prior to dose)								-	-
Immunogenicity (ADA)	-	Pre-dose samples on C1D1, C2D1, C4D1, C6D1, C10D1 and C14D1.								-	-
Bone marrow aspirate and/or biopsy sampling for cytogenetics, % plasma cells, [redacted]	X	[redacted] - BMA and BMB at time of CR confirmation for % plasma cells [redacted]							-	-	-

Table 3: Table of Events (Continued)

Events	Screening Period	Treatment Period								Safety Follow-up Visits	
		Cycle 1				Cycle 2-4 (±2 days for all visits)		≥ Cycle 5 (±2 days for all visits)	EOT (≤7 days from trt discon decision)	28 days (+3) after EOT	90 days (+3) after last DUR dose
	-28 to -1	D1[a]	D8	D15	D22	D1	D15	D1			
STUDY ENTRY AND GENERAL ASSESSMENTS											
[redacted]											
[redacted]											
[redacted]											
STUDY TREATMENT (DUR, LEN, dex)[f]											
COHORT A and Cohort B											
DUR IV administration[g]	-	X	-	-	-	X	-	X	-	-	-
Oral LEN	-	Days 1-21/28 day cycle							-	-	-
Oral dex [h]	-	Days 1, 8, 15, 22 / 28-day cycle							-	-	-
COHORT C											
DUR IV administration[g]	-	X	-	-	-	X	-	X	-	-	-
Oral LEN	-	Days 1-21/28 day cycle							-	-	-
IP Accountability	-	X	-	-	-	X	-	X	X	-	-

Abbreviations:
ADA = anti-drug antibody; AE = adverse event; AESI = adverse events of special interest; BMA = bone marrow aspirate; BMB = bone marrow biopsy; C = Cycle; CrCL = creatinine clearance; dex = dexamethasone; D= Day; DUR= 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; IMWG = International Myeloma Working Group; IRT= integrated response technology; IV = intravenous; LEN = lenalidomide; min = minutes; NGS = next generation sequencing; PD = progressive disease; PK = pharmacokinetics; PR = partial response; trt discon = treatment discontinuation

[a] On Cycle1 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.

[b] For Cohort C, only applies to the subjects who have a history of VTE.

[c] Per IMWG Uniform Response Criteria all response categories and progressive disease require 2 consecutive assessments. For details of the procedures and timing, see Section 6.4.5.

[d] Minimal residual disease levels will be measured by ClonoSIGHT™ NGS assay. Bone marrow aspirate samples will be collected at the screening, [redacted] (if not overlap with other BMA samples time points stated on section 6.4.2). Bone marrow aspirate samples collected at the time of multiple myeloma diagnosis must also be available for central analysis (ClonoSIGHT™ NGS assay) for subjects to be considered eligible for the study. The interval between BMA samplings should not be less than 6-months. With the exception of the screening visit, if the subject underwent BMA sampling within 6-months of the required sampling date, sampling will be delayed until 6-months after the previous sample.

[redacted]

[f] All subjects may continue to receive study treatment until disease progression or unacceptable toxicity, or withdrawal of consent.

[g] First and Second DURVA infusion: Subjects will be monitored during and after DUR infusion. Vital signs will be measured prior to DUR administration (- 30 minutes), every 15 minutes (± 5 minutes) during DUR administration, at the end of DUR infusion (± 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) after DUR infusion, followed by a 2-hour (± 15 minutes) period of observation. 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. For the first 3 subjects of each cohort in the dose-finding portion, there will be at least a 24-hour observation period and 24 to 48 hours after that to communicate safety data (e.g., adverse event [AE], basic laboratory, and vital signs) to the sponsor before the dosing of the next subject occurs.

[h] For Cohort B, the dex can be administered for up to 12 cycles.

[i] From Cycle 5 onwards only thyroid stimulating hormone (TSH) will be assessed, if TSH is abnormal, then testing for free T4 and free T3 will be performed.

6. PROCEDURES

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

6.1. Screening period

Screening evaluations will be performed for all subjects to determine study eligibility. These evaluations must be completed within 28 days of first dose unless noted otherwise below.

Any questions regarding subject eligibility should be directed to the Celgene Medical Monitor or designee. 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 adverse event reporting must be entered as an unscheduled visit on the electronic case report form (eCRF).

Screening laboratory values must demonstrate subject eligibility but may be repeated within the screening window, if necessary.

The following will be performed at screening as specified in Table 3, after informed consent has been obtained:

- Interactive Response Technology (IRT) Registration
- Demographics (date of birth, sex, race, and ethnicity, if allowed by local regulations, will be collected in the eCRF and/or IRT system)
- Complete medical history (all relevant medical conditions diagnosed/occurring prior to screening should also be included)
- Disease history (if available the date of initial diagnosis, staging at time of diagnosis, cytogenetics at diagnosis to be collected)
- Prior and ongoing concomitant procedures (including all procedures occurring ≤ 28 days before screening)
- Prior and ongoing concomitant medication evaluation (including those taken ≤ 28 days before screening)
- Physical examination, including assessment for potential venous thromboembolism events (VTEs) (can be source documented only)
- Vital signs (including blood pressure, temperature, and heart rate)
- Height
- Weight
- Clinical examination for peripheral neuropathy

- ECOG performance status (see Appendix C)
- 12-lead electrocardiogram (ECG)
- Efficacy assessment/ tumor evaluation (see Section 6.4)
- Cytogenetics (see Section 6.4.2)
- MRD status measurement (for Cohort C subjects only, see Section 6.4.2)
- Beta-2 microglobulin
- 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 normalize 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), aspartate aminotransferase (AST), alanine aminotransferase (ALT), lactate dehydrogenase (LDH), magnesium, bicarbonate, lipase, gamma glutamyl transferase (GGT), uric acid, triglycerides, cholesterol, amylase. **(NOTE: Tests for AST, ALT, ALP, direct bilirubin, indirect bilirubin, and total bilirubin must be conducted and assessed concurrently)**
- 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)
- Thyroid function tests (thyroid-stimulating hormone [TSH], Free tri-iodothyronine (T_3), and Free thyroxine (T_4) levels
- Urinalysis (color, appearance, specific gravity, pH, protein, glucose, ketones, blood, bilirubin)
- Pregnancy test is required for all female subjects of childbearing potential. Serum beta human chorionic gonadotropin (β-hCG) pregnancy test will be performed at Screening. Urine (or serum) pregnancy test will be performed to assess subject eligibility within 72 hours prior to the first administration of IP, if the initial serum pregnancy test did not already occur with 72 hours of dosing (negative results required for IP administration).
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted.

- Adverse event (including Adverse Events of Special Interest) evaluation begins when the subject signs the informed consent form. See Section 10 for detailed definitions and reporting requirement for AEs.
- Bone marrow aspiration/biopsy (for cytogenetics, % plasma cells, [redacted])
- [redacted]

6.2. Treatment Period

The subject will begin treatment upon confirmation of eligibility. The subject must start treatment within 28 days of signing the ICF. For all subsequent visits, an administrative window of ± 2 days is permitted. On Cycle 1 Day 1, 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 Cycle 1 Day 1 (C1D1), safety laboratory and physical examinations need not be repeated at C1D1.

Treatment cycles are 28 days in duration, and will occur as described in Section 7.2.

The following evaluations will be performed at the frequency specified in the Table of Events, Table 3. The evaluations should be performed prior to dosing on the visit day, unless otherwise specified.

- Interactive Response Technology (IRT) Registration
  - Subjects may be registered in the IRT up to 3 days prior to initiating study treatment on Cycle 1 Day 1 (C1D1)
- Concomitant medications evaluation, and including thromboembolism prophylaxis
- Concomitant procedures evaluation
- Physical examination including assessment for potential venous thromboembolism events (VTEs) (can be source documented only)
- Vital signs
- Weight
- Hematology panel
- Coagulation parameters
- Chemistry panel
- Estimation of renal function will be assessed using the creatinine clearance (CrCl)
- Thyroid function tests
  - Cycles 1 – 4: TSH, free T4, free T3
  - Cycle 5 onward: TSH, if TSH is abnormal, then reflex testing for free T4 and free T3

- 12-lead electrocardiogram (ECG) (only if clinical indicated during the treatment period)
- ECOG performance status (Day 1 of each treatment cycle)
- Immunogenicity of durvalumab (Day 1 of each treatment cycle)
- AE evaluation (including SPM)
- Counseling about pregnancy precautions and the potential risks of fetal exposure must be conducted. (Day 1 of each treatment cycle)
- Efficacy assessment (see Section 6.4*)*
- Urinalysis (only if clinically indicated)
- Urine (or serum) pregnancy test for FCBP (negative results required for study treatment [durvalumab, LEN, or dex] administration)
- Blood sampling for PK assessments (see Section 6.5)
- [redacted]
- [redacted]
- Study treatment administered (durvalumab, LEN, or dex) and 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 (+/- 3) after the decision to permanently discontinue treatment has been made.

The following evaluations will be performed as specified in the Table 3:

- IRT registration
- Physical examination including assessment for potential venous thromboembolism events (VTEs) (can be source documented only)
- Vital signs
- Weight
- Concomitant medications evaluation
- Concomitant procedures evaluation
- Estimation of renal function will be assessed using the creatinine clearance (CrCl)
- Thyroid function tests
- ECOG performance status
- 12-lead ECG

- AE evaluation (including SPM)
- Hematology panel
- Coagulation parameters
- Chemistry panel
- Urinalysis
- Urine β-hCG (for FCBP) and pregnancy counseling
- Efficacy assessment will be continued according to the schedule defined in the Table of Events, and does not need to be performed specifically for the EOT visit except as specified in Section 6.4.
- [redacted]
- [redacted]
- Study treatment (durvalumab, LEN, or dex), and 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 durvalumab for AE, including AESI, reporting, as well as SAEs made known to the investigator at any time thereafter that are suspected of being related to study IPs (durvalumab, LEN, 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 Table 3.

- Vital signs
- Weight
- Concomitant medications evaluation (monitored until 90 days after the last dose of durvalumab
- Concomitant procedures evaluation (monitored until 90 days after the last dose of durvalumab
- Adverse event evaluation (monitored until 90 days after last dose of durvalumab; SPM will continue to be monitored after above required 90 days visit and every 6 months up to 5 years after the last subject enrolled into the study). Data entry into the clinical database will continue until 15 Dec 2019. After this date, the occurrence of SPMs will continue to be monitored, and any events will continue to be recorded in the subject's source documents and reported to Celgene Drug Safety
- Hematology panel
- Coagulation parameters (90 [+ 3] days after the last dose of durvalumab only)
- Chemistry panel

- Renal function (CrCl)
- Thyroid function tests (90 [+ 3] days after the last dose of durvalumab only)
- Urine β-hCG test (for females of childbearing potential)
- Counseling about pregnancy precautions and the potential risks of fetal exposure for subjects receiving LEN
- [redacted]

6.4. Efficacy Assessment

6.4.1. Laboratory Assessments for Efficacy Parameters

All laboratory assessments for efficacy will be performed centrally.

If screening assessments are performed within 72 hours of C1D1, efficacy laboratory assessments need not be repeated at C1D1.

- Serum protein electrophoresis (sPEP) and urine protein electrophoresis (uPEP) test (performed on 24-hour urine collection) are required at screening, Day 1 of each cycle, and at End of Treatment.
- Serum and urine immunofixation (IFE) tests are required at screening, on Day 1 of each cycle, and at End of Treatment.
- Quantitative serum immunoglobulin assessment includes IgG, IgA, 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 End of Treatment.
- Serum free light-chain assay is required at screening, on Day 1 of each cycle, and at End of Treatment.
- Corrected serum calcium will be assessed as part of the serum chemistry labs performed at screening, Days 1 and 15 of every cycle, and at End of Treatment.
- Beta-2 microglobulin test is required at screening, on Day 1 of each cycle, and at the End of Treatment.

6.4.2. Bone Marrow Aspiration and/or Biopsy and Cytogenetics

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

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

- [redacted]
- For all the subjects on the Cohort C, BMA will also be collected at the screening, [redacted] for MRD measurement by ClonoSIGHT™ NGS assay, if not overlap with the above samples collection time points (see footnote d on Table 3); BMA samples collected at the time of multiple myeloma diagnosis must also be available for central analysis (ClonoSIGHT™ NGS assay) for subjects to be considered eligible for the study

The analysis of bone marrow for percentage of plasma cells will be performed locally. The bone marrow aspirate/biopsy samples for cytogenetics and biomarkers will be submitted to a central laboratory.

6.4.3. Bone Lesion Assessment

Bone lesion assessment (skeletal survey) by x-ray, or CT scan (including PET/CT), or MRI will be performed at Screening and when clinically indicated. The same method (x-ray or CT scan or MRI) 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, or MRI 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 (PA) chest
- AP pelvis
- AP upper extremities, shoulder to elbow
- AP lower extremities hip to knee

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

6.4.4. Extramedullary Plasmacytoma Assessments (EMPs)

Clinical assessment for EMPs will be performed at Screening, Day 1 of each cycle, and at End of Treatment.

Extramedullary plasmacytomas that are only assessable radiographically (by x-ray and/or conventional [spiral] CT/MRI scan) are required at Screening; at Cycle 3 Day 1 and every 3 cycles thereafter (C6D1, C9D1, etc.) during treatment; at End of Treatment, and when clinically indicated to confirm a response (≥ partial response [PR]). 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 IMWG Uniform Response Criteria (Rajkumar, 2011) (Appendix B) at every cycle on Day 1 and at the End of Treatment visit. Investigator assessment of response will be based on the central laboratory data to ensure consistency across investigative sites.

For subjects on Cohort C, the response need be assessed as following:

1) use the disease measure at the time of before ASCT as the baseline for response assessment;
2) starting from Cycle 2, compare the response assessments with the response at the C1D1 to determine response improvement.

NOTE: Per IMWG Uniform Response Criteria all response categories and progressive disease require 2 consecutive assessments

6.5. Pharmacokinetics

Pharmacokinetic assessments are mandatory and will be performed for all subjects enrolled into the study. Details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

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 electronic case report form (eCRF) pages.

6.5.1. Pharmacokinetics of Lenalidomide

Intense PK sampling will be performed for all subjects administered with LEN. The sampling time points will be as follows:

- C1D1: predose (-60 to -5 minutes prior to dose), 0.5 hour (± 5 minutes), 1 hour (± 10 minutes), 2 hours (± 10 minutes), 4 hours (± 10 minutes), and 8 hours (± 1 hour) after administration of lenalidomide
- C1D15: predose (-60 to -5 minutes prior to dose), 0.5 hour (± 5 minutes), 1 hour (± 10 minutes), 2 hours (± 10 minutes), 4 hours (± 10 minutes), and 8 hours (± 1 hour) after administration of lenalidomide

On both days, subjects will be asked NOT to take lenalidomide at home. Lenalidomide will be administered to these subjects at the study center after the collection of the predose PK blood sample.

6.5.2. Pharmacokinetics of Durvalumab

Intense PK sampling will be performed for all subjects administered with durvalumab. The sampling time points will be as follows:

- C1D1: preinfusion (-60 to -5 minutes prior to dose), end of infusion (EOI) (-15 to 0 minutes), 4 hours (± 1 hour), 168 hours (C1D8) (± 4 hour), 336 hours (C1D15) (± 4 hour) and 504 hours (C1D22) (± 4 hour) after administration of durvalumab on C1D1

- C2D1: preinfusion (-60 to -5 minutes prior to dose), EOI (-15 to 0 minutes), 4 hours (± 1 hour), and 336 hours (C2D15) (± 4 hour) after administration of durvalumab on C2D1
- C4D1, C6D1, C10D1, and C14D1: preinfusion (-60 to -5 minutes prior to dose)

6.5.3. Immunogenicity Samples of Durvalumab

Immunogenicity samples will be collected as follows:

- Predose samples on C1D1, C2D1, C4D1, C6D1, C10D1 and C14D1.

The samples will be stored and if warranted anti-drug antibodies (ADA) will be explored using these samples.

7. DESCRIPTION OF STUDY TREATMENTS

7.1. Description of Investigational Products

The IP supply will be managed by Interactive Response Technology (IRT). All IP must be stored in accordance with the product label in a secured area to prevent unauthorized access.

United States and Canada:

Durvalumab (MEDI4736) and lenalidomide 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 statements as applicable.

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

Outside the United States and Canada:

Durvalumab (MEDI4736) and lenalidomide and dexamethasone will be supplied by Celgene and labeled appropriately as investigational material. Labels will bear Celgene's name and address, the protocol number, EudraCT Number (if applicable), 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 statements as applicable.

Label(s) for IP supplied will contain information as required per local health authority.

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 liquid solution containing 500 mg (nominal) of investigational product at a concentration of 50 mg/mL. Durvalumab should be stored in accordance with the product label.

Site 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 durvalumab with other IV medications and solutions, other than normal saline, is not known, the durvalumab 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. Lenalidomide (LEN)

Lenalidomide (LEN) will be supplied by Celgene in appropriate strengths for oral administration. Investigational product will be supplied in labeled blister cards. Lenalidomide should be stored in accordance with the product label.

Please refer to the locally approved lenalidomide label for additional information on administration or storage information.

7.1.3. Dexamethasone (dex)

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

For additional details and storage information please refer to the Pharmacy Manual.

7.2. Treatment Administration and Schedule

The first day of study treatment dosing (durvalumab and LEN and/or dex) is considered Day 1 of a cycle.

7.2.1. Treatment Administration

7.2.1.1. Durvalumab

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.

Monitoring During/Post Durvalumab Infusion

First and Second DURVA infusion

Subjects will be monitored during and after infusion of durvalumab. Vital signs will be measured prior to durvalumab administration (± 30 minutes), every 15 minutes (± 5 minutes) during durvalumab administration, at the end of durvalumab infusion (± 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post infusion of durvalumab, followed by a 2-hour (± 15 minutes) period of observation.

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 durvalumab may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. In subjects experiencing Grade ≤ 2 infusion-related reactions, subsequent infusions may be administered at 50% of the initial rate.

Acetaminophen 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, treatment with durvalumab will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Therefore, 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 subjects to an intensive care unit if necessary.

7.2.1.2. Lenalidomide

Over 60% of a dose of lenalidomide is excreted in urine unmetabolized. Pharmacokinetic studies have revealed that the plasma area under the plasma concentration-time curve (AUC) of lenalidomide is inversely related to the CrCl (Chen, 2007). Therefore, the dose of lenalidomide must be adjusted for renal function on the first day of Cycle 1. The following are recommendations (see Table 4) for subjects enrolled into the study. The recommendations are applicable to renal function classified either by measured or Cockcroft-Gault estimated CrCl (Cockcroft, 1976; Luke, 1990)

If the CrCl of subjects who had moderate or severe renal insufficiency at baseline (Day 1 of Cycle 1) improves during study treatment with the study treatment, then the dosing regimen of lenalidomide can be escalated to the level appropriate to the improved estimated CrCl (see Table 4). Dose escalations are to be made at the start of the next cycle. Discuss with medical monitor if this occurs.

Table 4: Lenalidomide Dosing Guideline for Renal **Insufficiency for Cohort A and Cohort B**

Renal Function (CrCl)	Dosing
Normal to Mild RI (CrCl ≥ 50 mL/min)	25 mg once daily on Days 1 to 21 of each 28-day cycle
Moderate RI (30 ≤ CrCl < 50 mL/min)	10 mg[a] once daily on Days 1 to 21 of each 28-day cycle
Severe RI (CrCl < 30 mL/ min)	15 mg once every other day from Day 1 to 21 of each 28-day cycle

CrCl = creatinine clearance; RI = renal insufficiency.
[a] This dose may be escalated to 15 mg after 2 Cycles at the discretion of the treating physician if the subject tolerates the 10 mg dose of lenalidomide without dose-limiting toxicity.

The lenalidomide starting dose for subjects on Cohort C is 10 mg on Days 1 to 21 of each 28-day cycle.

7.2.1.3. Dexamethasone

On Day 1 of Cycle 1, the starting dose of dexamethasone is 40 mg once daily on Days 1, 8, 15, and 22 of a 28-day treatment cycle for subjects who are ≤ 75 years of age on the date of

randomization. For subjects who are > 75 years of age on the date of randomization, the starting dose of dexamethasone is 20 mg once daily on Days 1, 8, 15, and 22 of a 28-day cycle.

7.2.2. Treatment Schedule

Three treatment Cohorts (A, B, and C) will be enrolled in parallel in the dose-finding phase:

- Cohort A: durvalumab + LEN +dex on high risk TNE NDMM subjects
- Cohort B: durvalumab + LEN +dex (only up to 12 cycles) on ≥ 65 years old TNE NDMM subjects who are not high risk
- Cohort C: durvalumab + LEN on post-transplant high risk NDMM subjects as maintenance (the study treatment is to be initiated at 100 days [± 14 days] after transplant).

Initially, 6 subjects will be enrolled into each cohort, the detailed dosing schedule for each treatment Cohort is listed below in Table 5. See de-escalation rules in Section 3.1.

Table 5: Planned Dose Level by Treatment Cohorts

	Study IP	Treatment Cohort A	Treatment Cohort B	Treatment Cohort C
Starting dose level	IV DUR	1500 mg on Day 1 of a 28-day cycle	1500 mg on Day 1 of a 28-day cycle	1500 mg on Day 1 of a 28-day cycle
	Oral LEN	25 mg on Days 1 - 21 of a 28-day cycle (adjustable per the CrCl value, see detail in Table 4	25 mg on Days 1 - 21 of a 28-day cycle (adjustable per the CrCl value, see detail in Table 4	10 mg on Days 1 - 21 of a 28-day cycle
	Oral dex	40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle	40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle (for up to 12 cycles)	Not applicable
De-escalate dose level	IV DUR	750 mg on Day 1 of a 28-day cycle	750 mg on Day 1 of a 28-day cycle	750 mg on Day 1 of a 28-day cycle
	Oral LEN	25 mg on Days 1 – 21 of a 28-day cycle (adjustable per the CrCl value, see detail in Table 4	25 mg on Days 1 – 21 of a 28-day cycle (adjustable per the CrCl value, see detail in Table 4	10 mg on Days 1 – 21 of a 28-day cycle
	Oral dex	40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle	40 mg/day (≤ 75 years old) or 20 mg/day (> 75 years old) on Days 1, 8, 15, and 22 of a 28-day cycle (for up to 12 cycles)	Not applicable

Abbreviations: CrCl = creatinine clearance; dex = dexamethasone; DUR= durvalumab; IV = Intravenous; mg = milligrams; LEN = lenalidomide

Subjects who enrolled in the expansion phase will follow with the same study treatment schedule for the respective treatment cohort in the dose-finding phase (See Figure 1).

7.2.3. Overdose

Overdose, as defined for this protocol, refers to durvalumab, LEN, and dex dosing only. On a per dose basis, an overdose is defined as the following amount over the protocol-specified dose of durvalumab, LEN, or dex assigned to a given subject, regardless of any associated adverse events 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 anything 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 treatment is resumed.

- If durvalumab dosing is withheld, then LEN and dex dosing must also be withheld.
- If durvalumab is permanently discontinued, then the subject must be permanently discontinued from all study treatments. (The subjects may continue to receive the LEN and/or dex until the ongoing cycle be completed.)
- If LEN dosing is withheld or permanently discontinued, then durvalumab and dex dosing may be continued.
- If both LEN and durvalumab dosing are withheld, then dex must also be withheld.
- If DEX dosing is withheld or permanently discontinued, then LEN and durvalumab may be continued.

7.2.4.1. Dose Modification Instructions for Durvalumab

Refer to Appendix D for detailed instructions for durvalumab dose modifications and toxicity management

7.2.4.2. Dose Modification Instructions for Lenalidomide

Guidelines for lenalidomide dose interruptions and reductions are provided in Table 6, and Table 7 outlines the dose reduction steps for lenalidomide. For the full prescribing information refer to the respective current Prescribing Information, Summary of Product Characteristics (SmPC), or equivalent document for the specific region/country for lenalidomide.

If local or central laboratory test results (CrCl) show a clinically significant worsening of renal function, the investigator should contact the medical monitor to discuss if dose reduction is necessary. Dose reduction for worsening CrCl at subsequent visit is not required by the protocol,

but if warranted after discussion with medical monitor, the site should use dosing Table 6, and Table 7 for the appropriate lenalidomide dose reduction. Dose reduction would be a 1 dose level (see Table 8, Table 9, and Table 10) reduction from the current dose level as outlined in those tables.

In addition, G-CSF (granulocyte colony stimulating factor) may be used to support the neutrophil count after the DLT assessment period has been completed (Cycle 1).

Instructions for dose interruptions and reductions for LEN-related hematologic toxicity occurring during a cycle are as follows:

Table 6: Dose Modification Instructions for Lenalidomide for Hematologic Toxicity during a Cycle

Toxicity	Lenalidomide Dose Modification
Grade 4 neutropenia (ANC < 0.5 x 10^9/L) or Febrile neutropenia (fever ≥ 38.5°C and ANC < 1 x 10^9/L)	1) Stop lenalidomide dosing for the remainder of the cycle. 2) If the subject was not receiving G-CSF therapy, G-CSF therapy may be started at the discretion of the treating physician. On Day 1 of the next cycle, the dose of lenalidomide may be maintained if neutropenia was the only DLT and G-CSF treatments are continued. Otherwise, decrease by one dose level at start of next cycle (see Table 8, Table 9, and Table 10).
Grade 4 Thrombocytopenia (Platelets < 25 x10^9/L)	Stop lenalidomide dosing for remainder of cycle. Decrease by one dose level when dosing is resumed at next cycle (see Table 8, Table 9 and Table 10).
Other ≥ Grade 3 lenalidomide-related adverse events (excluding neutropenia, febrile neutropenia, and thrombocytopenia)	Stop lenalidomide dosing for remainder of cycle. Decrease by one dose level when dosing is resumed at next cycle (see Table 8, Table 9, and Table 10).

ANC = absolute neutrophil count; DLT = dose-limiting toxicity; G-CSF = granulocyte colony-stimulating factor.

Instructions for dose interruptions and reductions for lenalidomide-related non-hematologic toxicity occurring during a cycle are as follows:

Table 7: Dose Modification Instructions for Lenalidomide for Non-Hematologic Toxicity during a Cycle

Toxicity	Lenalidomide Dose Modification
Rash = Grade 3	Stop dose for remainder of cycle. Decrease by one dose level when dosing is resumed at next cycle (rash must resolve to ≤ Grade 1).
Rash = Grade 4 or Blistering	Discontinue lenalidomide.
Constipation ≥ Grade 3	Stop dose for remainder of cycle. Initiate bowel regimen. Decrease by one dose level when dosing is resumed at next cycle (constipation must resolve to ≤ Grade 2).

Table 7: Dose Modification Instructions for Lenalidomide for Non-Hematologic Toxicity during a Cycle (Continued)

Toxicity	Lenalidomide Dose Modification
Thrombosis/embolism ≥ Grade 3	If occurred during aspirin therapy or during a period of inadequate anticoagulation, initiate adequate anticoagulation treatment. Lenalidomide dosing may continue without interruption at the discretion of the treating physician. Dose level may be maintained at the discretion of the treating physician. If occurred during adequate anticoagulation treatment (prophylactic dose of anticoagulation therapy with LMW heparin, heparin or Coumadin®), discontinue lenalidomide.
Hypo/hyperthyroidism ≥ Grade 2	Initiate appropriate medical therapy. Maintain dosing and dose level at discretion of treating physician.
Peripheral Neuropathy = Grade 3	Stop dose for remainder of cycle. Decrease by one dose level when dosing is resumed at next cycle (neuropathy must resolve to ≤ Grade 1).
Peripheral Neuropathy = Grade 4	Discontinue lenalidomide.
Other ≥ Grade 3 lenalidomide-related adverse events	Stop dose for remainder of cycle. Decrease by one dose level when dosing is resumed at next cycle (adverse event must resolve to ≤ Grade 2).

d = dexamethasone; DLT = dose limiting toxicity; LMW = low molecular weight;

To re-start lenalidomide treatment following a dose interruption at a new cycle, the neutrophil count must be ≥ 1000/μL, the platelet count must be ≥ 50,000/μL, and non-hematologic AEs must be resolved or improved as described in Table 7.

The following table describes the dose reduction steps for lenalidomide given once daily.

Table 8: Lenalidomide Dose Reduction Steps (Daily Dosing) for Cohort A and Cohort B

Dose Levels	Lenalidomide on Days 1 to 21 of Every 28-Day Cycle
Starting Dose	25 mg/day on Days 1 to 21
Dose Level -1	20 mg/day on Days 1 to 21
Dose Level -2	15 mg/day on Days 1 to 21
Dose Level -3	10 mg/day on Days 1 to 21
Dose Level -4	5 mg/day on Days 1 to 21
Dose Level -5	2.5 mg/day on Days 1 to 21

The following table describes the dose reduction steps for lenalidomide given once every other day.

Table 9: Lenalidomide Dose Reduction Steps (Every Other Day Dosing) for Cohort A and Cohort B

Dose Levels	Lenalidomide from Day 1 to Day 21 of Each 28-Day Cycle
Starting Dose	15 mg once every other day from Day 1 to Day 21
Dose Level -1	10 mg once every other day from Day 1 to Day 21
Dose Level -2	5 mg once every other day from Day 1 to Day 21
Dose Level -3	2.5 mg once every other day from Day 1 to Day 21

The following table describes the dose reduction steps for lenalidomide given to subjects on Cohort C.

Table 10: Lenalidomide Dose Reduction Steps for Cohort C

Dose Levels	Lenalidomide from Day 1 to Day 21 of Each 28-Day Cycle
Starting Dose	10 mg on Days 1 to 21
Dose Level -1	7.5 mg on Days 1 to 21
Dose Level -2	5.0 mg on Days 1 to 21
Dose Level -3	2.5 mg on Days 1 to 21

If the dose of lenalidomide is reduced for a hematologic DLT, the dose of lenalidomide can be re-escalated up to the next higher dose level at the discretion of the treating physician if continued study treatment results in improved bone marrow function (no DLT for at least two consecutive cycles and an ANC ≥ 1,500/µL with a platelet count ≥ 100,000/µL at the beginning of a new cycle at the current dose level).

7.2.4.3. Dose Modification Instructions for Dexamethasone

Guideline for dexamethasone dose interruptions and reductions are outlined in Table 11 and Table 12. For the full prescribing information refer to the respective current Prescribing Information, Summary of Product Characteristics (SmPC), or equivalent document for the specific region/country for dexamethasone.

Table 11: Dose Modifications for Dexamethasone-related Toxicities

Toxicity	Dexamethasone Dose Modification
Dyspepsia = Grade 1-2	Maintain dose and treat with histamine (H2) blockers or equivalent. Decrease by one dose level if symptoms persist.
Dyspepsia ≥ Grade 3	Interrupt dose until symptoms are controlled. Add histamine (H2) blocker or equivalent and decrease one dose level when dosing is resumed.
Edema ≥ Grade 3	Use diuretics as needed and decrease dose by one dose level.

Table 11: Dose Modifications for Dexamethasone-related Toxicities (Continued)

Toxicity	Dexamethasone Dose Modification
Confusion or mood alteration ≥ Grade 2	Interrupt dose until symptoms resolve. When dose is restarted, decrease dose by one dose level.
Muscle weakness (steroid myopathy) ≥ Grade 2	Interrupt dose until muscle weakness ≤ Grade 1. When dose is restarted, decrease dose by one dose level.
Hyperglycemia ≥ Grade 3	Decrease dose by one dose level. Treat with insulin or oral hypoglycemic agents as needed.
Acute pancreatitis	Discontinue dexamethasone from treatment regimen.
Other ≥ Grade 3 dexamethasone-related adverse events	Stop dexamethasone dosing until the adverse event resolves to ≤ Grade 2. Decrease by one 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 12: 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
Dose Level -3	8 mg	4 mg
Dose Level -4	4 mg	NA

Dexamethasone-related dose-limiting toxicity must resolve as described in Table 11 in order to restart dexamethasone. If this condition is not met, a new cycle can be started, and dexamethasone will continue be interrupted, until adverse event resolution, then restarted dexamethasone in the ongoing cycle. If dex-related toxicity does not resolve as described in Table 11 within 14 days, then the dose of dex will be decreased by one dose level when dex treatment is resumed and the case should be discussed with the medical monitor (if a dexamethasone dose reduction is required for the new cycle due to dexamethasone-related toxicity that occurred during the previous cycle, an additional dex dose reduction step is not required for a delay of the start of a new cycle of > 14 days).

If a new cycle of LEN is initiated but dex is stopped, dex can only be restarted on a scheduled dosing day (Days 1, 8, 15, and 22).

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

For subjects who experience a dexamethasone withdrawal toxicity, a dose tapering over a two day period to limit symptoms can be initiated at the discretion of the treating physician.

7.3. Method of Treatment Assignment

Subjects will be assigned to either Cohort A, B, or C based on the eligibility criteria and current 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.

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

An IRT system will be used to track subject assignments to the treatment cohorts 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 IP return, disposal, and/or destruction including responsibilities for the site versus Celgene (or designee).

7.6. Investigational Product Compliance

Accurate recording of all study IP administration (durvalumab, LEN, 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 IP (durvalumab, LEN, 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 antiemetic medications, may be administered at the discretion of the Investigator.

See Appendix D for additional details on durvalumab toxicity management.

All concomitant medications, including blood and blood products, used from 28 days prior to first dose of study treatment until 90 days after the last dose of durvalumab must be reported on the eCRF.

For information regarding other drugs that may interact with IP and affect its metabolism, pharmacokinetics, or excretion, please see the Investigators Brochure and/or local package insert.

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 /red blood cell transfusions and hematopoietic growth factors are also permitted during the study. However, prophylactic use of platelet 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 non-cancer 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 the following during the study:

1. For subjects in the Dose-finding Phase, 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, or platelet eligibility criteria at screening CANNOT be re-tested for the study after being treated with growth factors or platelet 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. Use of immunosuppressive medications for the management of investigational product-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 use of corticosteroids for concurrent illnesses (eg, food allergies, CT scan contrast hypersensitivity, moderate to severe infusion-related reactions, etc) is 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

8.3. Required Concomitant Medications and Procedures

All subjects in Cohort A and Cohort B are required to receive anti-thrombotic prophylaxis medication while receiving the LEN treatment on this study; for Cohort C, only subjects who have a history of VTE are required to receive anti-thrombotic prophylaxis medication.

Subjects unable or unwilling to undergo anti-thrombotic prophylactic treatment will not be eligible to participate in this study.

9. STATISTICAL CONSIDERATIONS

9.1. Overview

All analyses will use descriptive statistics. No formal statistical comparison/testing will be performed.

The analyses will be done by treatment cohort and dose level. Subjects treated with the recommended dose in the expansion portion will be combined with the corresponding dose level in the dose-determination portion as one single dose level for efficacy and safety analysis.

9.2. Study Population Definitions

The following 5 analysis populations will be used:

- Safety population – includes all enrolled subjects who take at least one dose of study medication. All safety analyses will be based on this population
- Dose-determining population - includes all subjects from the safety set who meet the minimum exposure criterion and have sufficient safety evaluations, or experience a DLT during the first treatment cycle
- Full analysis population - includes all subjects enrolled into this study
- Efficacy evaluable population - includes all enrolled subjects who take at least one dose of study medication and who have measurable disease at baseline and at least one post-baseline response assessment
- Pharmacokinetic population - includes all subjects who receive at least one dose of study medication and have evaluable PK profiles. 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 their PK data in the statistical analysis.

9.3. Sample Size and Power Considerations

Up to 138 subjects are planned to be enrolled in the study: up to 36 total in the 3 cohorts for dose finding and up to 102 in the 3 cohorts for expansion. The actual number of subjects will depend on the number of dose level being tested.

Phase I expansion dose sample size estimation for Cohort A and Cohort B

Table 13 shows probability of observing an ORR ≥ 75% under different assumptions about the true ORR in this population. With a sample size of 40 subjects, this study has reasonable operating characteristics of observing an ORR ≥ 75% if the true ORR is 85% or higher.

Table 13: Decision Operating Characteristics of ORR with 40 in the Expansion Dose for Cohort A and Cohort B

True ORR	Probability of observing an ORR ≥ 75% with 40 patients (≥ 30 out of 40 patients)
60%	3.5%
65%	12.1%
70%	30.9%
75%	50.4%
80%	83.9%
85%	97.0%
90%	99.9%

Phase I expansion dose sample size estimation for Cohort C

Table 14 shows probability of observing a response improvement rate (RIR) ≥ 15% under different assumptions about the true RIR in this population. With a sample size of 40 subjects, this study has reasonable operating characteristics of observing an RIR ≥ 15% if the true RIR is 25% or higher.

9.4. Background and Demographic Characteristics

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 using frequency tabulations by MedDRA system organ class and preferred term.

9.6. Concomitant Medications and Procedures

All concomitant medications and procedures documented during the study will be summarized 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 using frequency and percent by cohort and dose level and follow-up phases. A summary of subjects enrolled by site will be provided.

Table 14: Decision Operating Characteristics of RIR with 40 in the Expansion Dose for Cohort C

True ORR	Probability of observing a RIR ≥ 15% in Cohort C with 40 patients (≥ 6 out of 40 patients)
5%	1.4%
10%	20.6%
15%	56.7%
20%	83.9%
25%	95.7%
30%	99.1%
35%	99.9%

9.8. Efficacy Analysis

9.8.1. Response Using the IMWG Uniform Response Criteria

Tumor response, including progressive disease, will be assessed by the investigators.

The overall response rate (ORR) will be calculated as the number of responders (at least a Partial Response [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 Uniform Response Criteria (ie, Stringent Complete Response [sCR], Complete Response [CR], Very Good Partial Response [VGPR], Partial Response [PR], Stable Disease [SD], and Progressive Disease [PD]) will be examined.

The best overall response categories (CR, VGPR, PR, SD, and progressive disease) will be tabulated by cohort and dose level.

9.8.2. Response Improvement Rate Using the IMWG Uniform Response Criteria

The Response improvement rate (RIR) analysis only be performed for subjects on Cohort C. The RIR defined response change from the assessment at the C1D1. The assessment by investigator using IMWG Uniform Response Criteria, will be tabulated by cohort and dose level.

9.8.3. Time to Response

Time to response (for responders only, per IMWG Uniform Response Criteria) is calculated as the time from the first date of dosing of study medication to the first date of documented response (PR or better).

Time to response will be summarized using descriptive statistics by cohort and dose level for Cohorts A and B.

9.8.4. Response Duration

Duration of response (for responders only, per IMWG Uniform Response Criteria) is defined as time from the earliest date of documented response (PR or better) to the earliest date of disease

progression as determined by the investigator per IMWG Uniform Response Criteria or death during the study treatment, whichever occurred first. Duration of response will be summarized using Kaplan-Meier estimates by cohort and dose level as appropriate for Cohorts A and B; no statistical test will be performed.

Efficacy evaluable population will be used for all response related analyses.

9.8.5. Progression Free Survival (PFS)

Progression free survival will be calculated as the time between enrollment and disease progression, as determined by the investigator using the IMWG Uniform Response Criteria, or death during study treatment, whichever occurred earlier. The PFS will be summarized using Kaplan-Meier estimates by cohort and dose level as appropriate; no statistical test will be performed.

Full analysis population will be used for PFS analysis.

9.8.6. Overall Survival (OS)

Overall survival is calculated as the time from enrollment to death due to any cause. Subjects who died will be considered as having events on the date of death. Subjects who were alive or lost to follow-up will be censored on the last-known-to-be-alive date. The OS will be summarized using Kaplan-Meier estimates by cohort and dose level as appropriate; no statistical test will be performed.

Full analysis population will be used for OS analysis.

9.9. Safety Analysis

All safety analyses will be conducted using the Safety population. All analyses will be presented by cohort and dose level.

Adverse events will be coded according to the Medical Dictionary for Regulatory Activities (MedDRA) version 18 or higher. The severity of AEs will be graded according to the NCI CTCAE version 4.03 or higher.

Treatment-emergent adverse events (TEAEs) are defined as any AE occurring or worsening on or after the first treatment of the study IPs (durvalumab, LEN, dex) and within 90 days after the last dose of durvalumab. Treatment-emergent AEs, AEs leading to study IP discontinuation, AEs leading to dose reduction/interruption, AEs related to study IP, SAEs and AEs leading to death will be summarized by system organ class, and preferred term for each treatment group. A summary of AEs with NCI CTCAE Grade 3 or higher, as well as the most frequent preferred terms, 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. Death within 90 days after the last dose of durvalumab will be summarized separately.

Clinical laboratory values will be graded according to NCI CTC 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' readings. Shift from baseline to worsen status during the treatment in the overall ECG interpretation will be displayed in cross–tabulations.

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

9.10. Interim Analysis

There is no interim analysis for this study.

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 plasma durvalumab and lenalidomide concentration-time profile. All concentration data and PK parameters will be summarized descriptively. The relationship between exposure and response (eg, toxicity and biomarkers) 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 pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded on the AE page of the eCRF rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity, or toxicity to an IP should be reported as an AE. Overdose, accidental or intentional, whether or not it is associated with an AE should be reported on the overdose eCRF. (See Section 7.2.3 for the definition of overdose.) Any sequela of an accidental or intentional overdose of an IP should be reported as an AE on the AE eCRF. If the sequelae of an overdose is an SAE, then the sequelae must be reported on an SAE report form and on the AE eCRF. The overdose resulting in the SAE should be identified as the cause of the event on the SAE report form and eCRF 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 durvalumab, LEN, 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 durvalumab, as well as those SAEs made known to the investigator at any time thereafter that are suspected of being related to study IPs (durvalumab, LEN, dex). Adverse events and SAEs will be recorded on the AE page of the eCRF 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 adverse events 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 eCRF. 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 eCRF and the SAE Report Form must be completed.

For each SAE, the investigator will provide information on severity, start and stop dates, relationship the study IPs (durvalumab, LEN, dex), action taken regarding the study IPs (durvalumab, LEN, dex), 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

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death – the event results in death

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

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

10.2.3. Causality

The investigator must determine the relationship between the administration of the study IPs (durvalumab, LEN, 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 study IPs (durvalumab, LEN, 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 study IPs (durvalumab, LEN, dex) caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the study IPs (durvalumab, LEN, dex) 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 treatment 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 study IPs (durvalumab, LEN, dex) as applicable (eg, discontinuation, interruption, or dose reduction of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

10.2.6. Outcome

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

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

10.3. Abnormal Laboratory Values

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

- results in discontinuation from the study;
- requires treatment, modification/ interruption of study IPs (durvalumab, LEN, 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 eCRF. 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 lenalidomide is also an immediately reportable event.

10.4.1. Females of Childbearing Potential:

Pregnancies and suspected pregnancies (including elevated 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 durvalumab are considered immediately reportable events. Investigational product is to be discontinued immediately and the subject instructed to return any unused portion of the study IPs to the investigator. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to Celgene Drug Safety immediately by email, phone or facsimile, or other appropriate method, using the 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 monitor 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 study IPs (durvalumab, LEN, 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 study IPs (durvalumab, LEN, or dex) becomes pregnant, the male subject taking study IPs (durvalumab, LEN, or dex) should notify the investigator, and the pregnant female partner should be advised to call her 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 eCRF. 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 the study IPs) that occur during the

study (from the time the subject signs informed consent until 90 days after the last dose of durvalumab) or any SAE made known to the investigator at any time thereafter that are suspected of being related to the study IPs (durvalumab, LEN, 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 durvalumab and lenalidomide based on the Investigator Brochure (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, 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 dexamethasone based on the EU Summary of Product Characteristics (SmPC).

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

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

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 the Investigational Product 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 this investigational product.

Further information on risks (eg, presenting symptoms) can be found in the current version of the Investigator Brochure including guidelines for their evaluation and treatment.

10.7.1. Second PrimaryMalignancies (SPMs)

Second primary malignancies will be monitored as events of interest and must be reported as serious adverse events regardless of the treatment Cohort the subject is in (see Section 10.5). This includes any second primary malignancy, regardless of causal relationship to IPs (study drugs or control), occurring at any time for the duration of the study, from the time of signing the ICD for at least 5 years after the last subject is enrolled into the study. 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 eCRF (ie, AE and SPM eCRF) and subject’s source documents. Documentation on the diagnosis of the second primary malignancy must be provided at the time of reporting as a serious adverse event (eg, any confirmatory histology or cytology results, X-rays, CT scans, etc.). Data entry into the clinical database will continue until 15 Dec 2019. After this date the occurrence of SPMs will continue to be monitored, and any events will continue to be recorded in the subject’s source documents and reported to Celgene Drug Safety.

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 (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 study will be conducted in compliance with International Council for Harmonisation (ICH) Good Clinical Practices (GCPs).

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 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 eCRFs and queries.

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

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

13.3. Subject Information and Informed Consent

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

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

13.4. Confidentiality

Celgene affirms the subject's right to protection against invasion of privacy and to be in compliance with ICH and other local regulations (whichever is most stringent). Celgene requires the investigator to permit Celgene's representatives and, when necessary, representatives from regulatory authorities, to review and/or copy any medical records relevant to the study in accordance with local laws.

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

13.5. Protocol Amendments

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

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

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

The IP can only be supplied to an investigator by Celgene or its authorized representative after documentation on all ethical and legal requirements for starting the study has been received by

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

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

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

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

13.7. Ongoing Information for Institutional Review Board/ Ethics Committee

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

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

13.8. Termination of the Study

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

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

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

14. DATA HANDLING AND RECORDKEEPING

14.1. Data/Documents

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

14.2. Data Management

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

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

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

All study documents should be made available if required by relevant health authorities. investigator 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, eCRFs, 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, eCRFs, 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 eCRFs 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 eCRFs 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 GCP guidelines and regulations.

The investigator is required to permit direct access to the facilities where the study took place, source documents, eCRFs and applicable supporting records of study subject participation for audits and inspections by IRB/ECs, regulatory authorities (eg, FDA, EMA, and 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 13.4 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.

17. REFERENCES

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18. APPENDICES

Appendix A: Table of Abbreviations

Abbreviation or Specialist Term	Explanation
ADA	Anti-drug antibody
ADL	Activity of daily life
AE	Adverse event
ALT	Alanine aminotransferase (SGPT)
AESI	Adverse event of special interest
ANC	Absolute neutrophil count
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase (SGOT)
AUC	Area under the plasma concentration-time curve
β-hCG	β-subunit of human chorionic gonadotropin
CBC	Complete blood count
CD	cluster of differentiation
C_{max}	Maximum plasma concentration of drug
CR	Complete response
CrCl	Creatinine clearance
CRF	Case report form
CRP	Clinical Research Physician
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ctDNA	Circulating tumor deoxyribonucleic acid
dex	Dexamethasone
DLT	Dose-limiting toxicity
DOR	Duration of response
DRT	Dose Review Team
DUR	Durvalumab (MEDI4736)
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic case report form
EMP	Extramedullary plasmacytoma

Abbreviation or Specialist Term	Explanation
EOT	End of treatment
Fc	Fragment crystallizable
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HIV	Human immunodeficiency virus
ICF	Informed consent form
ICH	International Council for Harmonisation
IND	Investigational New Drug
IP	Investigational Product
IRB	Institutional Review Board
IRT	Interactive Response Technology
ILD	Interstitial lung disease
irAE	Immune-related adverse event
IV	Intravenous
LEN	lenalidomide
mAb	Monoclonal anti-body
MedDRA	Medical Dictionary for Regulatory Activities
MM	Multiple myeloma
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NDMM	Newly diagnosed multiple myeloma
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease
Pd	Pharmacodynamic(s)
PD-1	Programmed Cell Death 1
PD-L1	Programmed Cell Death Ligand 1
PD-L2	Programmed Cell Death Ligand 2
PFS	Progression-free survival

Abbreviation or Specialist Term	Explanation
PK	Pharmacokinetic(s)
PR	Partial response
Q4W, Q3W, Q2W	Every 4 weeks; every 3 weeks; every 2 weeks
RBC	Red blood cell count
RIR	Response improvement rate
SAE	Serious adverse event
SAP	Statistical analysis plan
SC	Steering committee
sCR	Stringent complete response
SD	Stable disease
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
SOP	Standard operating procedure
SPM	Second primary malignancy
SUSAR	Suspected unexpected serious adverse reaction
$t_{1/2}$	Terminal elimination half-life
TILs	Tumor-infiltrating lymphocytes
TNE	Transplant non-eligible
ULN	Upper limit of normal
US/USA	United States of America
VGPR	Very Good Partial Response

Appendix B: International Myeloma Working Group Uniform Response Criteria

Response Category[a]	Response Criteria
Stringent Complete Response (sCR)	CR as defined below, *plus* Normal 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 assay is also unmeasurable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% In addition to the above, if present at baseline a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required.
Stable Disease (SD)	Not meeting criteria for CR, VGPR, PR, or progressive disease

Response Category[a]	Response Criteria
Progressive disease	**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: Adapted from Rajkumar, 2011

Appendix C: ECOG Performance Status

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

Source: Oken, 1982
Eastern Cooperative Oncology Group, Robert Comis, MD, Group Chair.

Appendix D: Durvalumab Treatment Modification and Toxicity Management Guidelines

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

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

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

	Dose Modifications	Toxicity Management
	Grade 3 Depending on the individual toxicity, may permanently discontinue durvalumab. Please refer to guidelines below	situation should be based upon a benefit/risk analysis for that patient
	Grade 4 Permanently discontinue durvalumab Note: For Grade 3 and above asymptomatic amylase or lipase levels hold durvalumab and if complete work up shows no evidence of pancreatitis, may continue or resume durvalumab	

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ILD	Grade of Pneumonitis (CTCAE version 4.03)	General Guidance	• Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below • Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan
	Grade 1 (Asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) • Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated • Consider pulmonary and infectious disease consult
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to ≤ Grade 1, then the decision to reinitiate durvalumab will be based upon treating physician's clinical	For Grade 2 (Mild to Moderate New Symptoms) • Monitor symptoms daily and consider hospitalization • Promptly start systemic steroids (eg, prednisone 1-2 mg/kg/day PO or IV equivalent) • Reimaging as clinically indicated

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		judgment and after completion of steroid taper.	• If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started • If still no improvement within 3-5 days despite IV methylprednisone at 2-4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg,infliximab at 5 mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[ab] • Consider pulmonary and infectious disease consult • Consider as necessary discussing with study physician
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	Permanently discontinue study drug/ study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Obtain pulmonary and infectious disease consult • Hospitalize the patient • Supportive Care (oxygen, etc.) • If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[a, b]

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Diarrhea/ Enterocolitis	Grade of Diarrhea (CTCAE version 4.03)	General Guidance	• Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) • Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) • Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event • Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 diarrhea (stool frequency of <4 over baseline per day)	No dose modification	For Grade 1 diarrhea: • Close monitoring for worsening symptoms • Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment
	Grade 2 diarrhea (stool frequency of 4-6 over baseline per day)	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 diarrhea: • 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 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			perforation, and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • If still no improvement within 3-5 days despite 2-4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5 mg/kg once every 2 weeks[a]). **Caution**: Important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab • Consult study physician if no resolution to ≤ Grade 1 in 3-4 days • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen	For Grade 3 or 4 diarrhea: • Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent • Monitor stool frequency and volume and maintain hydration • Urgent GI consult and imaging and/or colonoscopy as appropriate • If still no improvement within 3-5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e. g. infliximab at 5 mg/kg once every 2 weeks) • Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis**	Grade of Liver Function Test Elevation (CTCAE version 4.03) Any Grade Grade 1 (AST or ALT > to 3 times ULN and/or TB > to 1.5 times ULN)	No dose modification If it worsens, treat as Grade 2 event	• Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin • Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications) For Grade 1 AST or ALT and/or TB elevation • Continue LFT monitoring per protocol
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or TB >1.5-3.0 times ULN)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 If improves to ≤ Grade 1 or baseline then resume study drug/study after completion of steroid taper	For Grade 2 AST or ALT and or TB elevation: • Regular and frequent checking of LFTs (eg, every 1-2 days) until elevations of these are improving or resolved. • If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician. • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day PO or IV equivalent. • If still no improvement within 3-5 days despite 1-2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • If still no improvement within 3-5 days despite 2-4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[a] . Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used** • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 3 (AST or ALT >5-20 times ULN and/or TB > 3.0-10 times ULN	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN • Hold durvalumab dose until resolution to ≤ Grade 1 or baseline • Resume study drug/study regimen if elevations downgrade ≤ Grade 1 or baseline within 14 days and after completion of steroid taper Permanently discontinue durvalumab if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue durvalumab Permanently discontinue durvalumab for any case meeting Hy's law criteria (AST and/or ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (ie, elevated alkaline P04) and in the absence of any alternative cause[c]	For Grade 3 or 4 AST or ALT and/or TB elevation: • Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent • If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil) Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used** • Hepatology consult, abdominal workup, and imaging as appropriate. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 4 (AST or ALT > 20 times ULN and/or TB > 10 times ULN)	Permanently discontinue study drug/study regimen	

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Grade of Elevated Serum Creatinine (CTCAE version 4.03) Any Grade	General Guidance	• Consult with Nephrologist • Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc) • Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections etc.) • Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event
	Grade 1 [Serum Creatinine > 1-1.5X baseline; > ULN to 1.5X ULN]	No dose modification	For Grade 1 elevated creatinine: • Monitor serum creatinine weekly and any accompanying symptom – If creatinine returns to baseline, resume its regular monitoring per study protocol. – If it worsens, depending on the severity, treat as Grade 2 or Grade 3 or 4 • Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc
	Grade 2 [Serum Creatinine>1.5-3.0X baseline; >1.5X-3.0XULN]	Hold durvalumab until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 or Grade 4 If toxicity improves to ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper	For Grade 2 elevated creatinine: • Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. • Carefully monitor serum creatinine every 2-3 days and as clinically warranted • Consult Nephrologist and consider renal biopsy if clinically indicated • If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent • If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day PO or IV equivalent, additional

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started. • Once improving gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) • When event returns to baseline, resume durvalumab and routine serum creatinine monitoring per study protocol
	Grade 3 or 4 (Grade 3: Serum Creatinine > 3.0 X baseline; >3.0-6.0 X ULN Grade 4: Serum Creatinine > 6.0 X ULN)	Permanently discontinue study drug/study regimen	• Carefully monitor serum creatinine on daily basis • Consult Nephrologist and consider renal biopsy if clinically indicated • Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent • If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]
Rash (excluding Bullous skin formations)	Grade of Skin Rash (Please refer to NCICTCAE version 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	Monitor for signs and symptoms of dermatitis (rash and pruritus) **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND DURVALUMAB DISCONTINUED****
	Grade 1	No dose modification	For Grade 1:

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			• Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream)
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves ≤ Grade 1 or baseline then resume study drug/study regimen after completion of steroid taper	For Grade 2: • Obtain dermatology consult • Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream) • Consider moderate-strength topical steroid • If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent • Consider skin biopsy if persistent for >1-2 weeks or recurs
	Grade 3	Hold durvalumab until resolution to ≤ Grade 1 or baseline If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline within 30 days, then permanently discontinue study drug/study regimen	For Grade 3 or 4: • Consult dermatology • Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent • Consider hospitalization • Monitor extent of rash [Rule of Nines] • Consider skin biopsy (preferably more than 1) as clinically feasible. • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) • Discuss with Study Physician
	Grade 4	Permanently discontinue study drug/study regimen	

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC Grade/severity)	General Guidance	• Consult Endocrinologist • Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. • Patients should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, infections, etc.) • Monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine labs depending on suspected endocrinopathy. • If a patient experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
	Grade 1 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC Grade 1)	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) • Monitor patient with appropriate endocrine function tests • If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult
	Grade 2 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC Grade/severity 2)	For Grade 2 endocrinopathy other than hypothyroidism, hold durvalumab dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper Patients with endocrinopathies who may require prolonged or continued steroid	For Grade 2: (including those with symptomatic endocrinopathy) • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids • Initiate hormone replacement as needed for management • Evaluate endocrine function, and as clinically indicated, consider pituitary scan • For patients with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term,

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the patient is clinically stable as per investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10 mg/day or equivalent.	corticosteroids (eg, 1-2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, Levothyroxine, hydrocortisone, or sex hormones) • Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) • For patients with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated
	Grade 3 or 4 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 3 or 4)	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold durvalumab dose until endocrinopathy symptom(s) are controlled Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper	For Grade 3 or 4: • Consult endocrinologist • Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent • Administer hormone replacement therapy as necessary. • For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity • Once improving, gradually taper immunosuppressive steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) • Discuss with study physician
Immune mediated Neurotoxicity (to include but not	Grade of Neurotoxicity Depending on the type of neurotoxicity,		

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
limited to limbic encephalitis. autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	refer to NCI CTCAE version 4.03 for defining the CTC grade/severity		
	Any Grade	General Guidance	• Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc.) • Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) • Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations) • Symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	See "Any Grade" recommendations above.
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold durvalumab dose until resolution to ≤ Grade 1 • For sensory neuropathy/neuropathic pain, consider holding durvalumab dose until resolution to ≤ Grade 1. – If toxicity worsens then treat as Grade 3 or Grade 4 – Study drug/study regimen can be resumed once event and after completion of steroid taper	• Discuss with the study physician • Obtain Neurology Consult • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) • Promptly start systemic steroids prednisone 1-2 mg/kg/day PO or IV equivalent • If no improvement within 3-5 days despite 1-2 mg/kg/day prednisone PO or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IVIG)
	Grade 3	• Hold study drug/study regimen dose until resolution to ≤ Grade 1 • Permanently discontinue durvalumab if Grade 3 irAE does	For Grade 3 or 4: • Discuss with study physician • Obtain Neurology Consult

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		not resolve to ≤ Grade 1 within 30 days.	• Consider hospitalization • Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent • If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IVIG) • Once stable, gradually taper steroids over ≥28 days
	Grade 4	• Permanently discontinue study drug/study regimen	
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis		General Guidance	• The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability • Patients should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult • Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation • Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 1	No dose modification	• Discuss with the study physician • Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above • Obtain a neurology consult unless the symptoms are very minor and stable
	Grade 2	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue study drug/study regimen if it does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	Grade 2 • Discuss with the study physician • Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above • Obtain a Neurology Consult • Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc.) *MYASTHENIA GRAVIS* – 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. – Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. – If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* – Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically

	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 3	Hold durvalumab dose until resolution to ≤ Grade 1 Permanently discontinue study drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	For severe or life threatening (Grade 3 or 4) events: • Discuss with study physician • Recommend hospitalization • Monitor symptoms and obtain neurological consult *MYASTHENIA GRAVIS* – Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. – Patients unable to tolerate steroids may be candidates for treatment with plasmapharesis or IVIG. – If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE*: – Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 4	Permanently discontinue study drug/study regimen	

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

Infusion-Related Reactions		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Any Grade		• Management per institutional standard at the discretion of investigator • Monitor patients for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc.) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: • Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator • Consider premedication per institutional standard prior to subsequent doses • Steroids should not be used for routine premedication of ≤Grade 2 infusion reaction
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event. Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: • Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

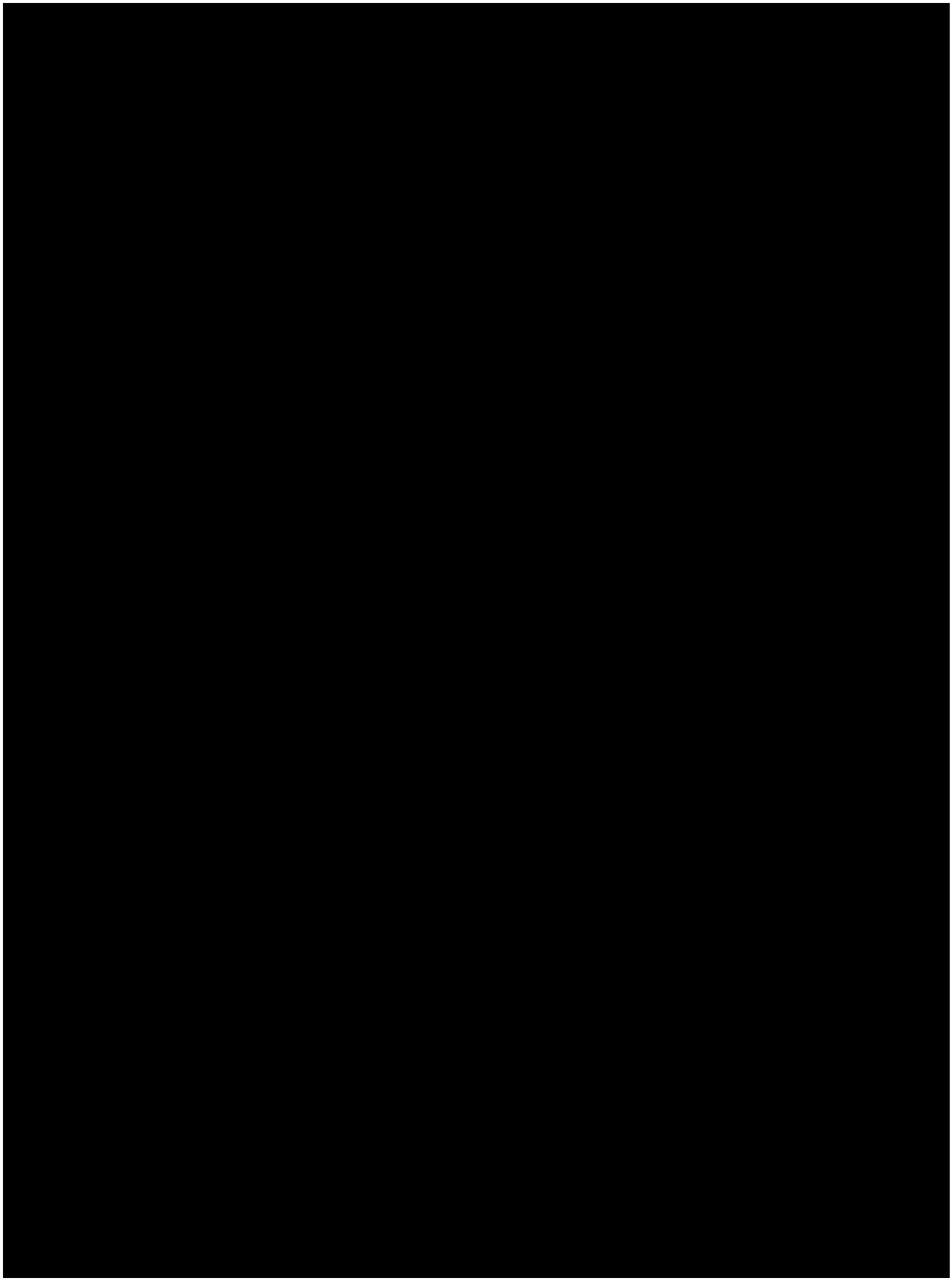
Appendix D-3: Durvalumab Treatment Modification and Toxicity Management Guidelines for Non-immune-mediated Reactions

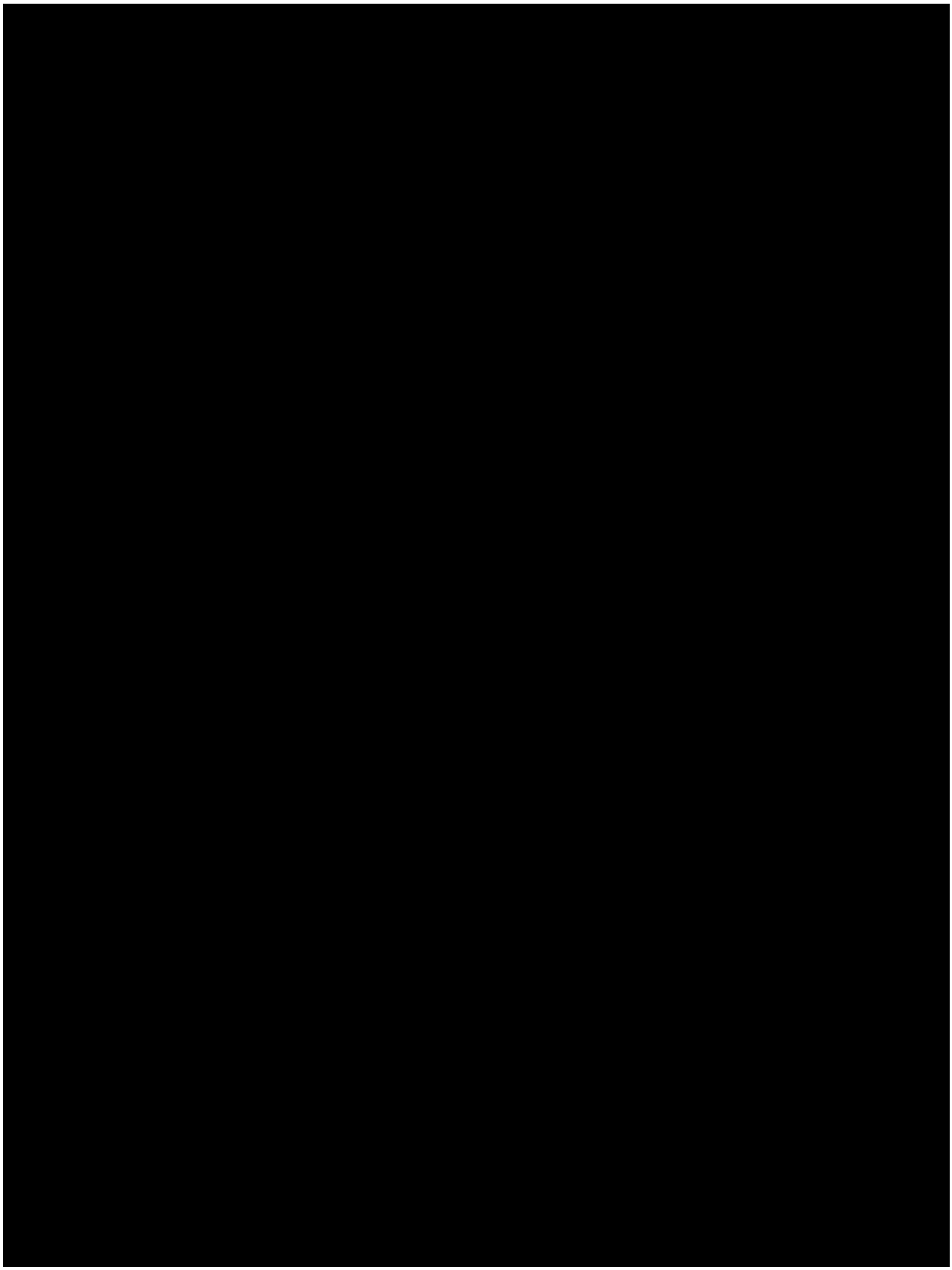
Non-immune Mediated Reactions Any event greater than or equal to Grade 2, please discuss with Study Physician		
Severity Grade of the Event (NCI CTCAE version 4.03)	**Dose Modification**	**Toxicity Management**
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related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

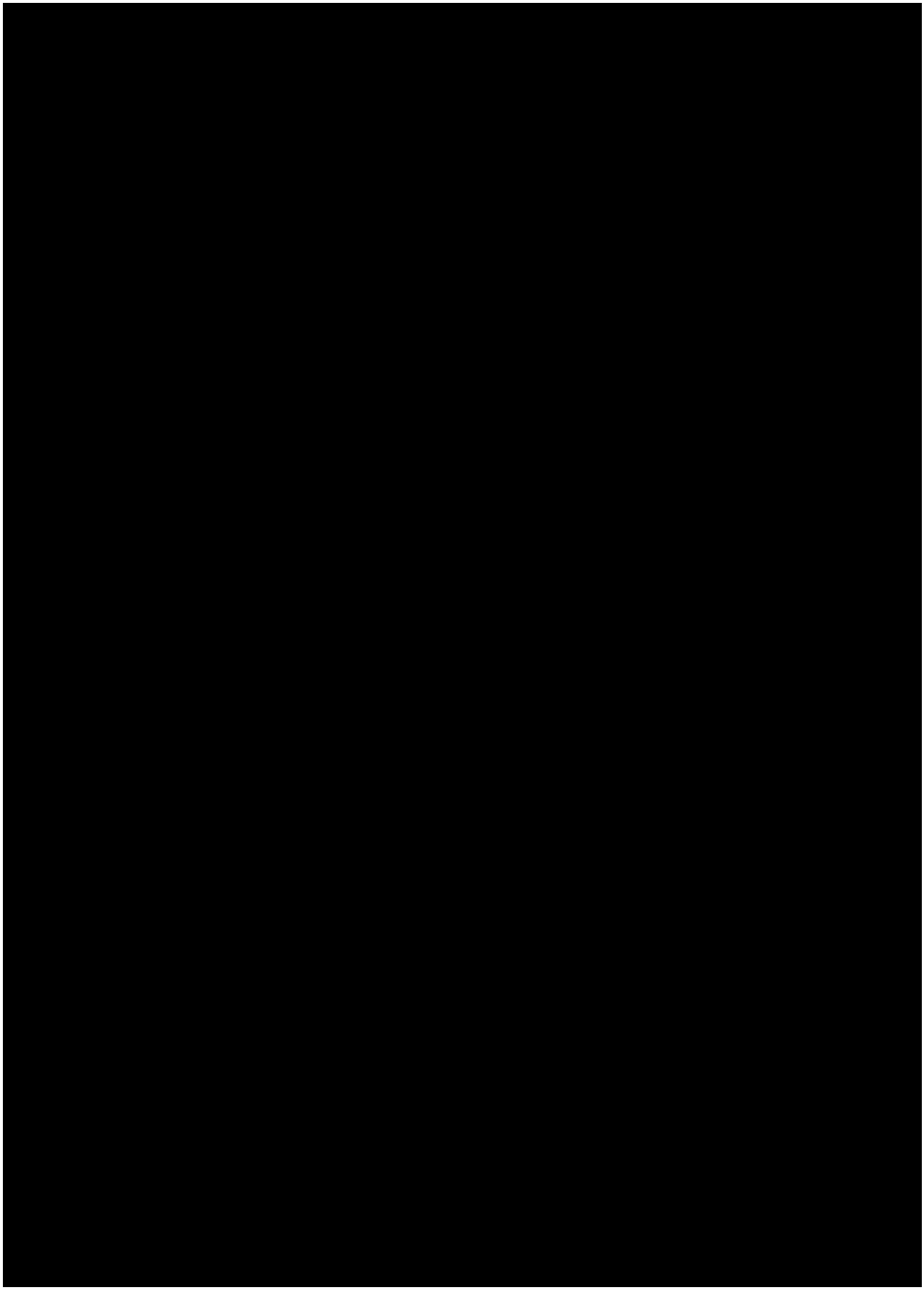
Abbreviations:
AChE = acetylcholine esterase; ADA = American Dietetic Association; ADL = activity of daily life; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; FDA = Food and Drug Administration; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; IVIG = intravenous immunoglobulin G; MRI = magnetic resonance imaging; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; NCCN = National Comprehensive Cancer Network; PCP = Pneumocystis pneumonia; PO = by mouth; TB = tuberculosis; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

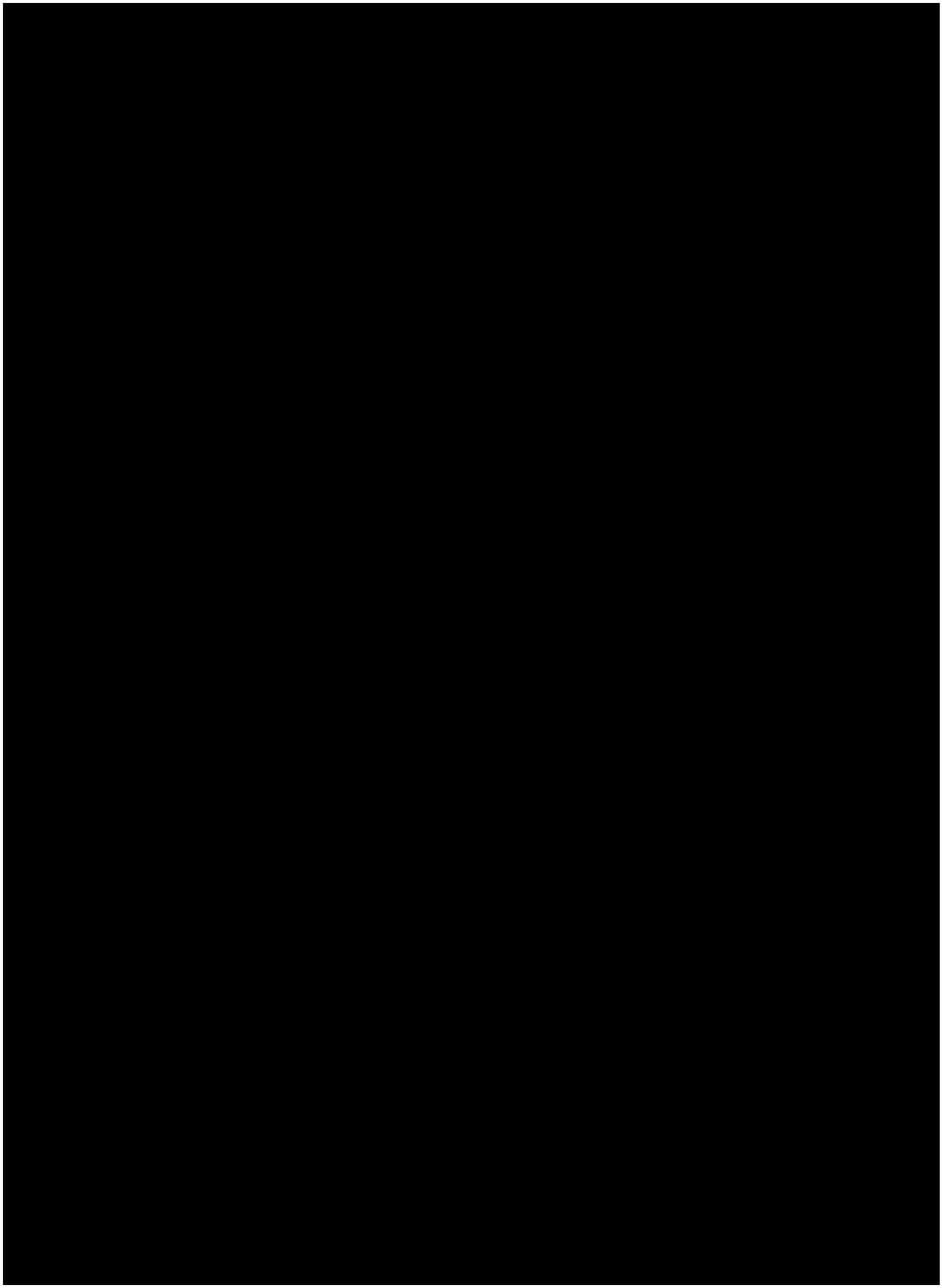
[a] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD

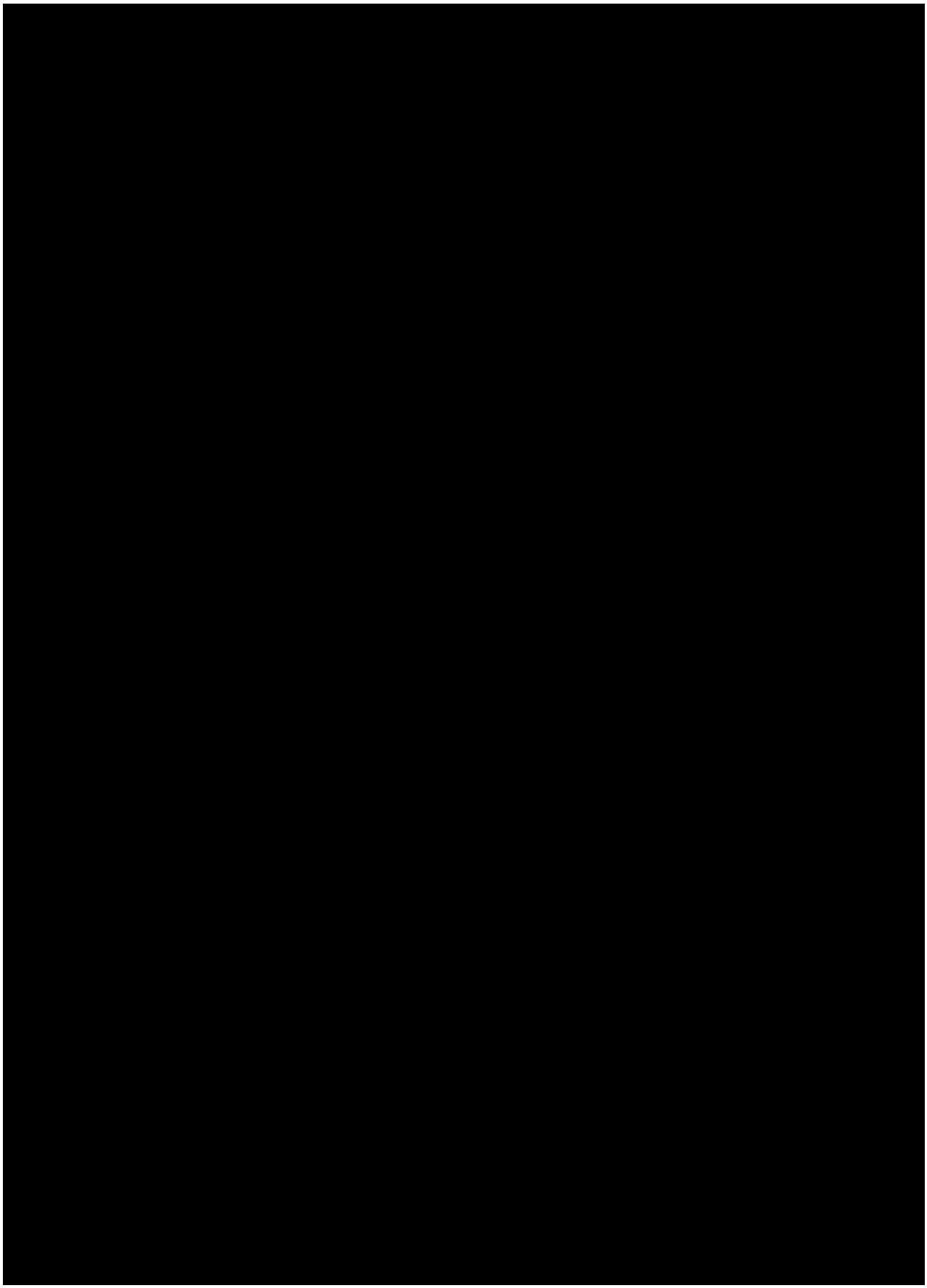
[b] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation, NCI CTCAE version 4.03

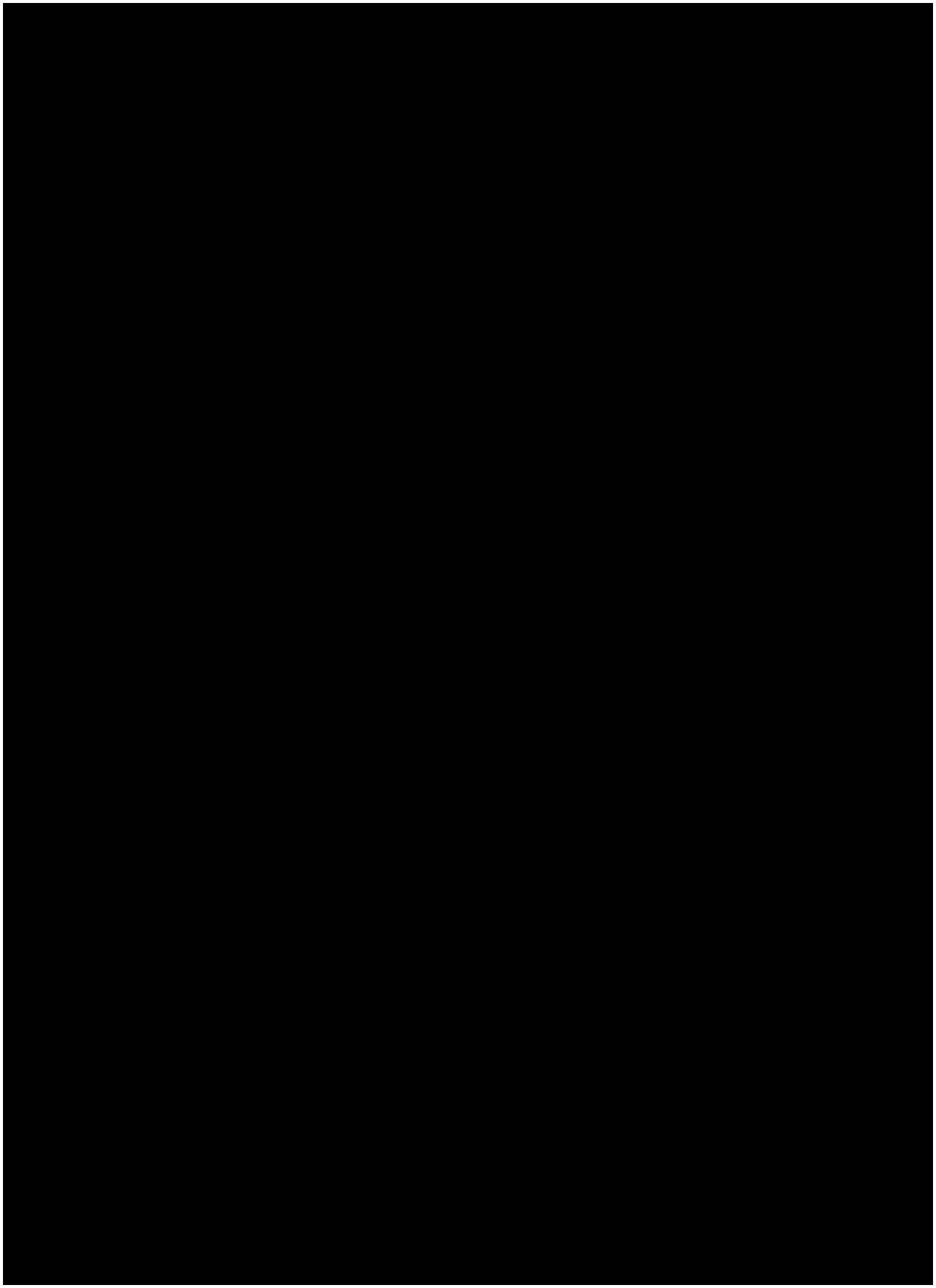


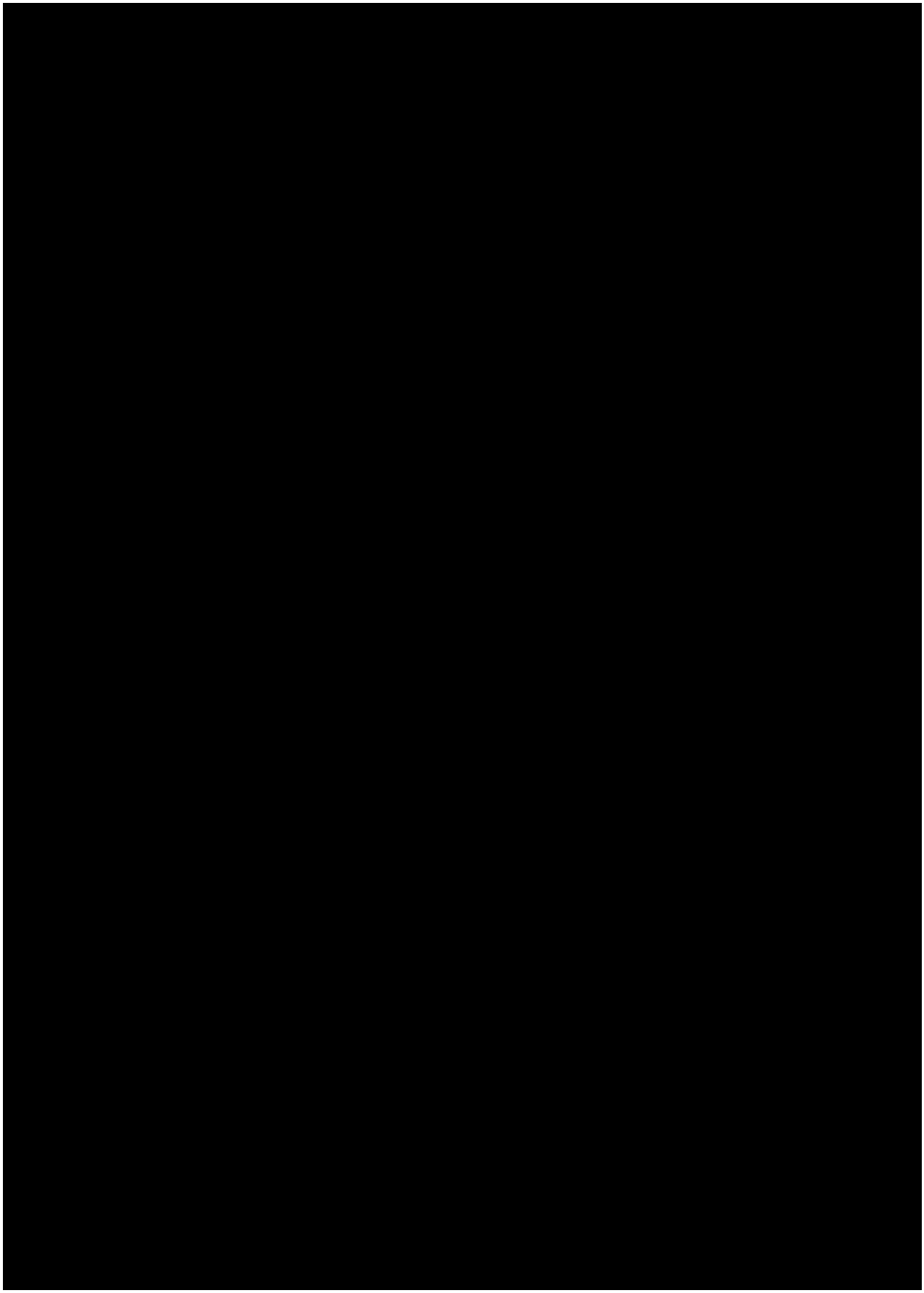












Celgene Signing Page

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UserName: [redacted]
Title: [redacted]
Date: Monday, 30 December 2019, 10:47 AM Eastern Daylight Time
Meaning: Approved, no changes necessary.
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1. JUSTIFICATION FOR AMENDMENT

The primary purpose of this Protocol Amendment 3.0 is to close the clinical database and set an end date for second primary malignancies (SPMs) data collection in the clinical database. The SPMs will then be recorded in subject's source documents and reported to Celgene Drug Safety.

There are no subjects in active treatment in this study. All remaining subjects are in the Follow-up Period (safety follow-up). For these subjects, the end date for data collection in the clinical database has been set for 15 Dec 2019. After this date, all subjects who have received lenalidomide, and are in safety follow-up, will continue to be followed for SPMs, as required by regulatory obligations. However, after this date, any reports of SPMs will be collected in the Celgene safety database and recorded in subject's source documents.

Title Page (updated)

1. Contact Information updated.

Protocol Summary

2. Addition of Clinical Hold on the study

Section 3.2.3 (updated)

3. Includes the end date for data entry in the clinical database. In addition, the SPMs will be recorded in subject's source documents and reported to Celgene Drug Safety.

Section 6.3.1 (updated)

4. Includes the end date for data entry in the clinical database. In addition, the SPMs will be recorded in subject's source documents and reported to Celgene Drug Safety.

Section 10.7.1 (updated)

5. Includes the end date for data entry in the clinical database. In addition, the SPMs will be recorded in subject's source documents and reported to Celgene Drug Safety.

The amendment also includes one other minor edition:

Editorial update, Section 10.6 - For the purpose of regulatory reporting, Celgene Drug Safety determine the expectedness of events (including events of disease progression) suspected of being related to durvalumab and lenalidomide based on the Investigator Brochure (IB), and dexamethasone based on the SmPC. Events of disease progression, including deaths due to disease progression for indications that are considered to be fatal, will not be assessed as expected adverse events.

1. JUSTIFICATION FOR AMENDMENT

Updates, clarifications, and corrections included in this amendment are summarized below:

- Update to the Medical Monitor/ Emergency Contact Information
- Update to disease background with more recent data/references. (Section 1.1)
- Additional information related to programmed death-ligand 1 (PD-L1) expression on tumor and infiltrating immune cells in the tumor microenvironment. It is predicted that patients with higher levels of PD-L1 in either tumor cells or immune cells will have more activation of the programmed death-1 (PD-1) pathway in the T-cells and will be more responsive to anti-PD-L1 therapy (Herbst, 2014, Higgs, 2015; Higgs, 2016). (Section 1.3.5)
- [redacted]
- Clarification of the definition of high risk cytogenetic factors in Inclusion Criteria (Section 4.2). Updated definition of high risk cytogenetic factor in Inclusion Criteria 8 and 10 from 1q rearrangement to 1q amplification.
- Clarification to thyroid function tests for thyroid stimulating hormone (TSH) assessment to be done from Cycle 5 onward (Table of Events and Section 6.2).
- Update to the pharmacokinetic windows to allow greater logistical flexibility (Sections 6.5.1 and6.5.2, and Table of Events)
- Update to name of International Council for Harmonisation (ICH): Site Principle Investigator Signature Page, Section 13.1, and Appendix A).
- Removal of Aiolos/Ikaros protein biomarker testing from the protocol (Protocol Summary, Section 1.3.5, Section 6.6, Table 3). The Aiolos/Ikaros test implemented at Covance is being removed across the entire Celgene MEDI4736 Program in immunomodulatory drug combination patients. Cereblon, Aiolos, and Ikaros will still be analyzed by RNA Seq analysis.
- Update to soluble factor biomarker collection timepoints (Section 6.6, Table 3). Removal of C1D8, C1D22 and C2D15 collections to align with MedImmune and minimize patient collections.
- Inclusion of circulating tumor deoxyribonucleic acid (ctDNA) biomarker testing language (Protocol Summary, Section 6.6). Addition of language covering ctDNA testing on plasma samples currently being collected for soluble factor testing is being implemented. MedImmune and others are investigating the use of this platform for less invasive monitoring of disease response and patient stratification assays. This platform could be utilized for a diagnostic assay for follow-on programs.

- Update to collect TCR Clonality and neoantigens PBMC sample at C2D15 timepoint (Section 6.6). This sample will be used to compare matched bone marrow and blood sampling at the same timepoint in TCR Clonality and neoantigen analyses. If the PBMC sample shows equivalency to the bone marrow sample this could lead to less invasive sample collection.
- Update to soluble PD-L1 (sPD-L1) testing timepoints (Section 6.6). The removal of all timepoints, except Screening and predose C1D1. mirrors what is being implemented across the entire Celgene MEDI4736 Program.
- Update to References (Section 17)
- Update to Durvalumab Treatment Modification and Toxicity Management Guidelines (Appendices D-1, D-2 and D-3)
- Corrections of minor spelling/grammatical errors.

References:

Herbst RS, Soria JC, Kowanetz M, Fine GD, Hamid O, Gordon MS, Sosman JA, et al. Predictive correlates of response to the anti-PD-L1 antibody MPDL3280A in cancer patients. Nature. 2014; 515:563-80.

Higgs BW, Robbins PB, Blake-Haskins JA, Morehouse C, Streicher K, Zhu W, et al. High tumoral IFNγ mRNA, PD-L1 protein and combined IFNγ mRNA/PD-L1 protein expression associates with response to durvalumab (anti-PD-L1) monotherapy in NSCLC patients [abstract]. ECCO-ESMO – The 18th ECCO - 40th ESMO European Cancer Congress: Reinforcing multidisciplinary. 2015 Sep 25-29; Vienna, Austria: Abstract 15LBA.

Higgs BW, Morehouse CA, Streicher KL, Rebelatto MC, Steele K, Jin X, et al. Baseline tumoral IFNγ mRNA and PD-L1 protein expression associated with overall survival in durvalumab-treated NSCLC patients [poster]. Poster presented at the American Society of Clinical Oncology (ASCO) Annual Meeting. 2016 Jun 3–7; Chicago, IL; USA: Poster 3036.

1. JUSTIFICATION FOR AMENDMENT

Significant changes included in this amendment are summarized below:

The monitoring of blood pressure and other vital signs during and post durvalumab infusion beyond Cycle 2 was modified to enable the study site to follow institutional standard practice or as clinically indicated at discretion of the treating physician. As reported in Durvalumab (MEDI4736) Investigator's Brochure version 9.0 dated 22Jan2016, in clinical studies with durvalumab as a monotherapy, the incidence of reported potential infusion-related reaction was low. In particular for the serious case reports of investigator assessed infusion-related reaction, 10 of 1,265 subjects treated with durvalumab in 5 sponsored monotherapy studies (CD-ON-MEDI4736-1108, D4190C00002, D4190C00007, D4191C00003, and D4193C00001) reported 14 cases of infusion-related reactions, giving an overall frequency of 0.8% (10/1,265). These events/reactions respond to antihistamine, drug interruption/withdrawal, decrease in infusion rate and supportive treatment. In addition, in the current ongoing MEDI4736-MM-001 study (durvalumab ± pomalidomide ± dexamethasone in relapsed and refractory multiple myeloma), as of 09Jun2016, no significant infusion reactions have been reported for the 21 subjects treated with either durvalumab monotherapy, durvalumab + pomalidomide, or durvalumab + pomalidomide + dexamethasone. (Section 5 footnote g and Section 7.2.1.1)

Minor clarifications and corrections are summarized below:

- Update to Table of Events to permit urinalysis to be performed by local laboratory (Section 5, Table of Events)
- Update to Section 3.2.2 and Table of Events to clarify that for the first 3 subjects of each cohort in the dose-finding portion, there will be at least a 24-hour observation period. The 24 hour observation period should be communicated to the sponsor within 24 to 48 hours. The report should include safety data (e.g., adverse event [AE], basic laboratory, and vital signs] to the sponsor before the dosing of the next subject occurs. (Section 3.2.2, and Section 5 footnote g)
- Update to Treatment Period from the time of Interactive Response Technology (IRT) to allow registration up to 3 days prior to initiating study treatment on Cycle 1 Day 1 (C1D1) (Section 6.2)
- Update from durvalumab given in combination with lenalidomide with "or" without dexmethasone, to with "and" without dexamethasone for grammatical clarity (Study Design, Section 1.3.3.2, and Section 3.1)
- Correction of minor spelling/grammatical errors (Section 6.4.3 and Section 8.2)
- Update from "Celgene Corporation" to "Celgene" for administrative reasons (Section 7.1.3)