

LUDWIG CANCER RESEARCH	Study Protocol	LUD2014-010	US-IND# 129021 NCT02716805
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Protocol Title
A Phase 1 Study to Assess Safety and Tolerability of Tremelimumab and Durvalumab, Administered with High Dose Chemotherapy and Autologous Stem Cell Transplant (HDT/ASCT)

Objectives and Synopsis	
<p>This is an open-label, multicenter, Phase 1 study of checkpoint therapy, tremelimumab (MEDI1123) and durvalumab (MEDI4736), administered to subjects with multiple myeloma who are at high risk for relapse. Four cohorts will be included in the study. The cohorts are based on subjects receiving tremelimumab 75 mg alone (Cohorts 1 and 2) or durvalumab 1500 mg + tremelimumab 75 mg (Cohorts 3 and 4) prior to and for 2 cycles post autologous stem cell transplant (ASCT) as well as 2 different schedules of post ASCT therapy: Late (Cohorts 1 and 3) and Early (Cohorts 2 and 4) as described below.</p> <p>Subjects will receive a single dose of tremelimumab 75 mg alone (Cohorts 1 and 2) or a single dose of durvalumab 1500 mg + tremelimumab 75 mg (Cohorts 3 and 4) at 21 days prior to steady state leukopheresis for the collection of autologous peripheral blood lymphocytes (PBLs). Leukopheresis will be followed by high dose therapy (HDT, melphalan 200 mg/m² IV) and ASCT using previously banked hematopoietic stem cells. Autologous PBLs will be infused into subjects on Day +3 following HDT/ASCT, and a single dose of tremelimumab 75 mg will be administered on the same day. Following HDT/ASCT, treatment will resume with tremelimumab 75 mg alone (Cohorts 1 and 2) or durvalumab 1500 mg + tremelimumab 75 mg (Cohorts 3 and 4) for the first 2 cycles post HDT/ASCT according to the following schedule:</p> <ul style="list-style-type: none"> • Late Post ASCT Treatment: <ul style="list-style-type: none"> ○ Cohort 1 - tremelimumab 75 mg alone on Day 100 (±10) and 4 weeks later (Cycles 1 and 2) ○ Cohort 3 -- tremelimumab 75 mg + durvalumab 1500 mg on Day 100 (±10) and 4 weeks later (Cycles 1 and 2) • Early Post ASCT Treatment: <ul style="list-style-type: none"> ○ Cohort 2- tremelimumab 75 mg alone on Day 30-40 and Day 100 (±10) (Cycles 1 and 2) ○ Cohort 4 – tremelimumab 75 mg + durvalumab 1500 mg on Day 30-40 and Day 100 (±10) (Cycles 1 and 2) <p>For Cycles 3 to 8, durvalumab alone (1500 mg every 4 weeks) will continue to be administered for all cohorts.</p> <p>Cohort enrollment will be sequential so that Cohort 1 will be treated first, followed by a safety review before each subsequent cohort will be opened.</p>	
Primary Objectives [Endpoints]	Safety and Tolerability of durvalumab/tremelimumab [DLTs, AEs according to CTCAE version 4.03].
Secondary Objectives [Endpoints]	Clinical efficacy [response by IMWG criteria, minimal residual disease assessment, one-year PFS and OS, 100-day ASCT related mortality].

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Exploratory Objective [Endpoints]	Biological Activity [Gene expression, mutation analysis, and protein expression of immune regulation markers of tumor cell populations. Effects of PBL and durvalumab / tremelimumab combination on immune reconstitution, T and B cell receptor diversity, and immune responses to Pevnar-13 and myeloma antigens].
DLT=Dose-limiting Toxicity; AE=adverse event; PFS=Progression-free Survival; OS=Overall Survival; CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; IMWG=International Myeloma Working Group; ASCT=Autologous stem cell transplant; PBL=Peripheral blood lymphocytes	

Sponsor: Ludwig Institute for Cancer Research	Study Chair: [REDACTED]
Sponsor representative Signature and Date	Study Chair Signature and Date

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1 Background

1.1 Multiple Myeloma

Multiple myeloma (MM) is a malignancy of plasma cells and is the second most common hematologic malignancy.(1) It is characterized by clonal expansion of malignant plasma cells and manifests symptoms encapsulated by the acronym CRAB; hyperCalcemia, Renal impairment, Anemia, and lytic Bone disease. The pathogenesis of MM is complex. Several studies have shown that myeloma cells acquire certain genetic changes that allow for uncontrolled growth, migration, and protection from apoptosis.(2-4) The bone marrow microenvironment also appears to play a critical role in the development and persistence of the disease, with interactions with osteoclasts, stromal cells, and cells of the immune system mediated by cell surface and soluble mediators.(5, 6)

Multiple myeloma represents 1% of all cancers in the United States, with approximately 27,000 new cases diagnosed each year with an incidence of 6.3 cases per 100,000 and 11,000 deaths yearly.(7) There are approximately 90,000 people living with MM in the United States. Worldwide, there are 103,000 new cases and 72,000 deaths from myeloma each year. The median age at diagnosis is 70, and because of anticipated changes in demographics, by the year 2020, it is predicted that there will be 140,000 new cases each year with 100,000 deaths (8). The incidence of MM in Europe is 6.0 cases per 100,000 per year with a median age at diagnosis between 63 and 70 years; the mortality is 4.1 cases per 100,000 per year.(9) Currently approved regimens commonly used for MM include combinations of the proteasome inhibitors bortezomib and/or immune modulatory drugs (IMiDs) including thalidomide or lenalidomide with corticosteroids for induction, high dose chemotherapy and autologous stem cell transplant (ASCT) for consolidation therapy, and combinations of novel agents with conventional cytotoxic chemotherapy for relapsed disease.(1)

Numerous clinical trials have demonstrated that high dose chemotherapy and ASCT confers improved disease-free and overall survival compared to conventional dose chemotherapy.(10-13) The survival benefit is most evident in subjects 65 years of age or younger with good performances status and few or no significant co-morbidities. In general, the conditioning regimen for this procedure consists of melphalan (L-PAM) as a single or split intravenous dose of 200 mg/m². Autologous stem cell transplant is now accepted in the standard-of-care management of newly diagnosed MM patients. Several studies have shown that a second ASCT is an effective salvage therapy in subjects with relapsed disease.(14-16) In general, second transplants feature conditioning regimens consisting of a reduced dose of melphalan (100-140 mg/m²) alone or in combination with other alkylating agents such as BCNU (carmustine) in order to reduce morbidity associated with the procedure. Although salvage ASCT has not been shown to improve overall survival, the response rates are high, and this strategy is commonly used to restore bone marrow reserve in patients in anticipation of further therapy.

Despite these advances, relapse is inevitable and the majority of patients will eventually succumb to multiple myeloma.

1.2 CTLA-4

Human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4; CD152) is a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation. The canonical coinhibitory receptor was cloned in 1987 (17); however, it took several years to appreciate the

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unique role of CTLA-4 in attenuating T cell activation.(18-20) Human cytotoxic T lymphocyte-associated antigen 4 engagement on activated T cells inhibits cytokine synthesis and restricts cell proliferation.(19-23) Characterization of CTLA-4 *-/-* knockout mice established a critical negative regulatory function for CTLA-4 *in vivo*. These mice develop a profound, hyperproliferative lymphocyte expansion, which is lethal within 3 weeks after birth.(24-27) On a cellular level, CTLA-4-mediated inhibition of T cell activation relies on several overlapping mechanisms. First, CTLA-4 competes with CD28 for interaction with the ligands B7-1 and B7-2. Secondly, CTLA-4 engagement impacts multiple intracellular pathways. Inhibitory signaling is thought to be mediated by (1) association with intracellular phosphatases like Src homology 2 (SH2) domain-containing phosphatase-1 (SHP-1), SHP-2, and protein phosphatase 2A (PP2A), (2) blockade of lipid-raft expression, and (3) disruption of microcluster formation (reviewed by Rudd et al. 2009 (27)).

1.3 PD-1 and PD-L1

Programmed death-1 (PD-1, cluster of differentiation [CD] 279) is a member of the immunoglobulin superfamily (IGSF) of molecules involved in regulation of T cell activation. Programmed death-1 acquired its name when it was identified in 1992 as a gene upregulated in T cell hybridoma undergoing cell death.(28) The structure of PD-1 is composed of one IGSF domain, a transmembrane domain, and an intracellular domain containing an immunoreceptor tyrosine-based inhibitory motif (ITIM) and an immunoreceptor tyrosine-based switch motif (ITSM).(29-32) Programmed Death-1 has two binding partners: PD-ligand 1 ([PD-L1] B7-H1, CD274) and PD-ligand 2 ([PD-L2] B7-DC, CD273), distant relatives of the B7-1 and B7-2 molecules. Discovered in 1999, PD-L1 is expressed quite broadly on both hematopoietic and non-hematopoietic lineages.(32, 33) It is found on T cell, B cells, macrophages, natural killer (NK) cells, dendritic cells (DCs), and mast cells. It has also been described on peripheral tissues including cardiac endothelium, lung, small intestine, keratinocytes, islet cells of the pancreas, and syncytiotrophoblasts in the placenta as well as a variety of tumor cell types.(18, 34-45) Programmed death-L1 is constitutively expressed on many hematopoietic cells, but may be upregulated in hematopoietic and non-hematopoietic cells. Regulation of PD-L1 is mediated, in part, by type I and type II interferons. Programmed death-ligand 2 was identified in 2001.(46, 47) Its expression is far more restricted and is confined to hematopoietic cells.

Engagement of PD-1 on T cells inhibits activation with downstream effects on cytokine production, proliferation, cell survival, and transcription factors associated with effector T cell function.(33, 48-52) Inhibitory signaling by PD-1 is thought to depend upon the cytosolic ITSM domain, which associates with phosphatases SHP-1 and SHP-2.(53, 54) While CTLA-4 and PD-1 are both inhibitory receptors, they fulfill distinct roles and mediate their effects through distinct mechanisms.(55) For example, PD-1 inhibits activation of the serine threonine kinase Akt via its effect on the phosphoinositide 3-kinase (PI3K) pathway, whereas CTLA-4 inhibits Akt in a PI3K independent manner.(49, 53, 56) Studies of PD-1 *-/-* knockout and PD-L *-/-* knockout mice support a unique role for PD-1: PD-L interaction in mediating peripheral tolerance and preventing autoimmunity.(37) The phenotype of the PD-1*-/-* knockout mouse depends upon the genetic background, but manifestations of spontaneous autoimmunity have been reported, including dilated cardiomyopathy and glomerulonephritis.(57, 58)

Programmed death-L1 and PD-L2 are expressed on many human tumors including urothelial, ovarian, breast, cervical, colon, pancreatic, gastric cancers as well as melanoma glioblastoma, and non-small cell lung cancer (NSCLC).(18, 34, 35, 38, 39, 43, 59-65) In addition, PD-L1 and PD-L2 have been

detected on several hematologic malignancies including: Hodgkin lymphoma, primary mediastinal B cell lymphoma, angioimmunoblastic T-cell lymphoma, multiple myeloma, acute myeloid leukemia chronic lymphocytic leukemia, and adult T-cell leukemia/lymphoma.(45, 66-69) Expression of PD-L has been correlated with prognosis in many of these malignancies, fueling the hypothesis that PD-L expression is a mechanism for tumor immune evasion.(60, 63, 64, 70) Additionally, PD-1 is highly expressed on lymphocytes infiltrating human tumors and circulating tumor-specific T cells, a phenotype correlated with impaired T cell function.(71-74) Together, these findings suggest that interrupting PD-1: PD-L interaction could be an effective anti-cancer therapy.

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 by delivering inhibitory signals to T cells through the PD-1 and CD80 receptors.

1.4 Tremelimumab (MEDI1123) - CTLA-4 blocking antibody

Tremelimumab is briefly described in this section. Refer to the current Investigator Brochure (IB) for complete and current information.

Tremelimumab is a human immunoglobulin (Ig) G2 monoclonal antibody (mAb) being investigated as a cancer immunotherapeutic agent. Tremelimumab is specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4; CD152), a cell surface receptor that is expressed primarily on activated T cells and acts to inhibit their activation.

As of the data cutoff date of 12Nov2014 (for all studies except D4190C00006 that has a cutoff date of 04Dec2014), 22 sponsored clinical studies have been conducted as part of the tremelimumab clinical development program. Of these studies, 13 have been completed and 9 are ongoing. Tremelimumab has been administered as monotherapy to 973 subjects participating in 10 of the 22 clinical studies, 2 of which are ongoing. An additional 497 subjects have received tremelimumab or placebo in the ongoing double-blinded, Phase 2b mesothelioma study, D4880C00003 (DETERMINE; data remain blinded). Tremelimumab in combination with other anticancer agents has been administered to 208 subjects with a variety of tumor types in 12 of the 22 clinical studies, 7 of which are ongoing.

In clinical subjects, tremelimumab exhibits linear (dose-proportional) PK following intravenous (IV) infusion.

Across the clinical development program for tremelimumab, a pattern of efficacy has emerged, also observed for the related anti-CTLA-4 antibody, ipilimumab, which appears to be consistent across tumor types for this mechanism of action. Response rates to anti-CTLA-4 antibodies are generally low, approximately 10%. However, in subjects who respond, the responses are generally durable, lasting several months even in subjects with aggressive tumors such as refractory metastatic melanoma. Some subjects may have what is perceived to be progression of their disease in advance of developing disease stabilization or a tumor response. Overall, the impact on conventionally-defined progression-free survival (PFS) can be small; however, the durable response or stable disease seen in a proportion of subjects can lead to significant prolongation of overall survival (OS).

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The profile of adverse events (AEs) and the spectrum of event severity have remained stable across the tremelimumab clinical program and are consistent with the pharmacology of the target. To date, no tumor type or stage appears to be associated with unique AEs (except for vitiligo that appears to be confined to subjects with melanoma).

As of the data cutoff date of 12Nov2014 (for all studies except D4190C00006 that has a cutoff date of 04Dec2014), AEs (all grades, regardless of causality) reported in > 10% of subjects in the completed and rollover tremelimumab monotherapy studies (N = 973, integrated data) were diarrhea (45.3%), fatigue (37.5%), nausea (32.5%), rash (28.8%), pruritus (27.3%), decreased appetite (22.8%), vomiting (22.5%), pyrexia (15.3%), cough (15.0%), constipation (14.4%), abdominal pain (13.9%), headache (13.8%), dyspnea (12.4%), and decreased weight (10.2%). Based on integrated data from completed studies of tremelimumab in combination with other agents (N = 116), AEs (all grades, regardless of causality) reported in > 15% of subjects were diarrhea (54.3%); nausea (40.5%); fatigue (38.8%); rash (35.3%); pruritus, decreased appetite (30.2% each); vomiting (27.6%); pyrexia (26.7%); influenza like illness (20.7%); arthralgia (19.8%); constipation (19.0%); thrombocytopenia, injection site reaction (18.1% each); and increased aspartate aminotransferase (15.5%). Most of these events occurred at a higher rate with tremelimumab plus sunitinib than with other combinations. The events of diarrhea, rash, and pruritus are considered identified risks of tremelimumab. Acute renal failure was reported in subjects who received the combination of tremelimumab and sunitinib; however, acute renal failure has not been an expected AE for single-agent tremelimumab. The incidence and/or severity of many of the AEs observed following administration of tremelimumab can be reduced by following current guidelines for the management of immune-related toxicities.

1.5 Durvalumab (MEDI4736) - PD-L1 Blocking Antibody

Durvalumab is briefly described in this section. Refer to the current Investigator Brochure (IB) for complete and current information.

Durvalumab is a human mAb of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of PD-L1 (B7 homolog 1 [B7-H1], CD274) to PD-1 (CD279) and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.

As of the data cutoff dates in the IB (15Apr2015 to 12Jul2015), a total of 1,883 subjects have been enrolled and treated in 30 ongoing durvalumab clinical studies, including 20 sponsored (6 monotherapy and 14 combination therapy) and 10 collaborative studies. Of the 1,883 subjects, 1,279 received durvalumab monotherapy, 440 received durvalumab in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which

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are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy / neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols.

Partial efficacy data are available for 2 monotherapy studies (CD-ON-MEDI4736-1108 and D4190C00007) and 2 combination therapy studies (CD-ON-MEDI4736-1161 and D4190C00006). Clinical activity has been observed across the 4 studies.

1.6 Peripheral Blood Mononuclear Cell Reconstitution in Autologous Stem Cell Transplant for Multiple Myeloma

Immune competence is a significant factor for consideration of immunologic therapy in the setting of ASCT. Subjects experience significant lymphopenia in the post ASCT period and have demonstrated poor or absent responses to infectious disease vaccines up to one year after ASCT.(75, 76) However, clinical studies demonstrate that immune competence can be restored by reconstitution of peripheral blood lymphocytes harvested prior to the myeloablative conditioning regimen of ASCT. In this strategy, peripheral blood mononuclear cells (PBMCs), including lymphocytes and NK cells, are harvested by leukopheresis prior to conditioning chemotherapy. In some studies, peripheral blood lymphocytes (PBLs) are then expanded *ex vivo* by co-incubation with recombinant human IL-2 and paramagnetic beads conjugated to activating monoclonal antibodies directed against the T cell activation receptors CD3 and CD28, and these PBL are re-infused into subjects after conditioning chemotherapy and stem cell rescue.(77, 78) Rapoport and colleagues demonstrated that this approach could successfully induce robust humoral and cellular immune responses to infectious disease or tumor antigen vaccines in MM subjects undergoing ASCT.(77, 78) The *ex vivo* activation step is not required for restoration of immune responsiveness. Reinfusion of unmanipulated PBMCs harvested prior to conditioning chemotherapy resulted in robust humoral immune responses to a recombinant MAGE-A3 vaccine administered to subjects undergoing ASCT for MM.(79) *Ex vivo* activated PBL reinfusion was associated in some cases with hyperleukocytosis and grade 1-3 GI and skin AEs that were indistinguishable from graft-versus-host disease.(80) In contrast, reconstitution of unmanipulated PBMC post-transplant was not reported to have significant adverse effects in the MAGE-A3 vaccine trial.

2 Study Rationale

Despite advances in MM, relapse in these patients is inevitable and the majority of patients will eventually succumb to the disease. The success of CTLA-4 and PD-1 directed immunotherapy in solid tumors has fueled clinical investigation of checkpoint blockade in hematologic malignancies. The mechanisms of action for CTLA-4 and PD-1 are non-redundant with respect to T-cell function, suggesting that targeting both pathways may have additive or synergistic activity.(81) Also, preclinical data in mouse models of transplantable solid tumors supports the superior anti-tumor activity of combination therapy over monotherapy.(82, 83) Based upon these observations, combination therapy may generate superior anti-tumor activity (compared to monotherapy), which may translate into high rates of response in tumors known to respond to immunotherapies, or increased likelihood of activity in tumors that have previously not shown high levels of responsiveness to immunotherapy.

Tremelimumab has a well characterized toxicity profile and evidence for clinical activity, as outlined above. The safety, tolerability, pharmacokinetics and antitumor activity of durvalumab alone and in combination with tremelimumab have also been characterized in ongoing studies. Although most of the data for these 2 drugs were generated from solid tumor studies, data from other checkpoint inhibitors (ipilimumab and nivolumab) indicate the toxicity is similar for hematologic cancers and no unexpected toxicities were seen in patients with hematologic cancers. There are sufficient data to identify doses to be used in this study.

The combination dose selection of 1 mg/kg Q4W for tremelimumab and 20 mg/kg Q4W for durvalumab was based on the identification of an optimal dose of durvalumab that would “yield sustained target suppression, optimize synergy of the combination, while maintaining the balance of safety in combination with tremelimumab.” This is consistent with the dosing regimen to be evaluated in the MedImmune program going forward.

The fixed dosing is based on information from MedImmune, which indicates that the dose and schedule of 1500 mg durvalumab Q4W and 75 mg tremelimumab Q4W was selected based on PK models as described below.

Using population PK models, simulations indicated that both body weight-based and fixed dosing regimens of durvalumab and tremelimumab yield similar median steady state PK concentrations with slightly less between-subject variability with fixed dosing regimens. A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, MedImmune considers it feasible to switch to fixed dosing regimens. Based on an average body weight of 75 kg, a fixed dose of 750 mg Q2W durvalumab is equivalent to 10 mg/kg Q2W, 1500 mg Q4W durvalumab is equivalent to 20 mg/kg Q4W, and 75 mg Q4W tremelimumab is equivalent to 1 mg/kg Q4W.

Fixed dosing for durvalumab is recommended only for subjects with > 30kg body weight due to endotoxin exposure. Subjects with a body weight ≤ 30 kg are not eligible for enrollment in the current study. If a subject's body weight drops to ≤ 30 kg while on the study, the subject will be dosed according to the details provided in Section 6.1.

The goal of this study is to build on prior work using ASCT as a novel area for the application of cellular and immune based therapies.(77, 78, 84, 85) Much of this work has been performed in

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subjects with multiple myeloma. In more recent studies, immune efficacy of autologous lymphocyte infusion early post ASCT was shown without a need for *ex vivo* manipulation. Administering checkpoint blockade in this setting seeks to investigate if an autologous lymphocyte product transferred into a favorable milieu for homeostatic reconstitution can effectively break immune tolerance against tumor-associated antigens that are either mutated or ectopically expressed. The safety and efficacy profile of leukopheresis followed by HDT/ASCT and lymphocyte infusions has been studied and is well characterized. This will make it easier to identify any safety signals related to the durvalumab / tremelimumab combination therapy. Compelling data regarding the combination of PD-1/PD-L1 and CTLA-4 blockade and their synergistic effects support evaluating the combination of the 2 drugs at a level at or below the maximum tolerated dose (MTD) established by ongoing solid tumor durvalumab / tremelimumab combination studies.

The cohorts proposed in the study are to evaluate the impact of checkpoint inhibitor therapy (using 1 or 2 checkpoint inhibitors) at different time points in the peri-transplant period. In a retrospective analysis, Rueff et al. demonstrated that CD8 T cell and NK cells achieved healthy donor levels at 1 month post ASCT.(86) This supports the inclusion of the early treatment cohorts at Day 30 post ASCT. The stable recovery of B, T and NK cell compartments at approximately Day 100 justifies the incorporation of the cohorts at Day 100 post ASCT.(77)

3 Experimental Plan

3.1 Study Design

This is an open-label, multicenter, Phase 1 study of checkpoint therapy, tremelimumab 75 mg and durvalumab 1500 mg, administered to subjects with multiple myeloma who are at high risk for relapse. Four cohorts will be included in the study. The cohorts are based on subjects receiving tremelimumab 75 mg alone (Cohorts 1 and 2) or durvalumab 1500 mg + tremelimumab 75 mg (Cohorts 3 and 4) prior to and for 2 cycles post autologous stem cell transplant (ASCT) as well as 2 different schedules of post ASCT therapy: Late (Cohorts 1 and 3) and Early (Cohorts 2 and 4) as described below.

3.1.1 Study Phase

Phase 1

3.1.2 Enrollment/Randomization

This is a multicenter study with central subject registration.

Cohort enrollment will be sequential so that Cohort 1 will be treated first, followed by a safety review before each subsequent cohort will be opened. Subjects will not be treated as part of a new cohort until all subjects in the previous cohort have completed the DLT observation period, and there was no more than one DLT observed in the previous cohort (see Section 3.1.9).

The second subject in each cohort should not start treatment until the first subject has completed early engraftment (approximately Day 12 to 18 post ASCT); therefore, the first subject in each cohort will receive the first dose of tremelimumab 75 mg or durvalumab 1500 mg + tremelimumab 75 mg and will be observed for a period of 7 weeks for toxicities before the next subject is enrolled.

Enrollment into the cohorts will be monitored for safety on an ongoing basis according to Section 3.1.14.

3.1.3 Blinding/Unblinding

This is an open-label study.

3.1.4 Subject Population

Subjects with high risk or relapsed multiple myeloma eligible for autologous stem cell transplant (ASCT) and with available cryopreserved stem cells.

For complete eligibility details, see Section 5.

3.1.5 No. of Sites/Subjects

The study will accrue up to 6 subjects in each cohort and will be performed at 2 sites.

3.1.6 Sample Size Considerations

A sample size of 6 subjects in each of the cohorts is deemed to be sufficient for the assessment of safety and tolerability as the primary objective and the exploration of clinical anti-tumor activity and other secondary and exploratory endpoints.

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Subjects will not be treated as part of the next cohort unless a DLT was observed in no more than 1 out of the 6 subjects in the previous cohort during the DLT observation period. Using this design, initiation of the next cohort is probable if the risk of DLT is low, and the likelihood of initiation decreases as the risk of DLT increases, as demonstrated in Table 1.

Table 1. Cohort Initiation/Toxicity Risk

True Risk of Toxicity	.10	.20	.30	.40	.50	.60
Probability of Cohort Initiation	.88	.66	.42	.23	.11	.04

Within each cohort of 6 subjects, the confidence interval of estimating the incidence of AEs of special interest (i.e., symptomatic and/or irreversible treatment-related Grade 4 pneumonitis, colitis, dermatitis, or hepatitis or any symptomatic treatment-related related Grade ≥ 3 neurological toxicity or uveitis) are provided in Table 2.

Table 2. Confidence Intervals

Number of Subjects with Event	Incidence	95% Exact Confidence Interval (Clopper Pearson)
1/6	0.17	(0.004, 0.64)
2/6	0.33	(0.04, 0.77)
3/6	0.50	(0.12, 0.88)
4/6	0.67	(0.22, 0.96)
5/6	0.83	(0.36, 0.99)

3.1.7 Treatment Cohorts and Treatment Schema

The study will consist of 4 cohorts; see Table 3, Figure 1, Figure 2, Figure 3, and Figure 4. Cohort enrollment will be sequential so that Cohort 1 will be treated first, followed by a safety review before each subsequent cohort will be opened. Subjects will not be treated as part of a new cohort until all subjects in the previous cohort have completed the DLT observation period, and there was no more than one DLT observed in the previous cohort (see Section 3.1.9).

The second subject in each cohort should not start treatment until the first subject has completed early engraftment (approximately Day 12 to 18 post ASCT); therefore, the first subject in each cohort will receive the first dose of tremelimumab 75 mg or durvalumab 1500 mg + tremelimumab 75 mg and will be observed for a period of 7 weeks for toxicities before the next subject is enrolled.

The 4 cohorts (see Table 3) are based on subjects receiving tremelimumab 75 mg alone (Cohorts 1 and 2) or durvalumab 1500 mg + tremelimumab 75 mg (Cohorts 3 and 4) prior to and for 2 cycles post autologous stem cell transplant (ASCT) as well as 2 different schedules of post ASCT therapy (late [Cohorts 1 and 3] and early [Cohorts 2 and 4]) as described below.

Subjects in each cohort will receive a single dose of tremelimumab 75 mg alone (Cohorts 1 and 2) or a single dose of durvalumab 1500 mg + tremelimumab 75 mg (Cohorts 3 and 4) on Day -31. The first dose is given 21 days prior to steady state leukopheresis, which occurs on Day -10 to Day -3 for the collection of autologous peripheral blood lymphocytes (PBLs).

Note: a dose of Pevnar-13 will be given on Day -33 \pm 2 days; however, the Pevnar-13 dose and the tremelimumab 75 mg dose on Day -31 must be separated by a minimum of 48 hours). Two

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additional doses of Prevnar-13 will be given during the period following HDT/ASCT according to flowchart in Section 3.2.

Leukopheresis will be followed by high dose therapy (HDT, melphalan 200 mg/m² IV according to institution practice) on Day -2 and autologous stem cell transplant (ASCT), using previously banked hematopoietic stem cells, on Day 0 of the study.

Autologous PBLs will be infused into subjects on Day +3 following ASCT. A single dose of tremelimumab 75 mg will be administered on the same day (within 24 hours) after the end of the PBL infusion.

Following HDT/ASCT, treatment will resume with tremelimumab 75 mg alone (Cohorts 1 and 2) or durvalumab 1500 mg + tremelimumab 75 mg (Cohorts 3 and 4) for the first 2 cycles post HDT/ASCT according to the following schedule:

- Late Post ASCT Treatment:
 - Cohort 1 - tremelimumab 75 mg alone on Day 100 (±10) and 4 weeks later (Cycles 1 and 2)
 - Cohort 3 — tremelimumab 75 mg+ durvalumab 1500 mg on Day 100 (±10) and 4 weeks later (Cycles 1 and 2)
- Early Post ASCT Treatment:
 - Cohort 2- tremelimumab 75 mg alone on Day 30-40 and Day 100 (±10) (Cycles 1 and 2)
 - Cohort 4 – tremelimumab 75 mg + durvalumab 1500 mg on Day 30-40 and Day 100 (±10) (Cycles 1 and 2)

For Cycles 3 to 8, durvalumab alone (1500 mg Q4W) will continue to be administered for all cohorts. Cycle 3 will start 28 days after Cycle 2 dose, and it will start no later than Day 156 (±4 days) for Cohorts 1 and 3; it will start no later than Day 128 (±4 days) for Cohorts 2 and 4.

Note for durvalumab fixed dosing:

The durvalumab fixed dosing is for subjects who weigh > 30 kg. If a subject's body weight drops to ≤ 30 kg while on the study, the subject will be dosed at 600 mg for durvalumab as long as the body weight remains ≤ 30 kg.

Note for enrollment into Cohorts 2 and 4

For subjects in Cohort 2 or 4, if Day 30 administration of study drug is delayed for >10 days due to extended recovery from transplant related toxicities, then the Cycle 1 dose of study medication can be administered to that subject on Day 100 (±10), at the Investigator's discretion and following a discussion with the Medical Monitor. The timing of further dosing and assessments for that subject should then follow the dosing schema for Cohort 1 or 3, respectively. The subject(s) originally scheduled for Cohort 2 or 4 will be replaced. If this situation occurs for 3 or more subjects in Cohort 2 or 4, the cohort will be considered not feasible and will be closed. If Cohort 2 is deemed not feasible, Cohort 4 will also be considered not feasible.

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Table 3: Tremelimumab and Durvalumab Treatment Schema for Cohorts 1 to 4

Cohorts		Cohort 1 T only and Late Treatment	Cohort 2 T only and Early Treatment	Cohort 3 T + D and Late Treatment	Cohort 4 T + D and Early Treatment
Cycle	Day	Tremelimumab 75 mg only (T)		Tremelimumab 75 mg + Durvalumab 1500 mg (T + D)	
Pre ASCT	Day -31	T	T	T + D	T + D
PBL	Day 3	T + PBL	T + PBL	T + PBL	T + PBL
Cycle 1 Post ASCT	Late Day 100±10	T		T + D	
	Early Day 30-40		T		T + D
Cycle 2 Post ASCT	Late Cycle 1 +28 days	T		T + D	
	Early Day 100±10		T		T + D
Cycles 3 to 8	28 days post Cycle 2	Durvalumab Q4W			

Cohort 1
Post ASCT: Late Tx

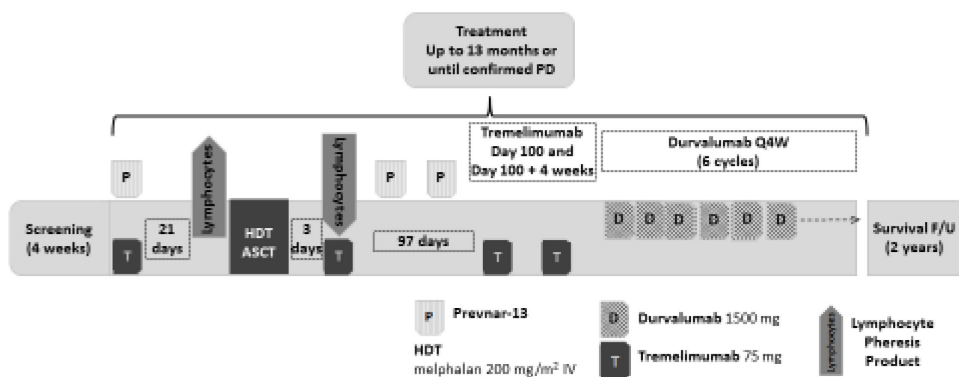


Figure 1: Treatment Schema for Cohort 1

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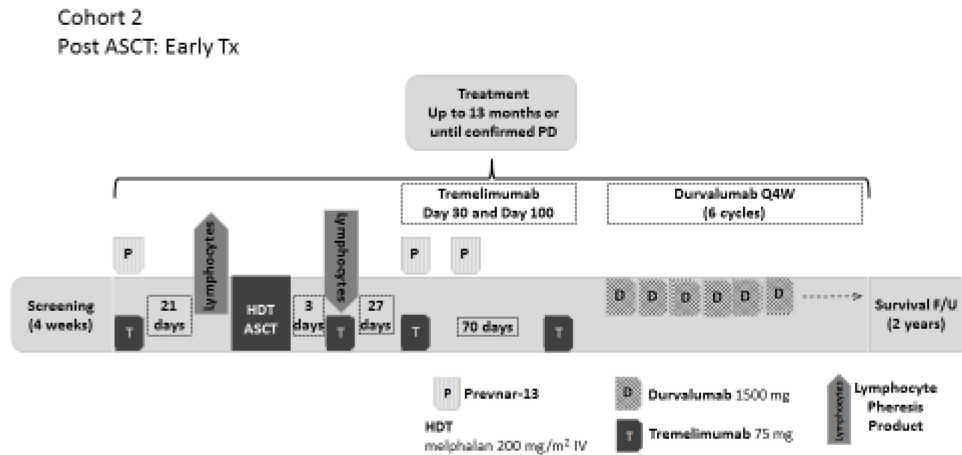


Figure 2: Treatment Schema for Cohort 2

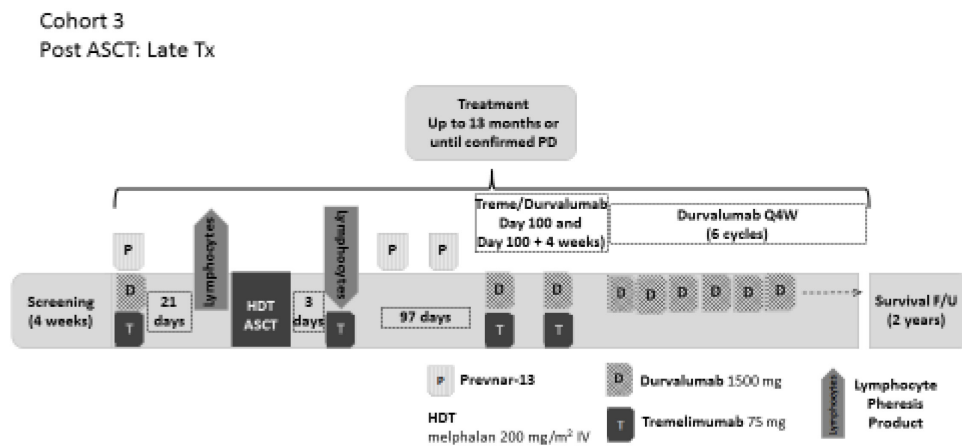


Figure 3: Treatment Schema for Cohort 3

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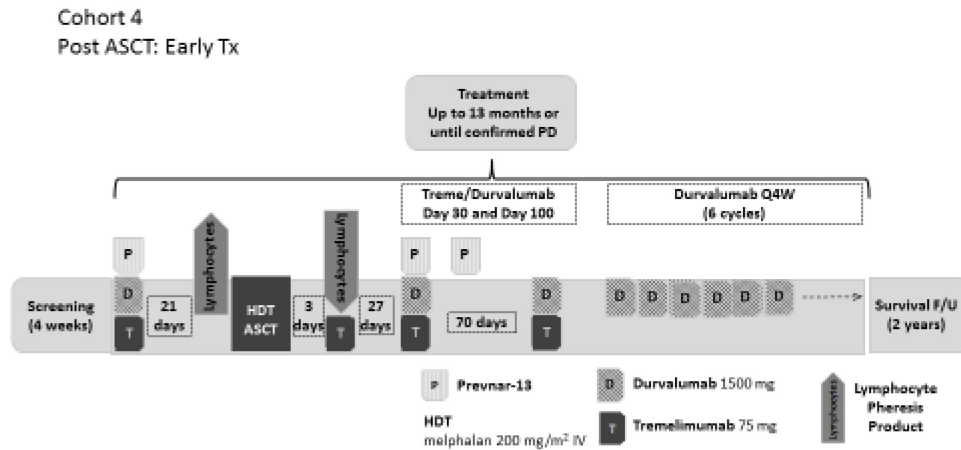


Figure 4: Treatment Schema for Cohort 4

3.1.8 Dosing Adjustments, Delays and Discontinuations

Durvalumab and tremelimumab administration may be modified or discontinued as a result of toxicities as described in Section 8.3.

3.1.9 Dose Limiting Toxicity (DLT) and MTD/RCD

MTD/RCD will not be determined for this study.

There will be an ongoing overall safety assessment according to Section 3.1.14.

DLTs will be assessed for the period from the first study drug administration up to and including the Cycle 2 administration (Day 128 for Cohorts 1 and 3 or Day 100 for Cohorts 2 and 4) of tremelimumab or tremelimumab + durvalumab post ASCT, defined as the **DLT Evaluation Period**, for each subject in Cohorts 1 through 4. Subjects will not be treated as part of a new cohort until all subjects in the previous cohort have completed the DLT Evaluation Period, and there was no more than one DLT observed in the previous cohort. DLTs occurring outside the DLT Evaluation Period will also be evaluated and may impact such decisions.

The occurrence of any of the below toxicities during the DLT Evaluation Period as defined above will be considered a DLT:

- 1) Delayed engraftment: Neutrophil engraftment will be defined as the first of 3 consecutive assessments with absolute neutrophil count $>500/\text{mm}^3$. Platelet engraftment will be defined as the first of 3 consecutive assessments of platelets $>20,000/\text{mm}^3$ without platelet transfusion in the prior 7 days. Engraftment will be considered delayed (and therefore a DLT) if the subject has not met criteria for both neutrophil and platelet engraftment by Day 30 after ASCT.
- 2) Grade 5 toxicity, treatment-related death.
- 3) Grade 4 toxicity, other than hematological toxicity.

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- 4) Grade 3 toxicity, other than hematological toxicity, fever, chills, dyspnea, infection, fatigue, abdominal pain, diarrhea, dysphagia, oral mucositis, oral pain, flu-like syndrome, pain, anorexia, dehydration, glucose intolerance, hypocalcemia, hypokalemia, hypomagnesemia, hyponatremia, hypophosphatemia, pain in extremity, headache, insomnia, hypoxia, dry skin, pruritus, hypertension, and hypotension.
- 5) Isolated Grade 3 electrolyte abnormalities (i.e., those occurring without clinical consequence), except those that resolve, with or without intervention, to <Grade 2 within 72 hours.
- 6) Any immune-related adverse event (irAE) that results in discontinuation from study treatment. See Section 8.3 for irAEs and dose adjustments due to durvalumab and tremelimumab. See Section 7.1.8 for adverse events of special interest.

IrAEs are defined as adverse events (AEs) of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. In the absence of clinical abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

While rules for adjudicating DLTs are specified above, an AE may also be defined as a DLT after consultation with the Sponsor and Investigators, based on the emerging safety profiles of tremelimumab and durvalumab. Likewise, subjects who become not evaluable for DLT, because they discontinued or interrupted treatment due to toxicities other than DLTs, may be counted as DLT subjects, if the toxicities cannot be managed in accordance with the dosing modifications described in Section 3.1.8.

Subjects who experience a DLT will be discontinued from study treatment and will enter the On Study and Post Study Follow-up phases of the study (see Section 3.1.16). However, if it is in the best interest of the subject, the Investigator and Sponsor may agree to continue treatment, possibly at a lower dose level or discontinue one or more of the study drugs.

3.1.10 Subject Withdrawal from Treatment or from Study

A subject will be **withdrawn from study treatment** for any of the following reasons:

1. Withdrawal of consent for further treatment
2. Pregnancy or intent to become pregnant.
3. Confirmation of symptomatic progressive disease by International Myeloma Working Group (IMWG) uniform response criteria. (87, 88) Subjects may be treated beyond asymptomatic progression if the Investigator believes there is potential for clinical benefit and the case is discussed with the Medical Monitor.
4. Significant protocol violation or noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal.
5. Development of intercurrent, non-cancer-related illnesses or complications that prevent either continuation of therapy or regular follow-up.
6. Best medical interest of the subject (at the discretion of the Investigator)

A subject will be **withdrawn from the study** for the following reasons:

1. Best medical interest of the subject at the discretion of the Investigator
2. Initiation of alternative anticancer therapy (marketed or investigational agent).
3. Withdrawal of consent for all follow-up.
4. Lost to follow-up.
5. Death.

Discontinuation from receiving study treatment does not mean that the subject is withdrawn from the study. If applicable, subjects who are withdrawn from study treatment should undergo the planned On Study Follow-up procedures followed by the Post Study follow-up period (see Section 3.2 and Section 3.1.16).

See also Section 8.3 for subject withdrawal from treatment due to necessary dosing interruptions or discontinuations.

Section 7.2.6 provides additional details regarding documentation for early subject withdrawal from study treatment and early withdrawal from study.

3.1.11 Subject Evaluability and Replacement

Subjects are fully evaluable for DLT if they fulfill the criteria for the Per-Protocol Population for DLT Assessment (as defined in Section 4.1.2).

Subjects who are not fully evaluable for DLT per Section 4.1.2 will be replaced.

Note: See Section 3.1.7 note for replacement of subjects in Cohorts 2 and 4 if Day 30 administration of study drug is delayed for >10 days due to extended recovery from transplant related toxicities.

3.1.12 Optional Study Treatment Extension

Treatment extensions beyond what is outlined in the protocol are not planned.

3.1.13 Interim Analysis

No formal interim analysis will be performed. Analyses will be performed to assess safety and tolerability on an ongoing basis throughout the study (Section 3.1.14) and DLTs will be assessed as part of the DLT Evaluation Period (Section 3.1.9).

3.1.14 Safety Monitoring and Study Stopping Rules

In accordance with the Administrative, Legal and Ethical Requirements (Section 7) of the protocol, Safety Monitoring will be performed by an internal data safety monitoring panel, consisting of the Principal Investigators (and co-investigators as needed), the Sponsor Medical Monitor, and drug safety personnel from MedImmune, the providers of the two study drugs. Additional Investigators and staff, or additional Sponsor personnel and consultants, shall participate in reviews as indicated. The safety monitoring panel will communicate by phone and/or email on a regular basis, and in particular, to review the safety of individual cohorts before the next cohort is initiated.

An Independent Data Monitoring Board will not be utilized for this open-label study.

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The study will be suspended and possibly stopped for any of the following reasons:

- (1) Death in any subject in which the cause of death is unexpected and assessed as at least probably related to durvalumab, tremelimumab, and/or PBL reinfusion.
- (2) Severe anaphylactic reaction to durvalumab, tremelimumab, and/or PBL reinfusion (i.e., with respiratory and cardiovascular failure) in any subject.
- (3) Any events that, in the judgment of the Medical Monitor, are deemed serious enough to warrant immediate review by the data safety monitoring panel. This may include any symptomatic and/or irreversible treatment-related grade 4 pneumonitis, colitis, dermatitis, or hepatitis or any symptomatic treatment-related related grade ≥ 3 neurological toxicity or uveitis.
- (4) Any other safety finding that, in the opinion of the internal data safety monitoring panel, contraindicates further dosing of study subjects.
- (5) Any interim findings that, in the opinion of the Investigators and the Sponsor, suggest that the study treatment has no clinical benefit for the subjects.

Study stopping rules may be applied to individual cohorts, if the data safety monitoring panel concludes that the identified risk to one cohort does not carry over to another.

General criteria for premature trial termination are outlined in Section 7.2.7.

3.1.15 Duration of Study

Enrollment Period:	24 months
Duration of Treatment	11 months
Length of Study:	35 months
Post Study Follow-up	24 months from initiation of treatment

End of study is defined as the date of the last protocol-specified visit/assessment for the last subject in the study or the date the study is closed by the Sponsor, whichever occurs first.

3.1.16 On Study and Post Study Follow-up

All subjects, whether they complete the study as planned, discontinue treatment, or prematurely withdraw from the study per Sections 3.1.10 and/or 7.2.6, will be followed according to institutional guidelines in accordance with the usual standard of care principles.

For subjects who complete the study or who discontinue treatment prematurely, On Study Follow-up will be conducted for 90 days after the last study drug administration according to the flowchart in Section 3.2. Refer to Section 7.1.5 for information on recording AEs during the On Study Follow-up.

If the determination is made to remove a subject from treatment at a visit that coincides with the first visit of the On Study Follow-up Period (which is 28 days after the last dose of study treatment), any assessments required in the first On Study Follow-up visit that are not covered as part of the last on-treatment visit (usually correlative labs) should be done as soon as possible. If these assessments cannot be done on the same day, the subject should be brought back in at the earliest opportunity. Any assessments or correlative samples required by both the last on-treatment visit and the first On Study Follow-up visit should not be repeated.

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In addition to the On Study Follow-up, there will be a Post Study Follow-up, during which clinical outcomes data (dates of progression/relapse, subsequent therapy, and survival) will be collected at least once every 6 months for up to 2 years from initiation of treatment.

The Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) during the 90 days since the last administration of study drug.

For subjects who do not continue Post Study Follow-up- at one of the study sites after the end of study, the Principal Investigators or the clinical team, under the supervision of the Principal Investigator, will obtain these data through review of outside records or communication with the subject or his/her physician.

3.1.16.1 End of Study Visit

If a subject is **withdrawn from study** according to the criteria defined in Section 3.1.10, an End of Study visit must be conducted at the time of withdrawal. For subjects who are not yet in On Study Follow-up, this End of Study visit will be the first planned visit of the On Study Follow-up. For subjects who are already in On Study Follow-up, this End of Study visit will be the next planned visit of the On Study Follow-up. However, any procedures/assessments that were done within 7 days of the End of Study visit need not be repeated. All subjects of childbearing potential who withdraw from study must have a serum pregnancy test done at the End of Study visit, unless it was done within 7 days prior to the End of Study Visit.

After the End of Study Visit, the subject will proceed into Post Study Follow-up as described above, unless otherwise unable to do so (e.g., subject withdraws consent for all follow-up).

3.2 Study Flowchart

Study Flowchart for Cohorts 1 and 3 - Late Post Tx Cohorts	Screening / Baseline	Treatment										
		Pre ASCT			HDT /ASCT		PBL	Post ASCT and PBL			Cycle 1	Cycle 2
Treatment weeks (based on ASCT)	-9 to -5				1			2	5	9	14	18
Cycle Day											1	1
Treatment days (based on ASCT)	-62 to -34	-33±2	-31±2	-10 to -3	-2	0	3	12 ±4	30 +10	60±4	100±10	128±4
Study Drugs and PBL Administration												
Tremelimumab (75 mg)			x ¹				x ²				X	X
Durvalumab (1500 mg)			x ⁸								x ⁸	x ⁸
HDT - Melphalan (200 mg/m ² IV)					x							
Autologous Stem cell transplant (ASCT)						x						
Peripheral blood lymphocyte (PBL) pheresis				x								
PBL infusion							x ²					
Prevnar - 13		x ¹							x ¹	x ¹		
Disease Assessments by IMWG uniform response criteria												
FDG PET/CT scan or MRI spine (As clinically indicated to evaluate for plasmacytoma(s) or soft tissue disease)	x										x	
Myeloma serum tests (SPEP, sFLC, Quantitative Igs, Serum IF, beta-2 microglobulin) ⁵	x			x							x	x
Myeloma urine tests (Total protein, Creatinine, UPEP, Urine IF) ⁵ (24-hour as applicable)	x			x							x	x
Study Procedures and Examinations												
Informed Consent (IC) and Eligibility Assessment ⁹	x											
Demographics (incl. DoB; sex; height; race; ethnicity)	x											
Physical Exam (incl. weight)	x	x	x	x	x	x	x	x	x	x	x	x
Medical history	x											
ECOG Performance Status	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs (T, HR, BP, RR) (see Section 6.5 for vital signs during infusion)	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead ECG	x											
ECHO	x											
Pulmonary function test with DLCO	x											
Concomitant Medication (name, indication, dose, route, start & end dates)/Concomitant Procedures	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events (starting or worsening after IC) ¹⁰	x	x	x	x	x	x	x	x	x	x	x	x
Routine Laboratory Samples												
Blood Hematology (complete blood count with differential & platelets & other parameters as clinically indicated; e.g., reticulocytes, blasts, etc.) ³	-40 to -33	x	x	x	x	x	x	x	x	x	x	x
Chemistry (gluc, BUN, creat, Na, K, Ca, Mg, Cl, CO ₂ , protein, alb., Tbil., AST, ALT, LDH, ALP) ³	-40 to -33	x	x	x	x	x	x	x	x	x	x	x
Chemistry cont. (Amylase and lipase) ³	-40 to -33	x	x	x	x	x	x	x	x	x	x	x
Endocrine panel (TSH, Free T3, Free T4, cortisol, ACTH) ³	-40 to -33				x						x	
Coagulation	-40 to -33	x	x	x	x	x	x	x	x	x	x	x
Urinalysis	-40 to -33	x	x	x	x	x	x	x	x	x	x	x
Serum pregnancy test (urine test only on Day -31) ³	-40 to -33		x			x	x				x	x
Bone Marrow Samples												
Trephine biopsy for antigen IHC	x										x	
Immune monitoring (banked BMMCs, flow cytometry, functional assays, immunodiversity)	x										x	
Minimal residual disease testing	x										x	
Whole Blood for Correlative Testing												
PBMC: Immune monitoring (flow cytometry, functional assays, immunodiversity)	x	x ³		x ⁴	x ³			x	x ³	x ³	x ³	x ³
Tumor antigen specific serology		x ³		x ⁴				x	x ³	x ³	x ³	x ³
Pneumococcal serology		x ³		x ⁴				x	x ³	x ³	x ³	x ³
Circulating soluble factors (cytokines, chemokines, auto-antibodies)			x ³					x				x ³
DNA/RNA profiling			x ³					x				x ³
Myeloid Derived Suppressor Cells	x	x ³						x			x ³	x ³
Long-Term Follow-up												
Overall Survival												
Progression Free Survival ⁶												
1. Prevnar dose and tremelimumab dose must be separated by a minimum of 48 hrs.												
2. Tremelimumab must be infused within 24 hours following PBL infusion												
3. Collect pre-dose (prior to drug administration) or other infusion. Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.												
4. Samples will be removed from the pheresis product												
5. If serum and urine IF are positive, subsequent analysis is not necessary unless the subject achieves a response of VGPR or greater												
6. For subjects who did not experience progression while on study												
7. Cycle 3 will start 28 days after Cycle 2 dose, and it will start no later than Day 156 for Cohorts 1 and 3												
8. Pre-ASCT and Cycle 1 and Cycle 2 Durvalumab dose for Cohort 3 only												
9. Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart												
10. See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration												

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Study Flowchart for Cohorts 1 and 3 - Late Post Tx Cohorts (cont)	Treatment						On Study Follow-up			Post Study Follow-up Every 6 months for up to 2 years from start of treatment
	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Last study drug +28 ±4 days	Last study drug +56 ±4 days	Last study drug +91 ±4 days End of Study	
Treatment weeks (based on ASCT)	22	26	30	34	38	42				
Cycle Day	1	1	1	1	1	1				
Treatment days (based on ASCT)	156 ±4	184 ±4	212 ±4	240 ±4	268 ±4	296±4				
Study Drugs and PBL Administration										
Tremelimumab (75 mg)										
Durvalumab (1500 mg)	X ⁷	X	X	X	X	X				
HDT- Melphalan (200 mg/m ² IV)										
Autologous Stem cell transplant (ASCT)										
Peripheral blood lymphocyte (PBL) pheresis										
PBL infusion										
Plevnar - 13										
Disease Assessments by IMWG uniform response criteria										
FDG PET/CT scan or MRI spine (As clinically indicated to evaluate for plasmacytoma(s) or soft tissue disease)							X			
Myeloma serum tests (SPEP, sFLC, Quantitative Igs, Serum IF, beta-2 microglobulin) ⁵	X	X	X	X	X	X	X	X	X	
Myeloma urine tests (Total protein, Creatinine, UPEP, Urine IF) ⁵ (24-hour as applicable)	X	X	X	X	X	X	X	X	X	
Study Procedures and Examinations										
Informed Consent (IC) and Eligibility Assessment ⁹										
Demographics (incl. DoB; sex; height; race; ethnicity)										
Physical Exam (incl. weight)	X	X	X	X	X	X	X	X	X	
Medical history										
ECOG Performance Status	X	X	X	X	X	X	X	X	X	
Vital Signs (T, HR, BP, RR) (see Section 6.5 for vital signs during infusion)	X	X	X	X	X	X	X	X	X	
12-Lead ECG							X			
ECHO										
Pulmonary function test with DLCO										
Concomitant Medication (name, indication, dose, route, start & end dates)/Concomitant Procedures	X	X	X	X	X	X	X	X	X	
Adverse Events (starting or worsening after IC) ¹⁰	X	X	X	X	X	X	X	X	X	
Routine Laboratory Samples										
Blood Hematology (complete blood count with differential & platelets & other parameters as clinically indicated; e.g., reticulocytes, blasts, etc.) ³	X	X	X	X	X	X	X	X	X	
Chemistry (gluc, BUN, creat, Na, K, Ca, Mg, Cl, CO ₂ , protein, alb., Tbili., ALT, AST, LDH, ALP) ³	X	X	X	X	X	X	X	X	X	
Chemistry cont. (Amylase and lipase) ³	X	X	X	X	X	X	X	X	X	
Endocrine panel (TSH, Free T3, Free T4, cortisol, ACTH) ³	X		X				X		X	
Coagulation	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	
Serum pregnancy test (urine test only on Day -31) ³		X		X		X	X		X	
Bone Marrow Samples										
Trephine biopsy for antigen IHC							X			
Immune monitoring (banked BMMCs, flow cytometry, functional assays, immunodiversity)							X			
Minimal residual disease testing							X			
Whole Blood for Correlative Testing										
PBMC: Immune monitoring (flow cytometry, functional assays, immunodiversity)	X ³			X ³		X ³	X	X	X	
Tumor antigen specific serology	X ³			X ³		X ³	X	X	X	
Pneumococcal serology				X ³		X ³	X	X	X	
Circulating soluble factors (cytokines, chemokines, auto-antibodies)	X ³			X ³		X ³	X	X		
DNA/RNA profiling				X ³		X ³				
Myeloid Derived Suppressor Cells	X ³			X ³		X ³	X	X		
Long-Term Follow-up										
Overall Survival										X
Progression Free Survival ⁶										X
1. Plevnar dose and tremelimumab dose must be separated by a minimum of 48 hrs.										
2. Tremelimumab must be infused within 24 hours following PBL Infusion										
3. Collect pre-dose (prior to drug administration) or other infusion. Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.										
4. Samples will be removed from the pheresis product										
5. If serum and urine IF are positive, subsequent analysis is not necessary unless the subject achieves a response of VGPR or greater										
6. For subjects who did not experience progression while on study										
7. Cycle 3 will start 28 days after Cycle 2 dose, and it will start no later than Day 156 for Cohorts 1 and 3										
8. Pre-ASCT and Cycle 1 and Cycle 2 Durvalumab dose for Cohort 3 only										
9. Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart										
10. See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration										

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Study Flowchart for Cohorts 2 and 4 - Early Post Tx Cohorts	Screening / Baseline	Treatment										
		Pre ASCT			HDT /ASCT		PBL			Cycle 1		Cycle 2
Treatment weeks (based on ASCT)	-9 to -5				1		2			5	9	14
Cycle Day												1
Treatment days (based on ASCT)	-62 to -34	-33±2	-31±2	-10 to -3	-2	0	3	12 ±4	30 ±10	60±4		100 ±10
Study Drugs and PBL Administration												
Tremelimumab (75 mg)			x ¹				x ²			X		X
Durvalumab (1500 mg)			X ⁸							X ⁸		X ⁸
HDT- Melphalan (200 mg/m ² IV)					x							
Autologous Stem cell transplant (ASCT)						x						
Peripheral blood lymphocyte (PBL) pheresis				x								
PBL infusion							x ²					
Plevnar - 13		x ¹								x ¹	x ¹	
Disease Assessments by IMWG uniform response criteria												
FDG PET/CT scan or MRI spine (As clinically indicated to evaluate for plasmacytoma(s) or soft tissue disease)	x											x
Myeloma serum tests (SPEP, sFLC, Quantitative Igs, Serum IF, beta-2 microglobulin) ⁵	x			x								x
Myeloma urine tests (Total protein, Creatinine, UPEP, Urine IF) ⁵ (24-hour as applicable)	x			x								x
Study Procedures and Examinations												
Informed Consent (IC) and Eligibility Assessment ⁹	x											
Demographics (incl. DoB; sex; height; race; ethnicity)	x											
Physical Exam (incl. weight)	x	x	x	x	x	x	x	x	x	x	x	x
Medical history	x											
ECOG Performance Status	x	x	x	x	x	x	x	x	x	x	x	x
Vital Signs (T, HR, BP, RR) (see Section 6.5 for vital signs during infusion)	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead ECG	x											
ECHO	x											
Pulmonary function test with DLCO	x											
Concomitant Medication (name, indication, dose, route, start & end dates)/Concomitant Procedures	x	x	x	x	x	x	x	x	x	x	x	x
Adverse Events (starting or worsening after IC) ¹⁰	x	x	x	x	x	x	x	x	x	x	x	x
Routine Laboratory Samples												
Blood Hematology (complete blood count with differential & platelets & other parameters as clinically indicated; e.g., reticulocytes, blasts, etc.) ³	-40 to -33	x	x	x	x	x	x	x	x	x	x	x
Chemistry (gluc, BUN, creat, Na, K, Ca, Mg, Cl, CO ₂ , protein, alb., Tbili., AST, ALT, LDH, ALP) ³	-40 to -33	x	x	x	x	x	x	x	x	x	x	x
Chemistry cont. (Amylase and lipase) ³	-40 to -33	x	x	x	x	x	x	x	x	x	x	x
Endocrine panel (TSH, Free T3, Free T4, cortisol, ACTH) ³	-40 to -33				x							x
Coagulation	-40 to -33	x	x	x	x	x	x	x	x	x	x	x
Urinalysis	-40 to -33	x	x	x	x	x	x	x	x	x	x	x
Serum pregnancy test (urine test only on Day -31) ³	-40 to -33		x			x	x		x			x
Bone Marrow Samples												
Trephine biopsy for antigen IHC	x											x
Immune monitoring (banked BMMCs, flow cytometry, functional assays, immunodiversity)	x											x
Minimal residual disease testing	x											x
Whole Blood for Correlative Testing												
PBMC: Immune monitoring (flow cytometry, functional assays, immunodiversity)	x	x ³		x ⁴	x ³			x	x ³	x ³	x ³	x ³
Tumor antigen specific serology		x ³		x ⁴				x	x ³	x ³	x ³	x ³
Pneumococcal serology		x ³		x ⁴				x	x ³	x ³	x ³	x ³
Circulating soluble factors (cytokines, chemokines, auto-antibodies)			x ³					x				
DNA/RNA profiling			x ³					x				
Myeloid Derived Suppressor Cells	x	x ³						x				x ³
Long-Term Follow-up												
Overall Survival												
Progression Free Survival ⁶												
1. Plevnar dose and tremelimumab dose must be separated by a minimum of 48 hrs.												
2. Tremelimumab must be infused within 24 hours following PBL infusion												
3. Collect pre-dose (prior to drug administration) or other infusion. Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.												
4. Samples will be removed from the pheresis product												
5. If serum and urine IF are positive, subsequent analysis is not necessary unless the subject achieves a response of VGPR or greater												
6. For subjects who did not experience progression while on study												
7. Cycle 3 will start 28 days after Cycle 2 dose, and it will start no later than Day 128 for Cohorts 2 and 4												
8. Pre-ASCT and Cycle 1 and Cycle 2 Durvalumab dose for Cohort 4 only												
9. Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart												
10. See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration												

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Study Flowchart for Cohorts 2 and 4 - Early Post Tx Cohorts (cont)	Treatment						On Study Follow-up			Post Study Follow-up Every 6 months for up to 2 years from start of treatment
	Cycle 3	Cycle 4	Cycle 5	Cycle 6	Cycle 7	Cycle 8	Last study drug +28 ±4 days	Last study drug +56 ±4 days	Last study drug +91 ±4 days End of Study	
Treatment weeks (based on ASCT)	18	22	26	30	34	38				
Cycle Day	1	1	1	1	1	1				
Treatment days (based on ASCT)	128±4	156 ±4	184 ±4	212 ±4	240 ±4	268 ±4				
Study Drugs and PBL Administration										
Tremelimumab (75 mg)										
Durvalumab (1500 mg)	X ⁷	X	X	X	X	X				
HDT - Melphalan (200 mg/m ² IV)										
Autologous Stem cell transplant (ASCT)										
Peripheral blood lymphocyte (PBL) pheresis										
PBL infusion										
Pprevnar -13										
Disease Assessments by IMWG uniform response criteria										
FDG PET/CT scan or MRI spine (As clinically indicated to evaluate for plasmacytoma(s) or soft tissue disease)								X		
Myeloma serum tests (SPEP, sFLC, Quantitative Igs, Serum IF, beta-2 microglobulin) ⁵	X	X	X	X	X	X	X	X	X	
Myeloma urine tests (Total protein, Creatinine, UPEP, Urine IF) ⁵ (24-hour as applicable)	X	X	X	X	X	X	X	X	X	
Study Procedures and Examinations										
Informed Consent (IC) and Eligibility Assessment ⁹										
Demographics (incl. DoB; sex; height; race; ethnicity)										
Physical Exam (incl. weight)	X	X	X	X	X	X	X	X	X	
Medical history										
ECOG Performance Status	X	X	X	X	X	X	X	X	X	
Vital Signs (T, HR, BP, RR) (see Section 6.5 for vital signs during infusion)	X	X	X	X	X	X	X	X	X	
12-Lead ECG							X			
ECHO										
Pulmonary function test with DLCO										
Concomitant Medication (name, indication, dose, route, start & end dates)/Concomitant Procedures	X	X	X	X	X	X	X	X	X	
Adverse Events (starting or worsening after IC) ¹⁰	X	X	X	X	X	X	X	X	X	
Routine Laboratory Samples										
Blood Hematology (complete blood count with differential & platelets & other parameters as clinically indicated; e.g., reticulocytes, blasts, etc.) ³	X	X	X	X	X	X	X	X	X	
Chemistry (gluc, BUN, creat, Na, K, Ca, Mg, Cl, CO ₂ , protein, alb., Tbili., AST, ALT, LDH, ALP) ³	X	X	X	X	X	X	X	X	X	
Chemistry cont. (Amylase and lipase) ³	X	X	X	X	X	X	X	X	X	
Endocrine panel (TSH, Free T3, Free T4, cortisol, ACTH) ³		X		X			X		X	
Coagulation	X	X	X	X	X	X	X	X	X	
Urinalysis	X	X	X	X	X	X	X	X	X	
Serum pregnancy test (urine test only on Day -31) ³		X		X		X	X		X	
Bone Marrow Samples										
Trephine biopsy for antigen IHC								X		
Immune monitoring (banked BMNCs, flow cytometry, functional assays, immunodiversity)								X		
Minimal residual disease testing								X		
Whole Blood for Correlative Testing										
PBMC: Immune monitoring (flow cytometry, functional assays, immunodiversity)	X ³	X ³		X ³		X ³	X	X	X	
Tumor antigen specific serology	X ³	X ³		X ³		X ³	X	X	X	
Pneumococcal serology	X ³			X ³		X ³	X	X	X	
Circulating soluble factors (cytokines, chemokines, auto-antibodies)	X ³	X ³		X ³		X ³	X	X		
DNA/RNA profiling	X ³			X ³		X ³				
Myeloid Derived Suppressor Cells	X ³	X ³		X ³		X ³	X	X		
Long-Term Follow-up										
Overall Survival										X
Progression Free Survival ⁶										X
1. Pprevnar dose and tremelimumab dose must be separated by a minimum of 48 hrs.										
2. Tremelimumab must be infused within 24 hours following PBL infusion										
3. Collect pre-dose (prior to drug administration) or other infusion. Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.										
4. Samples will be removed from the pheresis product										
5. If serum and urine IF are positive, subsequent analysis is not necessary unless the subject achieves a response of VGPR or greater										
6. For subjects who did not experience progression while on study										
7. Cycle 3 will start 28 days after Cycle 2 dose, and it will start no later than Day 128 for Cohorts 2 and 4										
8. Pre-ASCT and Cycle 1 and Cycle 2 Durvalumab dose for Cohort 4 only										
9. Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart										
10. See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration										

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4 Study Objectives and Endpoints

Primary Objectives [Endpoints]	Safety and Tolerability of durvalumab/tremelimumab [DLTs, AEs according to CTCAE version 4.03].
Secondary Objectives [Endpoints]	Clinical efficacy [response by IMWG criteria, minimal residual disease assessment, one-year PFS and OS, 100-day ASCT related mortality].
Exploratory Objective [Endpoints]	Biological Activity [Gene expression, mutation analysis, and protein expression of immune regulation markers of tumor cell populations. Effects of PBL and durvalumab / tremelimumab combination on immune reconstitution, T and B cell receptor diversity, and immune responses to Prevna-13 and myeloma antigens].
DLT=Dose-limiting Toxicity; AE=adverse event; PFS=Progression-free Survival; OS=Overall Survival; CTCAE=National Cancer Institute Common Terminology Criteria for Adverse Events; IMWG=International Myeloma Working Group; ASCT=Autologous stem cell transplant; PBL=Peripheral blood lymphocytes	

In order to be fully evaluable (per protocol) for the primary endpoint, major protocol violations that interfere with the assessment of the primary endpoint must be absent.

4.1 Safety and Tolerability

Assessment of safety and tolerability of the regimens will be performed by the internal data safety monitoring panel on an ongoing basis, based on data review and regular conference calls with the Investigators as described in Section 3.1.14. The safety and tolerability of each regimen will be evaluated using DLT criteria (Section 3.1.9).

4.1.1 Endpoints and Assessment Methods

Clinical laboratory tests, vital sign assessments, physical exams and any other medically indicated assessments and subject interviews will be performed to detect new abnormalities and deteriorations of any pre-existing conditions. The investigator will evaluate any laboratory abnormalities for clinical significance, and clinically significant abnormalities will be recorded as adverse events. All treatment-emergent clinically significant abnormalities and deteriorations that begin or worsen in severity after initial administration of durvalumab and/or tremelimumab should be recorded in the Case Report Forms (CRFs) as AEs and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03. See further adverse event documentation and reporting requirements in Section 7.1.

4.1.2 Subject Evaluation and Statistics

The **Per-Protocol (PP) Population for DLT Assessment** includes:

- All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9)
- All subjects with no DLT who receive at least 75% of the scheduled doses of durvalumab and tremelimumab (according to the respective cohort requirements), receive all associated transplant procedures per standard of care, and undergo respective safety assessments without major protocol violations over the entire DLT Evaluation Period (as defined in Section 3.1.9)

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See Section 3.1.11 for subject evaluability and replacement for DLT assessments.

The **Safety Population** is defined as all subjects who receive at least 1 dose of durvalumab or tremelimumab. The overall analysis of safety and tolerability will be based on the **Safety Population**.

Appropriate summaries of AEs, SAEs, laboratory data and vital signs data will be presented. Adverse events will be coded using the MedDRA dictionary. Incidences of treatment-emergent adverse events (TEAE, those events that started after dosing or worsened in severity after dosing) will be presented overall and by maximum severity and relationship to study medication. Adverse events will be listed individually per subject according to CTCAE version 4.03, and the number of subjects experiencing each AE will be summarized using descriptive statistics.

For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented for the shifts in these categories (i.e., low to normal, low to high, high to low, etc.) from baseline to each post-treatment assessment time point. Additionally, for each continuous hematology and chemistry parameter, descriptive statistics will be presented for the changes from baseline to each post-treatment assessment time point. Descriptive statistics will be presented for the changes in vital signs from baseline to each post-treatment assessment time point.

4.2 Clinical Efficacy

4.2.1 Endpoints and Assessment Methods

Clinical efficacy evaluation will include tumor response assessed by IMWG uniform response criteria for myeloma, 100-day post ASCT mortality rate, minimal residual disease assessment, one-year progression-free survival (PFS), and overall survival (OS).

4.2.1.1 Multiple Myeloma Response Assessment by IMWG Consensus Criteria

Response will be evaluated using the IMWG consensus criteria for uniform response assessments in clinical trials.(87, 88) Tumor Response by IMWG criteria is defined as PR, VGPR, CR or stringent CR. Stable disease is defined as not meeting criteria for response or progression. See Section 8.4 for definitions.

4.2.1.2 100-Day Post Autologous Stem Cell Transplant Mortality Rate

Subjects' survival status will be reported on Day 100 following ASCT.

4.2.1.3 Minimal Residual Disease Assessment

Bone marrow assessments at 100 days and approximately 1-year post ASCT (Day 324 \pm 4 days) will include evaluation of minimal residual disease by flow cytometry and genetic methods as noted in Section 3.2.

4.2.1.4 Progression-Free Survival (PFS)

One-year PFS (Day 324 \pm 4 days) will be determined for each subject with time origin at the start of the ASCT treatment (Day 0) until the first occurrence of confirmed progression by IMWG

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criteria or date of death if the subject dies from any causes before progression. Every effort will be made to follow subjects for progression after the last study drug administration. Long-term follow-up will continue for up to 2 years from start of treatment as described in Section 3.1.16. All four cohorts will be combined when estimating PFS.

4.2.1.5 Overall Survival (OS)

Overall survival (OS) will be measured for each subject with time origin at the start of the ASCT treatment (Day 0) until recorded date of death. Every effort will be made to follow subjects for overall survival after the last study drug administration. Long-term follow-up will continue for up to 2 years from start of treatment as described in Section 3.1.16. All four cohorts will be combined when estimating OS.

4.2.2 Subject Evaluation and Statistics

All subjects who received at least one dose of durvalumab and/or tremelimumab, as well as baseline and at least one post-baseline disease assessment, will be evaluated for clinical efficacy. Tumor Responses by IMWG, PFS, and OS will be summarized and analyzed descriptively.

4.3 Biological Activity

4.3.1 Endpoints and Assessment Methods

Samples for exploratory assessments will be collected at each visit and time points as noted in Section 3.2. Assessments include but may not be limited to the assays listed below.

4.3.1.1 Circulating Soluble Factors (Cytokine Profiling)

Blood samples at baseline and following protocol treatment will be collected for analyses of circulating levels of soluble factors such as CRP, cytokines and chemokines. They may include but are not limited to markers such as soluble CD80/86, soluble IL-6R, VEGF, FGF, IL-1 IL-2, IL-4, IL-6, IL-8, IL-10, soluble CTLA-4, granzyme B, IFN, LARGE, CXCL10, SOCS3, APRIL, BAFF, IGF-1, IGF-2, and autoantibodies to host, tumor, or pneumococcal antigens and explore their association with treatment and clinical outcome.

4.3.1.2 Pneumococcal Serology

Antibody responses to pneumococcal serotypes 1, 3, 4, 6B, 7F, 8, 9V, 14, 18C, 19F, 23F will be measured using a commercially available reagent (Focus Diagnostics, Cypress, CA). Prevnar-13 contains antigen to all serotypes except 8, which allows for an internal negative control for vaccine.

4.3.1.3 PBMC/BMMC Banking

Peripheral Blood Mononuclear Cells (PBMCs), serum, and bone marrow mononuclear cells (BMMC) will be isolated and banked as described below at time points designated in Section 3.2.

Peripheral blood mononuclear cells and bone marrow samples will be collected to assess immune cell phenotypes that may include T cell phenotype and activation markers, B cells,

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myeloid derived suppressor cells and/or immune diversity. These samples may be used to address several key questions:

- The diversity of the immune cell repertoire may be assessed in PBMCs and bone marrow aspirate, if feasible based on VDJ coding region analysis to determine if clinical responses are correlated with immunodiversity and if repertoire changes occur in response to treatment.
- Functional assays such as ELISPOT or tetramer staining or intracellular cytokine analysis may be employed to assess the activation state or antigen specificity of immune cell populations in the periphery.
- Flow cytometric analyses to examine additional markers not included in our primary panel may be performed on banked samples to supplement our understanding of a subject's immune status.

4.3.1.4 Flow cytometry for Immune Reconstitution (Immune monitoring)

Peripheral blood populations before and after treatment, including absolute lymphocyte counts, numbers of T cells, T-cell subsets, NK cells, B cells, and monocytes as well as their cellular phenotypes will be assessed by Flow cytometry to evaluate the association with treatment and subject responses.

4.3.1.5 Bone Marrow Biopsies

Consent for bone marrow biopsies is mandatory for all subjects, if clinically appropriate. Samples will be collected for immunohistochemistry (IHC) and additional correlative markers. Biopsy samples will be examined to evaluate the correlation between clinical activity, the expression level of PD-L1 on myeloma cells and tumor infiltrating macrophages, and tumor-infiltrating lymphocytes changes in biopsies pre and post treatment.

Bone marrow biopsy will be performed during screening and as indicated for subjects in Section 3.2.

Bone marrow samples (collected pre-treatment and/or post treatment) will be examined to evaluate biomarkers by dual color immunohistochemistry (IHC) and genomic techniques. This may include but is not limited to, the expression level and localization of immunosuppressive proteins such as PD-L1 on tumor cells and tumor infiltrating macrophages, tumor infiltrating lymphocytes (TILs), and/or markers of inflammatory/immune cell signatures, e.g. CTLA-4 CD3, CD4, CD8, CD45RO, IFN-gamma, FoxP3, and granzyme B and OX40. Any relationships between biomarker expression with subject response to treatment will be evaluated. Additionally, analyses of tumor mutations and polymorphisms may be performed through relevant methodologies in order to assess genetic alterations and their potential relationships with treatment outcome. Further, selected gene sequencing of samples may be employed to evaluate genetic alterations and relationships with treatment outcome with durvalumab and tremelimumab.

4.3.1.6 Additional translational and exploratory studies

Optional research studies may only be performed for subjects who voluntarily gave their consent for additional correlative research on the informed consent document. Subjects who declined consent to participate in additional translational studies will have their samples

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destroyed at the end of the study. Refusal to participate in this optional research will involve no penalty or loss of benefits to which the subject would otherwise be entitled. Based on the data generated during the study and/or in other studies, not all samples from subjects consenting to this optional research may be utilized.

4.3.1.7 Genomic Profiling

Whole blood samples, bone marrow mononuclear cells, and bone marrow samples will be collected pre/post treatment and preserved for possible future genomic analyses for, but not limited to somatic mutations, expression of tumor antigens, inflammatory cytokines / chemokines, or other factors. These analyses may be conducted to generate hypotheses associated with the mechanisms of action of immunotherapy and/or to identify subsets of subjects responsive to durvalumab and tremelimumab.

4.3.2 Subject Evaluation and Statistics

Only subjects who received at least one dose of tremelimumab (Cohorts 1 and 2) or one dose of both durvalumab and tremelimumab (Cohorts 3 and 4), and provided the baseline and at least one post-treatment sample (if applicable), will be evaluated.

The exploratory pharmacodynamic assessment of the immunologic changes in the bone marrow will include the correlation between clinical activity and the expression level of PD-L1 and tumor-infiltrating lymphocytes (TILs) changes in bone marrow biopsies pre and post treatment. Subjects will be classified as responders or non-responders based on IMWG. Within each response group, subjects' plasma cells will be assessed as positive or negative for PD-L1 expression. For the purpose of this exploratory analysis, Fisher's Exact Test will be used to assess whether there is an association between responder-status and PD-L1 expression. Confidence intervals for the overall odds ratio and the odds ratio within each cohort will be presented. The association between response and TILs changes (increase, decrease, or no change) will be evaluated similarly.

All other exploratory results will be summarized descriptively.

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5 Subject Eligibility

Note: Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart.

5.1 Inclusion Criteria

Eligible subjects **must fulfill** all of the following criteria:

1.	Histologically confirmed multiple myeloma
2.	Measurable disease either at enrollment, prior to most recent line of salvage therapy, or prior to most recent line of induction therapy. Measurable disease is defined by any of the following: <ul style="list-style-type: none">• Serum M-spike ≥ 0.5 g/dL• Serum free light chain ≥ 10mg/dL• Urine monoclonal protein ≥ 200 mg/24 hours• Multifocal plasmacytoma• $\geq 20\%$ bone marrow plasmacytosis
3.	Available CD34+ stem cells ($\geq 2 \times 10^6$ /kg)
4.	Eligible for autologous stem cell transplantation.
5.	Four or less prior lines of systemic therapy for multiple myeloma* *Induction, 1 st ASCT, consolidation, and maintenance are considered 1 line of therapy unless treatment was modified due to progression of disease (POD) as defined by IMWG criteria
6.	Able and willing to provide consent for required bone marrow biopsies.
7.	ECOG performance status of 0-1.
8.	Anticipated lifespan greater than 3 months.
9.	Adequate organ function, as defined below: <ul style="list-style-type: none">• Total bilirubin within normal ranges unless associated with hepatobiliary metastases or Gilbert syndrome, then total bilirubin $\leq 2 \times$ ULN• Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) $\leq 2.5 \times$ ULN• Creatinine ≤ 2.0 mg/dL• DLCO $\geq 50\%$
10.	Have been informed of other treatment options.
11.	Age ≥ 18 years.
12.	Able and willing to give valid written informed consent.
13.	Body weight > 30 kg.

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5.2 Exclusion Criteria

Subjects **may not** enter the study if they fulfill any of the following criteria:

1.	Prior exposure to tremelimumab or durvalumab or other anti-CTLA-4, anti-PD-1, anti-PD-L1 antibodies
2.	History of severe allergic reactions to any unknown allergens or any components of the study drugs.
3.	Active or prior autoimmune disease except for autoimmune thyroiditis, vitiligo, or psoriasis not requiring systemic therapy.
4.	Prior allogeneic transplantation
5.	Any prior Grade \geq 3 immune-related adverse event (irAE) or any prior corticosteroid-refractory irAE.
6.	Known active or chronic viral hepatitis or history of any type of hepatitis within the last 6 months.
7.	History of sarcoidosis syndrome.
8.	Active or history of inflammatory bowel disease (colitis, Crohn's), celiac disease, or other serious, chronic, gastrointestinal conditions associated with diarrhea. Active or history of systemic lupus erythematosus or Wegener's granulomatosis.
9.	Metastatic disease to the central nervous system for which other therapeutic options, including radiotherapy, may be available.
10.	Known immunodeficiency or active HIV.
11.	Other active serious illnesses (e.g., serious infections requiring antibiotics).
12.	Prior treatment in any other clinical trial involving another investigational agent within 4 weeks prior to Day -31 of the study; resolution of respective adverse event to Grade 1 or lower should have occurred. (See Section 5.3.1 for standard of care therapy).
13.	Major surgical procedure (as defined by the Investigator) within 30 days prior to Day -31 or still recovering from prior surgery.
14.	Mental impairment that may compromise the ability to give informed consent and comply with the requirements of the study.
15.	Lack of availability for immunological and clinical follow-up assessments.
16.	Women who are breastfeeding or pregnant as evidenced by positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG)
17.	Female subjects of childbearing potential who are sexually active with a nonsterilized male partner must use at least one <u>highly effective</u> method of contraception (see table below) from the time of screening, and must agree to continue using such precautions for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer). Non-sterilized male partners of a female subject must use male condoms plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

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	<p>Female subjects should refrain from breastfeeding throughout the period described above.</p> <p>Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal.</p> <p>Females will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:</p> <ul style="list-style-type: none"> • Females <50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy). • Females ≥50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy). <p>Women of childbearing potential must have a negative serum b-HCG pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) conducted during screening and a negative urine b-HCG pregnancy test conducted prior to study drug administration on Day -31. Ongoing serum pregnancy tests will be conducted according to the study flowchart in Section 3.2.</p> <p>Nonsterilized male subjects who are sexually active with a female partner of childbearing potential must use male condoms plus spermicide from screening through 90 days after last dose of durvalumab or through 6 months after the last dose of tremelimumab (whichever is longer). Female partners (of childbearing potential) of a male subject must use a <u>highly effective</u> method of contraception (see table below) throughout the period described above. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception.</p> <p>Male subjects should refrain from sperm donation throughout this period.</p> <p><u>Highly effective</u> methods of contraception are described in the table below. A highly effective method of contraception is defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Note that some contraception methods are <u>not</u> considered highly effective (e.g. male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action</p>
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	<p>[excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).</p> <p>Acceptable highly effective methods of contraception are described in the following table:</p> <table border="1"> <tr> <th colspan="2">Highly Effective^a Methods of Contraception</th></tr> <tr> <th>Barrier/Intrauterine Methods</th><th>Hormonal Methods</th></tr> <tr> <td> <ul style="list-style-type: none"> • Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena[®])^b </td><td> <ul style="list-style-type: none"> • “Implants”: Etonogestrel-releasing implants: e.g., Implanon[®] or Norplan[®] • “Intravaginal Devices”: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g., NuvaRing[®] • “Injection”: Medroxyprogesterone injection: e.g., Depo-Provera[®] • “Combined Pill”: Normal and low dose combined oral contraceptive pill • “Patch”: Norelgestromin / ethinylestradiol-releasing transdermal system: e.g., Ortho Evra[®] • “Minipill^c”: Progesterone based oral contraceptive pill using desogestrel: e.g., Cerazette[®] </td></tr> <tr> <td colspan="2"> <p>a - Highly effective (i.e. failure rate of <1% per year)</p> <p>b - This is also considered a hormonal method</p> <p>c - Cerazette[®] is currently the only highly effective progesterone based pill</p> </td></tr> </table>	Highly Effective ^a Methods of Contraception		Barrier/Intrauterine Methods	Hormonal Methods	<ul style="list-style-type: none"> • Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena[®])^b 	<ul style="list-style-type: none"> • “Implants”: Etonogestrel-releasing implants: e.g., Implanon[®] or Norplan[®] • “Intravaginal Devices”: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g., NuvaRing[®] • “Injection”: Medroxyprogesterone injection: e.g., Depo-Provera[®] • “Combined Pill”: Normal and low dose combined oral contraceptive pill • “Patch”: Norelgestromin / ethinylestradiol-releasing transdermal system: e.g., Ortho Evra[®] • “Minipill^c”: Progesterone based oral contraceptive pill using desogestrel: e.g., Cerazette[®] 	<p>a - Highly effective (i.e. failure rate of <1% per year)</p> <p>b - This is also considered a hormonal method</p> <p>c - Cerazette[®] is currently the only highly effective progesterone based pill</p>	
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<p>a - Highly effective (i.e. failure rate of <1% per year)</p> <p>b - This is also considered a hormonal method</p> <p>c - Cerazette[®] is currently the only highly effective progesterone based pill</p>									
18.	Any condition that, in the clinical judgment of the treating physician, is likely to prevent the subject from complying with any aspect of the protocol or that may put the subject at unacceptable risk.								
19.	Subjects must not donate blood while on study and for at least 90 days following the last durvalumab treatment or for 6 months following the last tremelimumab treatment, whichever is longer.								

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5.3 Restrictions on Concomitant Therapies

5.3.1 Non-Permitted Concomitant Therapies

Subjects ***may not*** receive the following concomitant therapies during the study:

1.	Systemic treatment with high dose corticosteroids (greater than Prednisone 10 mg daily or equivalent) or other immunosuppressive treatments (e.g. methotrexate, chloroquine, azathioprine). See Section 5.3.2 for exceptions. Wash-out period: 2 weeks prior to Day -31.
2.	Other cancer therapy (chemotherapy, radiation or immunotherapy). Wash-out period: 4 weeks or 5 half-lives (whichever is shorter) prior to Day -31; 6 weeks for nitrosoureas.
3.	Live/attenuated vaccines 1 month prior to Day -31 and for at least 6 months after the last dose of treatment.
4.	Sunitinib within 3 months after the last dose of tremelimumab.
5.	Palifermin, leuprolide acetate, or denosumab 1 month prior or 1 month after the last treatment on study.
6.	Drugs with laxative properties and herbal or natural remedies for constipation should be avoided through 90 days post last dose of tremelimumab because of the potential for exacerbation of diarrhea.

5.3.2 Permitted Concomitant Therapies

Subjects ***may*** receive the following concomitant therapies during the study:

1.	Inhaled or oral steroids for treating mild to moderate asthma or allergies, or topical steroids for localized (< 10% of body surface area) dermatitis.
2.	Antihistamines and other non-steroidal anti-allergy medication.
3.	Hormone or hormone-related anti-cancer therapy.
4.	Maintenance dose lenalidomide
5.	At the discretion of the Investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, including high dose corticosteroids and TNF-α inhibitors to treat adverse reactions.
All prescription and nonprescription drugs must be recorded in the concomitant medications section of the case report form, listing generic (preferably) or brand name, indication, dose, route and dates of administration. All non-drug therapies must be recorded in the respective sections of the Case Report Form.	

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6 Study Drugs Preparation and Administration

All study drugs are manufactured in accordance with Good Manufacturing Practices (GMP).

On the days when durvalumab and tremelimumab are to be administered together, durvalumab infusion will start at least 60 minutes after the end of tremelimumab infusion. On study drug administration days, vital sign assessments will be recorded according to the table in Section 6.5.

When Pevnar-13 is given, the Pevnar-13 dose and the tremelimumab dose must be separated by a minimum of 48 hours.

On the day of PBL infusion (Day 3 after ASCT), tremelimumab will be infused over a minimum of 60 ± 5 minutes after the end of the PBL infusion (within 24 hours).

6.1 Durvalumab (MEDI4736)

Durvalumab is supplied by the Sponsor. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose will be supplied by each site. See Section 7.2.8 for additional details.

6.1.1 Study Drug Information

Manufacturer	MedImmune		
Expiration/Retest Date	<i>Expiration/retest dates are documented in the QA Disposition of Investigational Medicinal Product (IMP) Report.</i>		
Container Description	Type: Single use vial	Clear glass	Size: 10 mL
Formulation	Durvalumab for infusion is supplied as a vial liquid solution containing 500 mg (nominal) durvalumab per vial. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0		
Active Ingredient Content	Mass/Weight: 500 mg	Volume: 10 mL	Concentration: 50 mg/mL
Storage Conditions	2°C to 8°C (36°F to 46°F) Do not freeze		
Labeling	Product name, lot number, route of administration, and storage conditions		

6.1.2 Durvalumab Investigational Product Inspection

Each vial of durvalumab selected for dose preparation should be inspected. If there are any defects noted with the investigational product (IP), the Investigator and Sponsor should be notified immediately.

6.1.3 Durvalumab Preparation

Preparation of durvalumab and preparation of the intravenous bag are to be performed aseptically by the IP manager or designated personnel. No incompatibilities between durvalumab and polyvinylchloride or polyolefin copolymers have been observed.

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Dose Calculation:

Subjects will receive a fixed dose of durvalumab: **1500 mg** for subjects > 30 kg. If a subject's body weight drops to ≤ 30 kg while on the study, the subject will be dosed at 600 mg for durvalumab as long as the body weight remains ≤ 30 kg.

The volume of durvalumab (in mL) to be added to the IV bag is calculated as follows:

Volume of Durvalumab (mL)	=	Dose level (mg)	÷	Durvalumab Concentration (nominal 50 mg/mL)
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Dose Preparation:

Durvalumab will be administered using a 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, and delivered through an IV administration set with a 0.2 or 0.22 µm in-line filter. A volume of diluent equal to the calculated volume of durvalumab to be added to the IV bag must be removed from the bag prior to addition of durvalumab. The calculated volume of durvalumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Example: For a 1500 mg dose (for subjects > 30 kg in weight), 30 mL of durvalumab is to be diluted in a 250 mL IV bag. First, 30.0 mL of diluent is removed from the IV bag, and then 30 mL of durvalumab is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted durvalumab is administered as described below.

Durvalumab does not contain preservatives; any unused portion must be discarded.

6.1.4 Durvalumab Administration

Following preparation of the dose, durvalumab will be administered according to the following guidelines:

- A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product(s). Fully functional resuscitation facilities should be available.
- Durvalumab must not be administered via IV push or bolus but as an IV infusion.
- Durvalumab solution should not be infused with other solutions or medications.
- Durvalumab must be administered at room temperature by controlled infusion into a peripheral vein or central line.
- Prior to the start of the infusion, the IV bag contents must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
- The entire contents of the IV bag should be administered as an IV infusion over approximately 60 ± 5 minutes, using a 0.2- or 0.22-µm in-line filter. **An infusion of less than 55 minutes is considered a deviation.**
- After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively,

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the infusion will be completed according to institutional policy to ensure the full dose is administered; documentation is required if the line was not flushed.

- The total time between needle puncture of the durvalumab vial to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion (total infusion time not to exceed 4 hours), the total allowed time for preparation and administration should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.
- The date, start time, interruption, and completion time of durvalumab administration must be recorded in the source documents.
- Subjects will be monitored before, during and after infusion with assessment of vital signs according to Section 6.5.
- See Section 8.3.1 for guidelines for infusion-related reactions.

6.2 Tremelimumab

6.2.1 Study Drug Information

Manufacturer	MedImmune		
Expiration/Retest Date	<i>Expiration/retest dates are documented in the QA Disposition of IMP Report</i>		
Container Description	Type: Single use vial	Material: clear glass	Size: 20 mL
Formulation	Liquid solution containing 400 mg tremelimumab per vial. The solution contains 20 mg/mL tremelimumab, 20 mM histidine/histidine hydrochloride, 222 mM trehalose dihydrate, 0.27 mM disodium edetate dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 5.5.		
Active Ingredient Content	Mass/Weight: 400 mg/vial	Volume: 20 mL	Concentration: 20 mg/mL
Storage Conditions	2°C to 8°C (36°F to 46°F) Do not freeze		
Labeling	Product name, lot number, route of administration, and storage conditions		

6.2.2 Tremelimumab Investigational Product Inspection

Each vial of tremelimumab selected for dose preparation should be inspected. If there are any defects noted with the investigational product (IP), the Investigator and Sponsor should be notified immediately.

6.2.3 Tremelimumab Preparation

The dose of tremelimumab for administration must be prepared by the IP manager or designated personnel using aseptic technique. No incompatibilities between tremelimumab and

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polyvinylchloride or polyolefin have been observed. However, administration sets containing cellulose-based filters should not be used with tremelimumab.

Dose Calculation:

Subjects will receive a fixed dose of tremelimumab: 75 mg.

The volume of tremelimumab (in mL) to be added to the IV bag is calculated as follows:

Tremelimumab Dose (mL)	=	dose level (mg)	÷	Tremelimumab concentration (20 mg/mL)
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Dose Preparation:

Tremelimumab will be administered using a 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter. The calculated volume of tremelimumab is added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

Example: The volume of tremelimumab required for 75 mg dose is 3.75 mL.

The corresponding volume of investigational product should be rounded according to institutional practice. For example, (for a 75 mg dose of tremelimumab), if the institutional practice is to round the volume to the nearest tenth mL, 3.75 mL would be rounded to 3.8 mL, which would be the volume of tremelimumab added to the bag; the bag is then mixed by gentle inversion.

Tremelimumab does not contain preservatives and any unused portion must be discarded.

6.2.4 Tremelimumab Administration

Following preparation of the dose, tremelimumab will be administered according to the following guidelines:

- A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available.
- Prior to the start of the infusion, the IV bag contents must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
- Tremelimumab must be administered at room temperature (25°C) by controlled infusion into a peripheral vein or central line.
- Tremelimumab solution should not be infused with other solutions or medications.
- Tremelimumab must not be administered via IV push or bolus but as a slow IV infusion.
- The entire contents of the IV bag should be administered as an IV infusion over approximately 60 (±5) minutes, using a 0.2, or 0.22-µm in-line filter. **An infusion of less than 55 minutes is considered a deviation.**
- After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively,

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the infusion will be completed according to institutional policy to ensure the full dose is administered; documentation is required if the line was not flushed.

- The total time from needle puncture of the tremelimumab vial to the start of administration should not exceed 4 hours at room temperature or 24 hours at 2 to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion (total infusion time not to exceed 4 hours), the total allowed time for preparation and administration should not exceed 8 hours at room temperature. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.
- The date, start time, interruption, and completion time of tremelimumab administration must be recorded in the source documents.
- Subjects' vital signs will be monitored before, during and after infusion as indicated in Section 6.5.
- See Section 8.3.1 for guidelines for infusion-related reactions.

6.3 Estimated Study Drug Requirements

Estimated drug requirements for the study are summarized in the following table:

<i>Drug</i>	<i>Required Quantity</i>
Durvalumab	540 vials
Tremelimumab	96 vials

6.4 Drug Overdose Management

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in this protocol by >10%. There are no known antidotes available for durvalumab or tremelimumab. Any overdoses with these drugs should be managed symptomatically and reported, with or without associated AEs/SAEs, according to Section 7.1.2.2.

6.5 Monitoring of Tremelimumab and Durvalumab Dose Administration

Subjects will be monitored during and after infusion with assessment of vital signs according to the table below:

Vital Signs Assessment on Study Drug Administration Days					
Drug	Pre Dose	During Infusion	End of Infusion (± 5 minutes)	30 (± 5) Minutes Post Infusion	60 (± 5) Minutes Post Infusion
Tremelimumab	X	Every 30 (± 5) minutes	X		
Durvalumab	X	Every 15 (± 5) minutes	X	X	X

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Note: When durvalumab and tremelimumab are to be administered on the same day, durvalumab infusion will start at least 60 minutes after the end of tremelimumab infusion even though vital signs assessment is not required during the entire 60 minute period post tremelimumab.

If a subject tolerates treatment well for the first 4 doses of durvalumab (i.e., no infusion reactions), subsequent infusions in that subject can be monitored according to the table below. A longer duration of observation after the end of infusion can be used if the Investigator deems it clinically necessary.

Vital Signs Assessment on study drug administration days (after first 4 doses)	Pre Dose	During Infusion	End of Infusion (± 5 minutes)	15 (± 5) Minutes Post Infusion
Durvalumab	X	Every 30 (± 5) minutes	X	X

C O N F I D E N T I A L

7 Administrative, Legal and Ethical Requirements

7.1 Documentation and Reporting of Adverse Events

7.1.1 Definitions

An **Adverse Event (AE)** is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with the treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

N.B.: The definition above, provided for in the GCP-ICH Guideline E6, is being extended for the purpose of Ludwig Institute for Cancer research (LICR) studies to include any events, intercurrent diseases and accidents observed while the subject is on study, i.e., during the actual treatment period, as well as during drug-free, pre- and post-treatment periods, under placebo or in a reference group receiving drug or non-drug therapy or no treatment.

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that:

1. Results in death,
2. Is life-threatening^A,
3. Requires inpatient hospitalization or prolongation of existing hospitalization,
4. Results in persistent or significant disability or incapacity,
5. Is a congenital anomaly / birth defect or
6. Is another medically important condition^B.

A The term “life-threatening” in the definition of “serious” refers to an event in which the subject is at risk of death at the time of the event; it does not refer to an event, which hypothetically might have caused death if it were more severe.

B Medically important conditions that may not result in death, be immediately life-threatening or require hospitalization may be considered as SAE when, based upon appropriate medical judgment, they may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

N.B.: The term “severe” is often used to describe the intensity (severity) of an event (such as: mild, moderate, or severe, e.g., pain). The event itself may be of relatively minor medical significance (such as severe headache). This is not the same as “serious”, which is based on subject/event outcome or action criteria usually associated with events that pose a threat to subject’s life or vital functions. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

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7.1.2 Additional Expedited Reporting Requirements for this Study

For the purpose of this study, the following events must be reported by phone or email to the Sponsor within 24 hours of knowledge of the event (see Section 7.1.6 for Sponsor contact information) **and may result in submission of an SAE based on certain criteria outlined below:**

1. Pregnancy
2. Overdose (as defined in Section 6.4)
3. Hepatic Function Abnormality (as defined in Section 7.1.8)

7.1.2.1 Pregnancy

7.1.2.1.1 Maternal Exposure

Female subjects should avoid becoming pregnant and breastfeeding during the study and for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer).

If a subject becomes pregnant during the course of the study, the study drugs should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the drug under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs (see Section 7.1.6). Elective abortions without complications should not be handled as AEs. The outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) should be followed up and documented even if the subject was discontinued from the study.

If any pregnancy occurs in the course of the study, the Investigator or other site personnel should inform the Sponsor (see Section 7.1.6 for Sponsor contact information) within 1 day, i.e., immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The Sponsor will work with the Investigator to ensure that all relevant information is provided within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

7.1.2.1.2 Paternal Exposure

Male subjects should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer).

Pregnancy of the subject's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject's partner. Therefore, the local study

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team should adopt the generic ICF template in line with local procedures and submit it to the relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

7.1.2.2 Overdose

Any overdose (as defined in Section 6.4) of a study subject, with or without associated AEs/SAEs, is required to be reported **within 24 hours of knowledge of the event** to the Sponsor (see Section 7.1.6 for Sponsor contact information). If the overdose results in an AE, the AE must also be recorded as an AE according to Section 7.1.5. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE according to Section 7.1.6. There is currently no specific treatment in the event of an overdose of durvalumab or tremelimumab. The Investigator will use clinical judgment to treat any overdose. See Section 6.4 for additional details.

7.1.2.3 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 7.1.8) in a study subject, with or without associated clinical manifestations, is required to be reported as “hepatic function abnormal” **within 24 hours of knowledge of the event** to the Sponsor, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed (see Section 7.1.6 for Sponsor contact information).

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the Investigator and evaluated by the Sponsor and MedImmune/AstraZeneca.

7.1.3 Severity of an Adverse Event

The severity of all serious and non-serious adverse events should be assessed according to the National Cancer Institute CTCAE Scale (Version 4.03).

7.1.4 Relationship of Adverse Events to Study Drug

The relationship of all serious and non-serious AEs to the investigational agent(s) will be determined by the Investigator on the basis of his/her clinical judgment, using one of the following terms (in accordance with NCI Guideline “Expedited Adverse Event Reporting Requirements for NCI Investigational Agents”, NCI Cancer Therapy Evaluation Program, January 2001):

Definitely related (The AE is *clearly related* to the investigational agent)

Probably related (The AE is *likely related* to the investigational agent)

Possibly related (The AE *may be related* to the investigational agent)

Unlikely related (The AE is *doubtfully related* to the investigational agent)

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Unrelated (The AE is *clearly not related* to the investigational agent)

N.B.: When making the assessment on causality, it should be taken into consideration that immune-therapeutic agents have the potential to cause very late and/or permanent effects on the immune system, i.e., a causal relationship could exist despite a lack of apparent temporal relationship. Information provided in the IB and/or in “Background” of this protocol may support these evaluations.

7.1.5 General Reporting Requirements

All serious and non-serious adverse events must be documented in the source records and on the respective section of the CRF, regardless of severity or the assumption of a causal relationship. The documentation includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4. This documentation is required for all AEs that occur:

- a. from the date of signing the informed consent, and
- b. until the off-study date or 90 days after the last administration of study drug, whichever is longer, or until a new treatment is initiated (see Section 3.1.10 for subjects who begin other anti-cancer treatment).

Immune Related Adverse Events (irAEs) will be collected from the time of informed consent through 90 days after the last dose of the last study treatment (regardless of initiation of another therapy).

7.1.6 Expedited Serious Adverse Event (SAE) Reporting Requirements

In addition to the General Reporting Requirements specified in Section 7.1.5, all events meeting the criteria for an SAE per Section 7.1.1, irrespective of suspected causation, must be reported by the Investigator to the Sponsor’s Drug Safety Contact (primarily) or, alternatively, to the Primary Sponsor Contact, within 24 hours of becoming aware of the event (see contact information below). SAEs should be reported via the Medidata RAVE data capture system (which utilizes “Safety Gateway”), using the respective Adverse Event and Safety Case Summary eCRFs. This includes any deaths that occur after the off-study date, but within 30 days of last study drug administration. In the event that the SAE cannot be reported via Medidata RAVE, the SAE should be reported using the “Initial Serious Adverse Event Report Form,” provided by the Sponsor.

Note: If an SAE cannot be reported via Medidata RAVE or the “Initial Serious Adverse Event Report Form” within 24 hours of becoming aware of the event, the Sponsor’s Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact, must be contacted by phone or email within 24 hours of becoming aware of the event. In this case, the phone or email notification can then be followed up through Medidata RAVE or an “Initial Serious Adverse Event Report Form” within one working day of the event.

If the “Initial Serious Adverse Event Report Form” is being used, the expedited reports should be directed by fax or e-mail to the Drug Safety Contact (primarily) or, alternatively, the Primary

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Sponsor Contact. Studies utilizing Medidata RAVE (and the “Safety Gateway”), built into the eCRF, and respective SAE reporting procedures, do not require reporting by fax or email. Questions related to Medidata RAVE and “Safety Gateway” procedures should be directed to the Drug Safety Contact or Primary Sponsor Contact (see table below for contact information).

In urgent cases, pre-notification via phone or informal e-mail should be considered.

Drug Safety Contact: [REDACTED] Senior Manager, Drug Safety Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave, 28th Floor New York, New York 10017 [REDACTED]	Primary Sponsor Contact: [REDACTED] Director Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave, 28th Floor New York, New York 10017 [REDACTED]
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Serious adverse events must also be reported by the Principal Investigator to the respective Institutional Review Board after being assigned an SAE tracking number by the Sponsor. Institutional Review Boards may have specific rules on which AEs need to be reported expeditiously, as well as, the time frames for such reporting.

Serious Adverse Event Reports will be evaluated by the Sponsor’s Medical Monitor. Regulatory authorities and other Investigators, as well as institutional and corporate partners, will be informed by the Sponsor as required by ICH guidelines, laws and regulations in the countries where the investigational agent is being administered. In particular, SAEs that are unexpected and for which a causal relationship with the study drug cannot be ruled out, will be reported by the Sponsor within 15 calendar days; if they are life-threatening or fatal, they will be reported within 7 Calendar days.

Serious adverse event reporting to Medimmune/AstraZeneca is described in a separate agreement.

7.1.7 Serious Adverse Event (SAE) Follow-up Requirements

Subjects experiencing SAEs should be followed closely until the condition resolves or stabilizes, and every effort should be made to clarify the underlying cause. Follow-up information related to SAEs must be submitted to the Sponsor as soon as relevant data are available.

7.1.8 Adverse Events of Special Interest (AESIs)

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

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

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

If an AESI also meets SAE criteria, the event will be reported as an SAE per Section 7.1.6.

AESIs observed with durvalumab and tremelimumab and those considered AESIs for the purpose of this study are listed below. Further information on these AESIs (e.g. presenting symptoms) can be found in the current versions of the durvalumab and tremelimumab Investigator's Brochures. Guidelines for the management of subjects experiencing these toxicities can be found in Section 8.3.1 and in the following Medimmune guideline: ***"Medimmune's Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 (durvalumab) Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)."***

- **Colitis**
Diarrhea and colitis are the most commonly observed treatment-emergent AEs following dosing with study medications. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome, if not properly managed.
- **Pneumonitis**
Adverse events of pneumonitis have been observed with anti-PD-1, and anti-PD-L1 antibodies.(89) Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Typically, pulmonary consultation is required.
- **Hepatic Function Abnormality (Hepatotoxicity, Hepatitis)**
Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies.(89) Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin. Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a concurrent or pre-existing disease (e.g.,

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cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Cases where a subject shows an AST **or** ALT $\geq 3 \times$ ULN **or** total bilirubin $\geq 2 \times$ ULN may need to be reported as SAEs. These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

- **Neurotoxicity (Neuropathy/Neuromuscular toxicity)**
Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis.
- **Endocrine Disorders**
Immune-mediated endocrinopathies include hypo- and hyper-thyroidism, adrenal insufficiency, hypophysitis/hypopituitarism and Type 1 diabetes mellitus.
Type 1 diabetes mellitus: For subjects with suspected diabetes mellitus, Investigators should obtain an endocrinology consult and institute appropriate management which may include the administration of insulin.
- **Dermatitis/Rash**
Prompt treatment with steroids (topical or systemic based on severity) is important as per current established toxicity management guidelines.
- **Nephritis and increases in serum creatinine**
A consult with a Nephrologist should be done as well as monitoring for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.). Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., 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.
- **Pancreatic Disorders**
Immune-mediated pancreatitis includes autoimmune pancreatitis (or labs suggestive of pancreatitis); increased serum lipase, increased serum amylase)
- **Hypersensitivity and Infusion Reactions**
Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy.(89) As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of monoclonal antibodies (MAbs) can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

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7.2 Administrative Sponsor Requirements

7.2.1 Study Master Files

The Investigator must retain a Sponsor-specified comprehensive and centralized filing system ("Study Master File") of all trial-related documentation that is suitable for inspection by the Sponsor and regulatory authorities. Upon completion of the trial, the Investigator is required to submit a summary report to the Sponsor.

The Investigator must arrange for the retention of the Study Master File for a period of time determined by the Sponsor. No part of the Study Master File shall be destroyed or relocated without prior written agreement between the Sponsor and the Investigator.

7.2.2 Case Report Form Data Collection

Electronic Case Report Forms (eCRF) will be completed in accordance with respective guidance and after training provided by the Sponsor. The use of eCRFs encompasses electronic data entry, query management and sign-off. Systems used for electronic data capture will be compliant with FDA regulations 21 CFR Part 11 and within the constraints of the applicable local regulatory agency guidelines (whichever provides the greatest protection to the integrity of the data).

All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF.

The Investigator will sign and date the completed eCRF sections. This signature will indicate a thorough inspection of the data in the CRF and will certify its content.

7.2.3 Language

The protocol is written in English. All correspondence between the study site and the Sponsor should be maintained in English. Case Report Forms must be completed in English. All written material to be used by subjects and para-clinical staff must use vocabulary that is clearly understood, and be in the language appropriate for the trial site.

7.2.4 Monitoring

The Sponsor will oversee the conduct of the study and perform clinical monitoring visits for site qualification, site initiation, routine monitoring and site close-out. Clinical Monitors and/or other Sponsor staff will meet with the Investigator staff and require direct access to source data/documents. Such access may also be required for Institutional Review Board review, and regulatory inspection/audits. Direct access is defined as permission to examine, analyze, verify, and reproduce any records and reports that are important to the evaluation of the study. All reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and Sponsor's proprietary information will be exercised.

It is the Clinical Monitor's responsibility to inspect the CRFs at regular intervals throughout the trial to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to GCP guidelines. The Clinical Monitor should have access to subject

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charts, laboratory reports, and other subject records needed to verify the entries on the CRFs (“source data verification”).

7.2.5 Protocol Amendments

Protocol amendments may be implemented only after approval by the Investigator, Sponsor, Institutional Review Board and, if required, the regulatory authorities. Amendments that are intended to eliminate an apparent immediate hazard to subjects may be implemented prior to such approvals; however, in this case, approval must be obtained as soon as possible after implementation. Implementation of administrative amendments that do not affect the safety of the subjects usually do not require prior Institutional Review Board approval, just notification.

When immediate deviation from the protocol is required to eliminate immediate hazard(s) to subjects, the Investigator will contact the Sponsor, if circumstances permit, to discuss the planned course of action. Any departures from the protocol must be fully documented in the source documentation.

7.2.6 Premature Subject Withdrawal from Treatment or from Study

A subject may withdraw from study treatment or from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the study site. Likewise, the Investigator and/or Sponsor have the right to withdraw subjects from treatment or from the study. Specific subject withdrawal criteria are listed in Section 3.1.10. Should a subject (or a subject’s legally authorized representative) decide to withdraw from study treatment or from the study, all efforts will be made to complete the required study procedures and report the treatment observations as thoroughly as possible.

For all subject withdrawals, a complete final evaluation should be made at the time of withdrawal. The appropriate form in the Case Report Form should be completed with an explanation of why the subject is withdrawing, and an attempt should be made to perform a follow-up evaluation.

7.2.7 Early Trial Termination

The Study Sponsor and Investigator have the right to terminate the study early. Specific study stopping rules are listed in Section 3.1.14 (Safety Monitoring and Study Stopping Rules). In such case, one party must notify the other in advance in writing about the intent of and the reasons for the termination. The Investigator must also notify the appropriate Institutional Review Board accordingly.

7.2.8 Study Drug Shipments and Accountability

Study drug shipments will be addressed to the Principal Investigator’s authorized designee, preferably, the site’s pharmacy. The recipient will verify the amount and condition of the drug and will return a signed Acknowledgment of Receipt to the shipper.

A drug dispensing log (inventory) will be kept by the study site, containing at least the following:

- the subject’s identification (subject number and code)
- date and quantity of drug dispensed

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- date and quantity of drug returned to the Investigator/pharmacy (if applicable)
- date and quantity of accidental loss of drug (if any)

These inventories must be made available for inspection by the Clinical Monitor. The Investigator is responsible for seeing to it that all used and unused trial supplies are accounted for. At the end of the study, the Clinical Monitor will also collect the original study drug dispensing records.

At the end of the study, or as directed by the Sponsor, all used and unused supplies, including partially used or empty containers, will be disposed of or transferred as instructed by the Sponsor, and in accordance with local written procedures, if applicable. Any disposal or transfer of investigational agent shall be noted on the investigational drug disposition log and signed by a second person. At the end of the study, the Clinical Monitor will collect the original drug disposition logs.

7.3 Regulatory, Legal and Ethical Requirements

7.3.1 Good Clinical Practice (GCP), Laws and Regulations

The Investigator must ensure that he/she and all authorized personnel for the study are familiar with the principles of Good Clinical Practice (GCP) and that the study is conducted in full conformity with the current revision of the Declaration of Helsinki, ICH Guidelines, and applicable local laws and regulations, with the understanding that local laws and regulations take precedence over respective sections in the Declaration of Helsinki and/or the ICH Guidelines.

7.3.2 Informed Consent

The Investigator must obtain witnessed (if applicable) written Informed Consent from the subject or the subject's legally authorized representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any study procedures are performed. The subject should be given a copy of the Informed Consent documentation. The original signed and dated Informed Consent form must be retained in the study records at the study site, and is subject to inspection by representatives of the Sponsor, or representatives from regulatory agencies.

7.3.3 Institutional Review Board

The Investigator must obtain written approval from the appropriate Institutional Review Board for the protocol and Informed Consent, and all amendments thereof, prior to recruitment of subjects and prior to shipment of investigational agents.

The Investigator must report SAEs to the appropriate Institutional Review Board in accordance with the Institutional Review Board's rules and guidelines (see also Section 7.1).

The Investigator must assure that continuing review (at least once per year) of the study is performed by the Institutional Review Board throughout the duration of the study. If so required by the Institutional Review Board, the Investigator must provide study reports on an annual basis and upon completion of the study.

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All correspondence with, and reports to, the Institutional Review Board must be maintained in the study files at the study site and copies must be sent to the Sponsor.

7.3.4 Subject Confidentiality

The Investigator must ensure that the subject's privacy is maintained. A subject should only be identified by their initials, date of birth and subject number on the CRFs or other documents submitted to the Sponsor. Documents that are not submitted to the Sponsor (e.g., signed Informed Consent form) should be kept in a strictly confidential section of the study file by the Investigator.

The Investigator shall permit the Sponsor and authorized representatives of regulatory agencies to review the portion of the subject's medical record that is directly related to the study. As part of the Informed Consent process, the subject must have given written consent that his/her records will be reviewed in this manner.

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8 Appendices

8.1 Protocol Version History

Original Issue Issue date: 17-DEC-2015 Summary of Changes: not applicable
Amendment 001 Issue date: 16-FEB-2016 Summary of Changes: <ol style="list-style-type: none">1. Synopsis, Section 3.2, Section 4: sample collections and assessments were removed for PK (durvalumab and tremelimumab) ADA (durvalumab and tremelimumab) and sPD-L1.2. Section 3.1.7, next to last paragraph: ± 4 days was added to Day 128 and Day 156.3. Section 3.1.16: The following was added: "The first Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) since the last study visit. If the first Post Study Follow-up is less than 90 days since the last administration of study drug, any irAEs occurring since the last study visit will continued to be collected and be recorded at the subsequent Post Study Follow-up visit."4. Section 3.2:<ol style="list-style-type: none">a. Deleted footnote 5 and re-numbered footnote 9 to footnote 5. This was done due to removal of PK from flowchart.b. Amylase and lipase assessments were added to flowchartc. Study Flowchart for Cohorts 2 and 4: coagulation and urinalysis were added to On Study Follow-up.5. Sections 4.2 (PK), 4.3 (Immunogenicity) and 4.5.1.1 (sPD-L1) were deleted, and other sections were re-numbered as appropriate.6. Section 7.1.7: The phrase "using the "SAE Follow-up Report form", provided by the Sponsor" was deleted; directions are provided in the previous section.7. Section 8.3.1:<ol style="list-style-type: none">a. Deleted paragraph, which referenced the package inserts for ipilimumab, nivolumab, and pembrolizumab.b. MED4736 was changed to durvalumab in the table.8. General spelling, capitalization, grammatical and formatting changes were implemented, as needed.
Amendment 002 Issue date: 16-MAR-2016 Summary of Changes: <ol style="list-style-type: none">1. Synopsis, Section 3.1, Section 3.1.7, Table 3, Figures 1-4 and Section 3.2, Flowchart: Added doses for durvalumab (1500 mg), tremelimumab (75 mg)2. Synopsis, Section 3.1.7, Figures 1-4, and Section 3.2: added dose regimen for HDT - melphalan (200 mg/m² IV); first occurrence was defined as melphalan 200 mg/m² IV according to institution practice.3. Section 3.1.9: the following changes were made to the DLT criteria:

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- a. Grade 3 toxicity: the exceptions for “rash,” “pneumonitis,” and “increase in AST, ALT, bilirubin, and alkaline phosphatase” were deleted.
 - b. “Isolated Grade 3 electrolyte abnormalities (i.e., those occurring without clinical consequence), except those that resolve, with or without intervention, to <Grade 2 within 72 hours” was added
 - c. “Grade 5 toxicity, treatment-related death” was added.
4. Section 3.1.14, #4: removed the phrase “assessed as related to durvalumab, tremelimumab, and/or PBL reinfusion.”
5. Section 3.1.16: the 5th paragraph was changed **FROM:** “The first Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) since the last study visit. If the first Post Study Follow-up is less than 90 days since the last administration of study drug, any irAEs occurring since the last study visit will continued to be collected and be recorded at the subsequent Post Study Follow-up visit.”
TO: The Post Study Follow-up will include a query to determine if there were any immune-related adverse events (irAEs) during the 90 days since the last administration of study drug.”
6. Section 3.2:
 - a. The following was added to blood hematology blood sample: “.....& other parameters as clinically indicated; e.g., reticulocytes, blasts, etc.”
 - b. Footnote 9 was added: “Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart.”
 - c. Concomitant procedures was added to Concomitant medications line.
 - d. “x” was removed from PFS line at first On Study Follow-up, as it was a misplaced mark.
7. Section 5, Subject Eligibility: The following note was added: “Note: Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart.”
8. Section 5.3.1: Added the following to non-permitted concomitant therapies: “Drugs with laxative properties and herbal or natural remedies for constipation should be avoided through 90 days post last dose of tremelimumab because of the potential for exacerbation of diarrhea.”
9. Section 7.2.2: the following statement was added: “All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF.”
10. Section 8.3.1: Durvalumab and tremelimumab dose modifications for all other AEs (last portion of table) was changed as follows:
 - a. Grade 3 was separated from Grade 2 modifications
 - b. Grade 3 modifications were added: “Hold D and T. If AEs downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume D and T administration at next scheduled dose. Otherwise, discontinue D and T permanently.”
 - c. Grade 4, bullet 2: the phrase “in consultation with the Sponsor” was added
11. Section 8.3.2:
 - a. For Point 2, “7 days or less” was changed to “≤ half the planned dosing interval.”
 - b. For Point 3, “7 days” was changed to “half the planned dosing interval.”

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12. Administrative:

- a. Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.
- b. Monitor and Study Monitor were standardized as “Clinical Monitor” in Sections 7.2.4 and 7.2.8.
- c. List of abbreviations was updated

Amendment 3

Issue date: 28-MAR-2017

Summary of Changes:

1. Section 2 (Study Rationale): the following paragraph was added based on clarification provided by Medimmune/AstraZeneca: “Fixed dosing for durvalumab is recommended only for subjects with > 30kg body weight due to endotoxin exposure. Subjects with a body weight \leq 30 kg are not eligible for enrollment in the current study. If a subject’s body weight drops to \leq 30 kg while on the study, the subject will be dosed according to the details provided in Section 6.1.”
2. Section 3.1.7 (Treatment Cohorts): the following paragraph was added: “**Note for durvalumab fixed dosing:** The durvalumab fixed dosing is for subjects who weigh > 30 kg. If a subject’s body weight drops to \leq 30 kg while on the study, the subject will be dosed at 600 mg for durvalumab as long as the body weight remains \leq 30 kg.”
3. Section 3.1.9 (DLT and MTD/RCD). #1 was changed to clarify the need for 3 consecutive assessments (changes in bold): “Delayed engraftment: Neutrophil engraftment will be defined as the first of 3 consecutive **days assessments** with absolute neutrophil count $>500/\text{mm}^3$. Platelet engraftment will be defined as the first of 3 consecutive **days assessments** of platelets $>20,000/\text{mm}^3$ without platelet transfusion in the prior 7 days. Engraftment will be considered delayed (and therefore a DLT) if the subject has not met criteria for both neutrophil and platelet engraftment by Day 30 after ASCT.
4. Section 3.1.10 (Subject Withdrawal from Treatment/Study): For the “withdrawn from study” category, # 2 was clarified (changes in bold): “Initiation of alternative anticancer therapy **including another (marketed or** investigational agent).”
5. Sections 3.1.11 (Subject Evaluability and Replacement) and 4.1.2 (Subject Evaluation and Statistics) were re-organized to clarify the per-protocol population for DLT evaluation.

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- a. Section 3.11 was changed **FROM**: “Subjects are fully evaluable for DLT if: (1) They experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9), or (2) In the absence of a DLT, they receive at least 75% of the total dose of each study drug, receive all associated transplant procedures per standard of care, and undergo respective safety assessments, without major protocol violations, over the entire DLT evaluation period. Subjects who are not fully evaluable for DLT will be replaced.” **TO**: “Subjects are fully evaluable for DLT if they fulfill the criteria for the Per-Protocol Population for DLT Assessment (as defined in Section 4.1.2). Subjects who are not fully evaluable for DLT per Section 4.1.2 will be replaced.”
- b. Section 4.1.2 was changed **FROM**: “See Section 3.1.11 for subject evaluability and replacement for DLT assessments. In addition, all subjects who receive at least 1 dose of durvalumab or tremelimumab will be assessed for overall safety and tolerability.” **TO**: “The **Per-Protocol (PP) Population for DLT Assessment** includes: (1) All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9); (2) All subjects with no DLT who receive at least 75% of the scheduled doses of durvalumab and tremelimumab (according to the respective cohort requirements), receive all associated transplant procedures per standard of care, and undergo respective safety assessments without major protocol violations over the entire DLT Evaluation Period (as defined in Section 3.1.9)
See Section 3.1.11 for subject evaluability and replacement for DLT assessments. The **Safety Population** is defined as all subjects who receive at least 1 dose of durvalumab or tremelimumab. The overall analysis of safety and tolerability will be based on the **Safety Population**.”
- c. Section 4.1.2: The following paragraph was added: “For each continuous laboratory parameter, results will be categorized as low, normal, or high based on the laboratory normal ranges. Frequencies and percentages will be presented for the shifts in these categories (i.e., low to normal, low to high, high to low, etc.) from baseline to each post-treatment assessment time point. Additionally, for each continuous hematology and chemistry parameter, descriptive statistics will be presented for the changes from baseline to each post-treatment assessment time point. Descriptive statistics will be presented for the changes in vital signs from baseline to each post-treatment assessment time point.”
6. Section 3.1.14 (Safety Monitoring and Study Stopping Rules): Removed Celgene from Safety Review, as Celgene is not involved in this review.
7. Section 3.1.16 (On Study and Post Follow-up): 3rd paragraph was changed (changes in bold): “If the determination is made to remove a subject from treatment at a visit that coincides with the first visit of the On Study Follow-up Period (which is 28 days after the last dose of study treatment), any assessments required in the ~~28-day post-last treatment~~ **first On Study Follow-up** visit that are not covered as part of the **last** on-treatment visit (usually correlative labs) should be done as soon as possible. If these assessments cannot be done on the same day, the subject should be brought back in at the earliest opportunity. Any assessments or correlative samples required by both the **protocol last on-treatment visit** and the ~~28-day post-last treatment~~ **first On Study Follow-up** visit should not be repeated.

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8. Section 3.1.16.1 (End of study Visit): section was added.
9. Section 3.2 (Flowchart):
 - a. Added ECOG PS to On Study Follow up +56 and +91 to align with physical exams.
 - b. Deleted pre-existing conditions from medical history line; this is consistent with current protocols.
 - c. Added Mg to chemistry analytes; it was previously inadvertently omitted.
 - d. Added beta-2 microglobulin to myeloma serum tests
 - e. Added "24-hr as applicable" to myeloma urine tests; deleted N-telopeptide as it is no longer assayed.
 - f. For Cohorts 2 and 4, moved FDG/PET assessment and Bone Marrow samples from first On Study Follow-up to Second On Study Follow-up visit; this was done in order to align the 1-year measurements uniformly at approximately Day 324 post ASCT for Cohorts 1/3 and Cohorts 2/4.
 - g. Added the following note to Footnote 3 "Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing."
 - h. Added Footnote 10: "See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration."
10. Section 4.2.1.4 (PFS): The first sentence was clarified (changes in bold): "One-year PFS (**Day 324 ± 4 days**) will be determined for each subject.
11. Section 5.1 (Inclusion Criteria):
 - a. #2 was clarified (changes in bold): "**Measurable disease either at enrollment, prior to most recent line of salvage therapy, or prior to most recent line of induction therapy.** Measurable disease ~~as is~~ defined by any of the following:"
 - b. #13 was added based on updated requirements from Medimmune/ AstraZeneca: "Body weight > 30 kg."
12. Section 5.2 (Exclusion Criteria):
 - a. #17, Contraception information, was updated based on current recommendations from Medimmune/ AstraZeneca.
 - b. #19, blood donation restriction, was added based on recommendation from Medimmune/AstraZeneca.
13. Section 5.3.2 (Permitted Concomitant Therapies), last sentence was corrected per current standard language (changes in bold): "All non-drug therapies must be recorded in the respective sections of the Case Report Form ~~or as adverse events~~."
14. Section 6 (Study Drug Administration), second sentence was updated per current standard language (changes in bold): "On the days when durvalumab and tremelimumab are to be administered together, durvalumab infusion will start **at least 60** ~~±5~~ minutes after the end of tremelimumab infusion.
15. Sections 6.1 (Durvalumab) and 6.2 (Tremelimumab):
 - a. Entire sections were reorganized and re-written per current Medimmune/ AstraZeneca standard language
 - b. Weight restriction for fixed dosing was added (for durvalumab only)
 - c. 5% dextrose was added as an alternate diluent
 - d. Requirement for an infusion pump was removed
16. Section 6.5 (Monitoring of tremelimumab and durvalumab dose administration). The following note was added: "Note: When durvalumab and tremelimumab are to be

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administered on the same day, durvalumab infusion will start at least 60 minutes after the end of tremelimumab infusion even though vital signs assessment is not required during the entire 60 minute period post tremelimumab.”

17. Section 7.1.2 (Additional Expedited Reporting Requirements for This Study). Paragraph 1 was changed per current standard protocol language **FROM:** “For the purpose of this study, the following events are considered medically important conditions and must be reported in an expedited manner (see Section 7.1.6 for Sponsor contact information:” **TO:** “For the purpose of this study, the following events must be reported by phone or email to the Sponsor within 24 hours of knowledge of the event (see Section 7.1.6 for Sponsor contact information) **and may result in submission of an SAE based on certain criteria outlined below:**”
18. Section 7.1.2.1.1 (Maternal Exposure). The follow paragraph was added: “Female subjects should avoid becoming pregnant and breastfeeding during the study and for 90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer).”
19. Section 7.1.2.1.2 ((paternal Exposure). The first paragraph was updated to current standard language (changes in bold): “Male subjects should refrain from fathering a child or donating sperm during the study and for ~~6 months after the final dose of investigational product~~ **90 days after the last dose of durvalumab or for 6 months after the last dose of tremelimumab (whichever is longer).**”
20. Section 7.1.5 (General Reporting Requirements) was re-written per current standard language; changed **FROM:** “Documentation of serious and non-serious AEs includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4. All serious and non-serious AEs occurring between the date of signing the informed consent and the off-study date must be documented in the source records and on the respective section of the CRF, regardless of the assumption of a causal relationship. During the On Study Follow-up period, all AEs will continue to be documented for 90 days after the last dose of study drug.” **TO:** “All serious and non-serious adverse events must be documented in the source records and on the respective section of the CRF, regardless of severity or the assumption of a causal relationship. The documentation includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as, the causal relationship between the event and the study drug in accordance with Section 7.1.4. This documentation is required for all AEs that occur: (a) from the date of signing the informed consent, and (b) until the off-study date or 90 days after the last administration of study drug, whichever is longer, or until a new treatment is initiated (see Section 3.1.10 for subjects who begin other anti-cancer treatment). Immune Related Adverse Events (irAEs) will be collected from the time of informed consent through 90 days after the last dose of the last study treatment (regardless of initiation of another therapy).”
21. Section 7.1.6 (Expedited SAE Reporting Requirements):
 - a. Primary Sponsor Contact was changed from [REDACTED]
 - b. The following statement was added: “Serious adverse event reporting to Medimmune/AstraZeneca is described in a separate agreement.”
22. Section 7.1.8 (AESI): additional details were added for the AESIs per current recommendations from Medimmune/AstraZeneca.

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23. Section 8.2 (Participating Study Sites, etc). The following details were added:

Participating Study Sites:

[REDACTED]

24. Section 8.3.1 (Durvalumab and Tremelimumab Dose Modification Due to Toxicity).

Updates were made based on current recommendations from Medimmune/AstraZeneca (19Aug2016).

25. Section 8.3.2 (Durvalumab and Tremelimumab Dose Modification Not Due to Treatment-related Toxicities). Section was changed per current standard language **FROM:**

“Durvalumab and tremelimumab administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative reasons, whereby the following rules should apply: (1) If the subject misses 2 consecutive planned doses, the subject should be discontinued from treatment. (2) If the dosing interruption is \leq half the planned dosing interval, the originally planned drug administration should be given. The respective protocol deviation should be documented. (3) If the dosing interruption is greater than half the planned dosing interval, the dosing should be skipped and the next scheduled drug administration should be performed. The respective protocol deviation should be documented. (4) See Section 3.1.7 for details on handling subjects in Cohorts 2 or 4 if Day 30 administration of study drug is delayed for >10 days due to extended recovery from transplant related toxicities. **TO:** “Durvalumab and tremelimumab administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative reasons, whereby the following rules should apply: (1) The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two doses shall be no less than 21 days. All resulting protocol deviations should be documented. (2) If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued. (3) If the dosing interruption is \leq half the planned dosing interval, the originally planned dose should be given and the next dose(s) should be adjusted in accordance with #1, if necessary. (4) If the dosing interruption is greater than half the planned dosing interval, the dose should be skipped and the next dose(s) should be adjusted in accordance with #1, if necessary. (5) See Section 3.1.7 for details on handling subjects in Cohorts 2 or 4 if Day 30 administration of study drug is delayed for >10 days due to extended recovery from transplant related toxicities.

26. Administrative:

- a. Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.
- b. List of abbreviations was updated

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8.2 Participating Study Sites, Investigators and Staff, Laboratories, and Sponsor Information

Participating Study Sites:



Additional information is maintained in the Clinical Study File

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8.3 Dose Adjustments and Delays for Durvalumab and Tremelimumab

8.3.1 Durvalumab and Tremelimumab Dose Modification Due to Toxicity

Durvalumab (MEDI4736) and tremelimumab administration may be modified or discontinued as a result of toxicities as described in the table below.

Additional information and guidance regarding dose modification due to toxicity are provided from MedImmune in the following guideline: ***“MedImmune’s Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy).”***

Dose modifications will not be required for AEs that are clearly not attributed to durvalumab or tremelimumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

Durvalumab (D) and Tremelimumab (T) Dose Modification Due to Toxicity
Note: If D and T dosing is held temporarily until resolution of the event as per instructions below, treatment should resume at the next <u>scheduled</u> treatment date.
<u>Immune-related Adverse Events (irAEs)</u> Immune-related adverse events are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. Maximum supportive care, including immunosuppressive medications, such as high dose steroids, is allowed to induce resolution of the event. However, infliximab should not be used for management of immune-related hepatitis. In addition to the criteria for permanent discontinuation of D and T depicted below, <u>permanently discontinue D and T</u> also for: <ul style="list-style-type: none">Any Grade rash with bullous skin formations.Inability to reduce corticosteroid to a dose of ≤ 10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/regimen.Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing. Grade 1 <ul style="list-style-type: none">In general, no dose modification required.For <i>pneumonitis/interstitial lung disease</i>, consider holding D and T dosing as clinically appropriate and during diagnostic work-up for other etiologies. Grade 2 <ul style="list-style-type: none">In general, hold D and T until resolution to \leq Grade 1 and after the end of any steroid taper, and discontinue D and T permanently if such resolution does not occur within 60 days (30 days for neurotoxicities). Criteria for temporary hold or permanent discontinuation of D and T may differ by event as detailed below.For <i>pneumonitis/interstitial lung disease</i>, the decision to reinitiate D and T upon resolution shall be based upon treating physician’s clinical judgment (as long as the event does not meet DLT criteria).

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Durvalumab (D) and Tremelimumab (T) Dose Modification Due to Toxicity

- For *peripheral neuromotor syndromes*, such as *Guillain-Barre* and *Myasthenia Gravis*, follow general instructions above, but always discontinue D and T permanently if there are signs of respiratory insufficiency or autonomic instability.
- For *endocrinopathies, other than isolated hypothyroidism*, follow general instructions above, but subjects may be retreated if the endocrinopathy is controlled and the subject is clinically stable while requiring steroid doses of ≤ 10 mg/day prednisone equivalent.
- For *isolated hypothyroidism* managed with hormone replacement therapy, and for *sensory neuropathy/neuropathic pain*, holding D and T is at the discretion of the investigator.
- For *elevated creatinine* or *rash*, D and T should be held until resolution to \leq Grade 1 or baseline.
- For *vitiligo*, no dose modification required.

Grade 3

- In general, hold D and T until resolution to \leq Grade 1, and after the end of any steroid taper, and discontinue D and T permanently if such resolution does not occur within 60 days (30 days for neurotoxicities and rash). Criteria for permanent discontinuation of D and T may differ by event as detailed below.
- For *peripheral neuromotor syndromes* (such as *Guillain-Barre* and *Myasthenia Gravis*), apply respective Grade 2 rules.
- For *endocrinopathies*, follow Grade 2 instructions above.
- For *pneumonitis/interstitial lung disease, diarrhea/enterocolitis and elevated serum creatinine* (e.g., *nephritis or renal dysfunction*), always discontinue D and T permanently.
- For *asymptomatic increases of amylase or lipase* levels, hold D and T, and if complete work up shows no evidence of pancreatitis, D and T may be continued.
- For *hepatitis*, discontinue D and T permanently for (1) transaminases or bilirubin not resolving to \leq Grade 1 or baseline within 14 days, (2) transaminases $> 8 \times$ the upper limit of normal (ULN) or bilirubin $> 5 \times$ ULN, or (3) any case meeting Hy's law criteria (as defined in FDA Guidance Document "Drug-Induced Liver Injury").
- For *rash*, M and T should be held until resolution to \leq Grade 1 or baseline.

Grade 4

- In general, discontinue D and T permanently.
- For *endocrinopathies*, follow Grade 2 instructions above.
- For *asymptomatic increases of amylase or lipase* levels, hold D and T, and if complete work up shows no evidence of pancreatitis, D and T may be continued.

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Durvalumab (D) and Tremelimumab (T) Dose Modification Due to Toxicity
<p><u>Infusion-related Reactions</u></p> <p>Grade 1</p> <ul style="list-style-type: none"> The infusion rate of D and T may be decreased 50% or temporarily interrupted until resolution of the event; total infusion time not to exceed 4 hours. Acetaminophen and/or antihistamines may be administered per institutional standards at the discretion of the Investigator. Premedication for subsequent doses should be considered. Steroids should not be used for routine premedication of ≤Grade 2 infusion reactions. <p>Grade 2:</p> <ul style="list-style-type: none"> Same as Grade 1, but consider giving subsequent infusions at 50% of the initial infusion rate; total infusion time not to exceed 4 hours. <p>Grade 3 and 4:</p> <ul style="list-style-type: none"> The infusion must be stopped immediately and treatment permanently discontinued. Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).
<p><u>All other Adverse Events</u></p> <p>Grade 1</p> <ul style="list-style-type: none"> No dose modification required. <p>Grade 2</p> <ul style="list-style-type: none"> Hold D and T until resolution to ≤ Grade 1 or baseline, and discontinue D and T permanently if such resolution does not occur within 60 days. <p>Grade 3</p> <ul style="list-style-type: none"> Hold D and T. If AEs downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume D and T administration at next scheduled dose. Otherwise, discontinue D and T permanently. <p>Grade 4</p> <ul style="list-style-type: none"> In general, discontinue D and T permanently. For isolated lab results, decision to discontinue should be based on accompanying clinical signs/symptoms and per Investigator's clinical judgment in consultation with the Sponsor.

8.3.2 Durvalumab and Tremelimumab Dose Modification Not Due to Treatment-related Toxicities

Durvalumab and tremelimumab administration may be modified or discontinued as a result of events other than toxicity, e.g., intercurrent illness or logistical/administrative reasons, whereby the following rules should apply:

- (1) The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two doses shall be no less than 21 days. All resulting protocol deviations should be documented.

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- (2) If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued.
 - (3) If the dosing interruption is \leq half the planned dosing interval, the originally planned dose should be given and the next dose(s) should be adjusted in accordance with #1, if necessary.
 - (4) If the dosing interruption is greater than half the planned dosing interval, the dose should be skipped and the next dose(s) should be adjusted in accordance with #1, if necessary
 - (5) See Section 3.1.7 for details on handling subjects in Cohorts 2 or 4 if Day 30 administration of study drug is delayed for >10 days due to extended recovery from transplant related toxicities.
- .

8.4 International Myeloma Working Group (IMWG) Criteria for Multiple Myeloma

References: (87, 88)

Table A1.1. IMWG Uniform Response Criteria	
Response Category	Response criteria^a
sCR	CR as defined below plus: normal FLC ratio and absence of clonal cells in bone marrow ^b by immunohistochemistry or immunofluorescence ^c
CR	Negative immunofixation on the serum and urine and disappearance of any soft tissue plasmacytomas and <5% plasma cells in bone marrow ^b
VGPR	Serum and urine M-protein detectable by immunofixation but not on electrophoresis OR ≥ 90% reduction in serum M-protein plus urine M-protein level <100 mg per 24 h
PR	≥50% reduction of serum M-protein and reduction in 24-h urinary M-protein by ≥90% or to <200mg per 24 h. If the serum and urine M-protein are unmeasurable, a ≥50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria ^d If serum and urine M-protein are unmeasurable, and 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 listed criteria, if present at baseline, a ≥50% reduction in the size of soft tissue plasmacytomas is also required
SD (not recommended for use as an indicator of response; stability of disease is best described by providing the time to progression estimates)	Not meeting criteria for CR, VGPR, PR, or progressive disease
<p>Abbreviations: CR, complete response; FLC, free light chain; PR, partial response; SD, stable disease; sCR, stringent complete response; VGPR, very good partial response.</p> <p>a - All response categories require two consecutive assessments made at any time before the institution of any new therapy; all categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. Radiographic studies are not required to satisfy these response requirements.</p> <p>b - Confirmation with repeat bone marrow biopsy not needed.</p> <p>c - Presence/absence of clonal cells is based upon the kappa/lambda ratio. An abnormal kappa/lambda ratio by immunohistochemistry and/or immunofluorescence requires a minimum of 100 plasma cells for analysis. An abnormal ratio reflecting presence of an abnormal clone is kappa/lambda of >4:1 or <1:2.</p> <p>d - Refer to Table A1.3 for definitions of measurable disease.</p>	

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Table A1.2. IMWG Disease Progression and Relapse Definitions	
Relapse Category	Relapse criteria
<p>Progressive disease^a</p> <p>To be used for calculation of time to progression and progression-free survival end points for all subjects including those in CR (includes primary progressive disease and disease progression on or off therapy)</p>	<p>Progressive Disease: requires any <u>one or more</u> of the following:</p> <p>Increase of $\geq 25\%$ from baseline in:</p> <ol style="list-style-type: none"> 1. Serum M-component and/or (the absolute increase must be ≥ 0.5 g/dL)^b 2. Urine M-component and/or (the absolute increase must be ≥ 200 mg/24 h) 3. Only in subjects without measurable serum and urine M-protein levels: the difference between involved and uninvolved FLC levels. The absolute increase must be >10 mg/dL. 4. Bone marrow plasma cell percentage: the absolute % must be $\geq 10\%$^c 5. Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas 6. Development of hypercalcemia (corrected serum calcium >11.5 mg/dL or 2.65 mmol/L) that can be attributed solely to the plasma cell proliferative disorder
Clinical relapse ^a	<p>Clinical relapse requires one or more of:</p> <p>Direct indicators of increasing disease and/or end organ dysfunction (CRAB features)^b It is not used in calculation of time to progression or progression-free survival but is listed here as something that can be reported optionally or for use in clinical practice</p> <ol style="list-style-type: none"> 1. Development of new soft tissue plasmacytomas or bone lesions 2. Definite increase in the size of existing plasmacytomas or bone lesions. A definite increase is defined as a 50% (and at least 1 cm) increase as measured serially by the sum of the products of the cross-diameters of the measurable lesion 3. Hypercalcemia (>11.5 mg/dL) [2.65 mmol/L] 4. Decrease in hemoglobin of ≥ 2 g/dL [1.25 mmol/L] 5. Rise in serum creatinine by 2 mg/dL or more [177 μmol/L or more]
<p>Relapse from CR^a</p> <p>(To be used only if the end point studied is DFS)^d</p>	<p>Any one or more of the following:</p> <ol style="list-style-type: none"> 1. Development of $\geq 5\%$ plasma cells in the bone marrow^c 2. Reappearance of serum or urine M-protein by immunofixation or electrophoresis 3. Appearance of any other sign of progression (i.e., new plasmacytoma, lytic bone lesion, or hypercalcemia)
<p>Abbreviations: CR, complete response; DFS, disease-free survival.</p> <p>a - All relapse categories require two consecutive assessments made at any time before classification as relapse or disease progression and/or the institution of any new therapy.</p> <p>b - For progressive disease, serum M-component increases of ≥ 1 g/dL are sufficient to define relapse if starting M-component is ≥ 5 g/dL.</p> <p>c - Relapse from CR has the 5% cutoff versus 10% for other categories of relapse.</p>	

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d -For purposes of calculating time to progression and progression-free survival, CR subjects should also be evaluated using criteria listed above for progressive disease.

Table A.1.3. IMWG Definitions of Measurable Disease

Response criteria for all categories and subcategories of response except CR are applicable only to subjects who have 'measurable' disease as defined in Section 5.1.

Response criteria for CR are applicable for subjects who have abnormalities on one of the three measurements. Note that subjects who do not meet any of the criteria for measurable disease can only be assessed for stringent CR, and cannot be assessed for any of the other response categories

8.5 Laboratory Procedures

Please refer to the Study Laboratory Manual for information on testing to be done and instructions on specimen handling and logistics.

C O N F I D E N T I A L

8.6 ECOG Performance Status

Eastern Cooperative Oncology Group Performance Status

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

Reference: (90)

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8.7 List of Abbreviations

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
ASCT	autologous stem cell transplant
AST	aspartate aminotransferase
BMMC	Bone marrow mononuclear cells
CBC	Complete Blood Chemistry
CD	Cluster of differentiation
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DC	Dendritic cell
DLT	dose-limiting toxicity
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GMP	Good manufacturing practice
HDT	High dose therapy
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IGSF	Immunoglobulin superfamily
IHC	Immunohistochemistry
IMiD	Immune modulatory drug
IMP	Investigational medicinal product
IMWG	International myeloma working group
IND	Investigational new drug
IP	Investigational product
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	intravenous
LICR	Ludwig Institute for Cancer Research
mAb	Monoclonal antibody
MM	Multiple Myeloma
MTD	maximum tolerated dose

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NSCLC	Non-small cell lung cancer
NK	Natural killer
OS	Overall survival
PBL	Peripheral blood leukocytes
PBMC	Peripheral blood mononuclear cell
PD-1	Programmed death-1
PD-L	Programmed death ligand
POD	Progression of disease
PFS	Progression free survival
Q2W	Every 2 weeks
Q4W	Every 4 weeks
SAE	Serious Adverse Event
SCT	Stem cell transplant
TIL	tumor-infiltrating lymphocyte
ULN	Upper limit of normal
VDJ	variable, diverse, and joining gene segments

9 References

1. Kyle RA, Rajkumar SV. Multiple myeloma. *Blood*. 2008;111(6):2962-72.
2. Morgan GJ, Walker BA, Davies FE. The genetic architecture of multiple myeloma. *Nat Rev Cancer*. 2012;12(5):335-48.
3. Egan JB, Shi CX, Tembe W, Christoforides A, Kurdoglu A, Sinari S, et al. Whole-genome sequencing of multiple myeloma from diagnosis to plasma cell leukemia reveals genomic initiating events, evolution, and clonal tides. *Blood*. 2012;120(5):1060-6.
4. Leung-Hagesteijn C, Erdmann N, Cheung G, Keats JJ, Stewart AK, Reece DE, et al. Xbp1s-negative tumor B cells and pre-plasmablasts mediate therapeutic proteasome inhibitor resistance in multiple myeloma. *Cancer cell*. 2013;24(3):289-304.
5. Chauhan D, Singh AV, Brahmandam M, Carrasco R, Bandi M, Hideshima T, et al. Functional interaction of plasmacytoid dendritic cells with multiple myeloma cells: a therapeutic target. *Cancer cell*. 2009;16(4):309-23.
6. Gorgun G, Calabrese E, Soydan E, Hideshima T, Perrone G, Bandi M, et al. Immunomodulatory effects of lenalidomide and pomalidomide on interaction of tumor and bone marrow accessory cells in multiple myeloma. *Blood*. 2010;116(17):3227-37.
7. Siegel R, Ma J, Zou Z, Jemal A. Cancer statistics, 2014. *CA: a cancer journal for clinicians*. 2014;64(1):9-29.
8. : World Health Organization International Agency for Research on Cancer; 2012. Available from: <http://globocan.iarc.fr/Default.aspx>.
9. Harousseau JL, Dreyling M, Group EGW. Multiple myeloma: ESMO clinical recommendations for diagnosis, treatment and follow-up. *Annals of oncology : official journal of the European Society for Medical Oncology / ESMO*. 2009;20 Suppl 4:97-9.
10. Harousseau JL. Stem cell transplantation in multiple myeloma (0, 1, or 2). *Current opinion in oncology*. 2005;17(2):93-8.
11. Cavo M, Rajkumar SV, Palumbo A, Moreau P, Orlowski R, Blade J, et al. International Myeloma Working Group consensus approach to the treatment of multiple myeloma patients who are candidates for autologous stem cell transplantation. *Blood*. 2011;117(23):6063-73.
12. Koreth J, Cutler CS, Djulbegovic B, Behl R, Schlossman RL, Munshi NC, et al. High-dose therapy with single autologous transplantation versus chemotherapy for newly diagnosed multiple myeloma: A systematic review and meta-analysis of randomized controlled trials. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2007;13(2):183-96.
13. Barlogie B, Kyle RA, Anderson KC, Greipp PR, Lazarus HM, Hurd DD, et al. Standard chemotherapy compared with high-dose chemoradiotherapy for multiple myeloma: final results of phase III US Intergroup Trial S9321. *Journal of clinical oncology : official journal of the American Society of Clinical Oncology*. 2006;24(6):929-36.
14. Atanackovic D, Schilling G. Second autologous transplant as salvage therapy in multiple myeloma. *British journal of haematology*. 2013;163(5):565-72.
15. Gertz MA, Lacy MQ. Salvage autologous stem cell transplant is an effective regimen for relapsed multiple myeloma. *Leukemia & lymphoma*. 2013;54(10):2096-7.
16. Michaelis LC, Saad A, Zhong X, Le-Rademacher J, Freytes CO, Marks DI, et al. Salvage second hematopoietic cell transplantation in myeloma. *Biology of blood and marrow*

transplantation : journal of the American Society for Blood and Marrow Transplantation. 2013;19(5):760-6.

17. Brunet JF, Denizot F, Luciani MF, Roux-Dosseto M, Suzan M, Mattei MG, et al. A new member of the immunoglobulin superfamily--CTLA-4. *Nature*. 1987;328(6127):267-70.
18. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al. Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target. *Proceedings of the National Academy of Sciences of the United States of America*. 2004;101(49):17174-9.
19. Krummel MF, Allison JP. CD28 and CTLA-4 have opposing effects on the response of T cells to stimulation. *The Journal of experimental medicine*. 1995;182(2):459-65.
20. Walunas TL, Lenschow DJ, Bakker CY, Linsley PS, Freeman GJ, Green JM, et al. CTLA-4 can function as a negative regulator of T cell activation. *Immunity*. 1994;1(5):405-13.
21. Brunner MC, Chambers CA, Chan FK, Hanke J, Winoto A, Allison JP. CTLA-4-Mediated inhibition of early events of T cell proliferation. *J Immunol*. 1999;162(10):5813-20.
22. Greenwald RJ, Boussiotis VA, Lorschach RB, Abbas AK, Sharpe AH. CTLA-4 regulates induction of anergy in vivo. *Immunity*. 2001;14(2):145-55.
23. Walunas TL, Bakker CY, Bluestone JA. CTLA-4 ligation blocks CD28-dependent T cell activation. *The Journal of experimental medicine*. 1996;183(6):2541-50.
24. Tivol EA, Borriello F, Schweitzer AN, Lynch WP, Bluestone JA, Sharpe AH. Loss of CTLA-4 leads to massive lymphoproliferation and fatal multiorgan tissue destruction, revealing a critical negative regulatory role of CTLA-4. *Immunity*. 1995;3(5):541-7.
25. Waterhouse P, Penninger JM, Timms E, Wakeham A, Shahinian A, Lee KP, et al. Lymphoproliferative disorders with early lethality in mice deficient in *Ctla-4*. *Science*. 1995;270(5238):985-8.
26. Chambers CA, Kuhns MS, Egen JG, Allison JP. CTLA-4-mediated inhibition in regulation of T cell responses: mechanisms and manipulation in tumor immunotherapy. *Annu Rev Immunol*. 2001;19:565-94.
27. Rudd CE, Taylor A, Schneider H. CD28 and CTLA-4 coreceptor expression and signal transduction. *Immunological reviews*. 2009;229(1):12-26.
28. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. *The EMBO journal*. 1992;11(11):3887-95.
29. Finger LR, Pu J, Wasserman R, Vibhakkar R, Louie E, Hardy RR, et al. The human PD-1 gene: complete cDNA, genomic organization, and developmentally regulated expression in B cell progenitors. *Gene*. 1997;197(1-2):177-87.
30. Shinohara T, Taniwaki M, Ishida Y, Kawaichi M, Honjo T. Structure and chromosomal localization of the human PD-1 gene (PDCD1). *Genomics*. 1994;23(3):704-6.
31. Zhang X, Schwartz JC, Guo X, Bhatia S, Cao E, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. *Immunity*. 2004;20(3):337-47.
32. Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. *Nat Med*. 1999;5(12):1365-9.
33. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. *The Journal of experimental medicine*. 2000;192(7):1027-34.
34. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic

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factors of human ovarian cancer. *Proceedings of the National Academy of Sciences of the United States of America*. 2007;104(9):3360-5.

35. Inman BA, Sebo TJ, Frigola X, Dong H, Bergstralh EJ, Frank I, et al. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. *Cancer*. 2007;109(8):1499-505.
36. Ishida M, Iwai Y, Tanaka Y, Okazaki T, Freeman GJ, Minato N, et al. Differential expression of PD-L1 and PD-L2, ligands for an inhibitory receptor PD-1, in the cells of lymphohematopoietic tissues. *Immunology letters*. 2002;84(1):57-62.
37. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. *Annu Rev Immunol*. 2008;26:677-704.
38. Nakanishi J, Wada Y, Matsumoto K, Azuma M, Kikuchi K, Ueda S. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. *Cancer immunology, immunotherapy : CII*. 2007;56(8):1173-82.
39. Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2007;13(7):2151-7.
40. Ohigashi Y, Sho M, Yamada Y, Tsurui Y, Hamada K, Ikeda N, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2005;11(8):2947-53.
41. Parsa AT, Waldron JS, Panner A, Crane CA, Parney IF, Barry JJ, et al. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. *Nat Med*. 2007;13(1):84-8.
42. Schreiner B, Mitsdoerffer M, Kieseier BC, Chen L, Hartung HP, Weller M, et al. Interferon-beta enhances monocyte and dendritic cell expression of B7-H1 (PD-L1), a strong inhibitor of autologous T-cell activation: relevance for the immune modulatory effect in multiple sclerosis. *Journal of neuroimmunology*. 2004;155(1-2):172-82.
43. Wu C, Zhu Y, Jiang J, Zhao J, Zhang XG, Xu N. Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance. *Acta histochemica*. 2006;108(1):19-24.
44. Yamazaki T, Akiba H, Iwai H, Matsuda H, Aoki M, Tanno Y, et al. Expression of programmed death 1 ligands by murine T cells and APC. *J Immunol*. 2002;169(10):5538-45.
45. Liu J, Hamrouni A, Wolowiec D, Coiteux V, Kuliczowski K, Hetuin D, et al. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN- γ and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. *Blood*. 2007;110(1):296-304.
46. Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. *Nat Immunol*. 2001;2(3):261-8.
47. Tseng SY, Otsuji M, Gorski K, Huang X, Slansky JE, Pai SI, et al. B7-DC, a new dendritic cell molecule with potent costimulatory properties for T cells. *The Journal of experimental medicine*. 2001;193(7):839-46.
48. Bennett F, Luxenberg D, Ling V, Wang IM, Marquette K, Lowe D, et al. Program death-1 engagement upon TCR activation has distinct effects on costimulation and cytokine-driven proliferation: attenuation of ICOS, IL-4, and IL-21, but not CD28, IL-7, and IL-15 responses. *J Immunol*. 2003;170(2):711-8.

CONFIDENTIAL

49. Carter L, Fouser LA, Jussif J, Fitz L, Deng B, Wood CR, et al. PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2. *European journal of immunology*. 2002;32(3):634-43.
50. Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. *Immunological reviews*. 2008;224:166-82.
51. Nurieva R, Thomas S, Nguyen T, Martin-Orozco N, Wang Y, Kaja MK, et al. T-cell tolerance or function is determined by combinatorial costimulatory signals. *The EMBO journal*. 2006;25(11):2623-33.
52. Saunders PA, Hendrycks VR, Lidinsky WA, Woods ML. PD-L2:PD-1 involvement in T cell proliferation, cytokine production, and integrin-mediated adhesion. *European journal of immunology*. 2005;35(12):3561-9.
53. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. *J Immunol*. 2004;173(2):945-54.
54. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. *Proceedings of the National Academy of Sciences of the United States of America*. 2001;98(24):13866-71.
55. Parry RV, Chemnitz JM, Frauwirth KA, Lanfranco AR, Braunstein I, Kobayashi SV, et al. CTLA-4 and PD-1 receptors inhibit T-cell activation by distinct mechanisms. *Molecular and cellular biology*. 2005;25(21):9543-53.
56. Sheppard KA, Fitz LJ, Lee JM, Benander C, George JA, Wooters J, et al. PD-1 inhibits T-cell receptor induced phosphorylation of the ZAP70/CD3zeta signalosome and downstream signaling to PKCtheta. *FEBS letters*. 2004;574(1-3):37-41.
57. Nishimura H, Nose M, Hiai H, Minato N, Honjo T. Development of lupus-like autoimmune diseases by disruption of the PD-1 gene encoding an ITIM motif-carrying immunoreceptor. *Immunity*. 1999;11(2):141-51.
58. Nishimura H, Okazaki T, Tanaka Y, Nakatani K, Hara M, Matsumori A, et al. Autoimmune dilated cardiomyopathy in PD-1 receptor-deficient mice. *Science*. 2001;291(5502):319-22.
59. Brown JA, Dorfman DM, Ma FR, Sullivan EL, Munoz O, Wood CR, et al. Blockade of programmed death-1 ligands on dendritic cells enhances T cell activation and cytokine production. *J Immunol*. 2003;170(3):1257-66.
60. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. *Nat Med*. 2002;8(8):793-800.
61. Konishi J, Yamazaki K, Azuma M, Kinoshita I, Dosaka-Akita H, Nishimura M. B7-H1 expression on non-small cell lung cancer cells and its relationship with tumor-infiltrating lymphocytes and their PD-1 expression. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2004;10(15):5094-100.
62. Thompson RH, Dong H, Kwon ED. Implications of B7-H1 expression in clear cell carcinoma of the kidney for prognostication and therapy. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2007;13(2 Pt 2):709s-15s.
63. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al. Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. *Cancer*. 2005;104(10):2084-91.

CONFIDENTIAL

64. Thompson RH, Kuntz SM, Leibovich BC, Dong H, Lohse CM, Webster WS, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. *Cancer research*. 2006;66(7):3381-5.
65. Wintterle S, Schreiner B, Mitsdoerffer M, Schneider D, Chen L, Meyermann R, et al. Expression of the B7-related molecule B7-H1 by glioma cells: a potential mechanism of immune paralysis. *Cancer research*. 2003;63(21):7462-7.
66. Dorfman DM, Brown JA, Shahsafaei A, Freeman GJ. Programmed death-1 (PD-1) is a marker of germinal center-associated T cells and angioimmunoblastic T-cell lymphoma. *The American journal of surgical pathology*. 2006;30(7):802-10.
67. Rosenwald A, Wright G, Leroy K, Yu X, Gaulard P, Gascoyne RD, et al. Molecular diagnosis of primary mediastinal B cell lymphoma identifies a clinically favorable subgroup of diffuse large B cell lymphoma related to Hodgkin lymphoma. *The Journal of experimental medicine*. 2003;198(6):851-62.
68. Tamura H, Dan K, Tamada K, Nakamura K, Shioi Y, Hyodo H, et al. Expression of functional B7-H2 and B7.2 costimulatory molecules and their prognostic implications in de novo acute myeloid leukemia. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2005;11(16):5708-17.
69. Xerri L, Chetaille B, Serriari N, Attias C, Guillaume Y, Arnoulet C, et al. Programmed death 1 is a marker of angioimmunoblastic T-cell lymphoma and B-cell small lymphocytic lymphoma/chronic lymphocytic leukemia. *Human pathology*. 2008;39(7):1050-8.
70. Iwai Y, Ishida M, Tanaka Y, Okazaki T, Honjo T, Minato N. Involvement of PD-L1 on tumor cells in the escape from host immune system and tumor immunotherapy by PD-L1 blockade. *Proceedings of the National Academy of Sciences of the United States of America*. 2002;99(19):12293-7.
71. Ahmadzadeh M, Johnson LA, Heemskerk B, Wunderlich JR, Dudley ME, White DE, et al. Tumor antigen-specific CD8 T cells infiltrating the tumor express high levels of PD-1 and are functionally impaired. *Blood*. 2009;114(8):1537-44.
72. Fourcade J, Kudela P, Sun Z, Shen H, Land SR, Lenzner D, et al. PD-1 is a regulator of NY-ESO-1-specific CD8+ T cell expansion in melanoma patients. *J Immunol*. 2009;182(9):5240-9.
73. Matsuzaki J, Gnjjatic S, Mhawech-Fauceglia P, Beck A, Miller A, Tsuji T, et al. Tumor-infiltrating NY-ESO-1-specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107(17):7875-80.
74. Wong RM, Scotland RR, Lau RL, Wang C, Korman AJ, Kast WM, et al. Programmed death-1 blockade enhances expansion and functional capacity of human melanoma antigen-specific CTLs. *International immunology*. 2007;19(10):1223-34.
75. Anderson KC, Soiffer R, DeLage R, Takvorian T, Freedman AS, Rabinowe SL, et al. T-cell-depleted autologous bone marrow transplantation therapy: analysis of immune deficiency and late complications. *Blood*. 1990;76(1):235-44.
76. Guillaume T, Rubinstein DB, Symann M. Immune reconstitution and immunotherapy after autologous hematopoietic stem cell transplantation. *Blood*. 1998;92(5):1471-90.
77. Rapoport AP, Aqui NA, Stadtmauer EA, Vogl DT, Fang HB, Cai L, et al. Combination immunotherapy using adoptive T-cell transfer and tumor antigen vaccination on the basis of hTERT and survivin after ASCT for myeloma. *Blood*. 2011;117(3):788-97.

78. Rapoport AP, Stadtmauer EA, Aqui N, Badros A, Cotte J, Chrisley L, et al. Restoration of immunity in lymphopenic individuals with cancer by vaccination and adoptive T-cell transfer. *Nat Med*. 2005;11:1230-7.
79. Cohen AD, Lendvai N, Gnjjatic S, Jungbluth AA, Bertolini S, Pan L, et al., editors. MAGE-A3 Recombinant Protein (recMAGE-A3) Immunotherapy and Autologous Peripheral Blood Lymphocyte (PBL) Infusion Is Safe and Induces Robust Humoral Immune Responses In Multiple Myeloma (MM) Patients Undergoing Autologous Stem Cell Transplantation (autoSCT). American Society of Hematology Annual Meeting; 2013; New Orleans, LA.
80. Rapoport AP, Stadtmauer EA, Aqui N, Vogl D, Chew A, Fang HB, et al. Rapid immune recovery and graft-versus-host disease-like engraftment syndrome following adoptive transfer of Costimulated autologous T cells. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2009;15(13):4499-507.
81. Pardoll DM. The blockade of immune checkpoints in cancer immunotherapy. *Nat Rev Cancer*. 2012;12(4):252-64.
82. Curran MA, Montalvo W, Yagita H, Allison JP. PD-1 and CTLA-4 combination blockade expands infiltrating T cells and reduces regulatory T and myeloid cells within B16 melanoma tumors. *Proceedings of the National Academy of Sciences of the United States of America*. 2010;107(9):4275-80.
83. Mangsbo SM, Sandin LC, Anger K, Korman AJ, Loskog A, Totterman TH. Enhanced tumor eradication by combining CTLA-4 or PD-1 blockade with CpG therapy. *J Immunother*. 2010;33(3):225-35.
84. Rapoport A, Aqui N, Stadtmauer E, et al. Combination immunotherapy after ASCT for multiple myeloma using MAGE-A3/Poly-ICLC immunizations followed by adoptive transfer of vaccine-primed and costimulated autologous T cells. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2014;20:1355-65.
85. Stadtmauer EA, Vogl DT, Luning Prak E, Boyer J, Aqui NA, Rapoport AP, et al. Transfer of influenza vaccine-primed costimulated autologous T cells after stem cell transplantation for multiple myeloma leads to reconstitution of influenza immunity: results of a randomized clinical trial. *Blood*. 2011;117(1):63-71.
86. Rueff J, Medinger M, Heim D, Passweg J, Stern M. Lymphocyte subset recovery and outcome after autologous hematopoietic stem cell transplantation for plasma cell myeloma. *Biology of blood and marrow transplantation : journal of the American Society for Blood and Marrow Transplantation*. 2014;20(6):896-9.
87. Rajkumar SV HJ, Durie B, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. *Blood*. 2011;117(18):4691-5.
88. Durie BG, Harousseau JL, Miguel JS, Blade J, Barlogie B, Anderson K, et al. International uniform response criteria for multiple myeloma. *Leukemia*. 2006;20(9):1467-73.
89. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. *N Engl J Med*. 2012;366(26):2455-65.
90. Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol*. 1982;5(6):649-55.