LUDWIG CANCER RESEARCH	Study Protocol	LUD2013-003 NCT01975831	US IND# 118511
	Amendment 8	FINAL	08-JAN-2019

A Phase 1 Study to Evaluate the Safety and Tolerability of anti-PD-L1, MEDI4736, in combination with tremelimumab in Subjects With Advanced Solid Tumors

Study Synopsis and Objectives

Prior to Amendment 5, this was an open label Phase 1 study of a MEDI4736 and tremelimumab combination, utilizing a 3+3 dose-escalation phase, with doses of MEDI4736 0.3, 1, 3 and 10 mg/kg and tremelimumab 1, 3 and 10 mg/kg (see Figure 2: Dose-escalation Schema), followed by an expansion phase with 6 disease-specific cohorts in subjects with ovarian cancer, colorectal cancer (CRC), non-small cell lung cancer (NSCLC), head and neck cancer, renal cell carcinoma (RCC) and cervical cancer, who are not eligible for, declined or failed standard treatment, treated at the identified maximum tolerated dose (MTD or maximum dose tested).

Per Amendment 5, the disease states of NSCLC and head and neck cancer were removed from the study and were replaced by non-triple negative breast cancer for a total of 5 expansion cohorts. Cohort sample sizes were increased from 12 to 15, for a total of 75 subjects in the expansion phase.

Prior to Amendment 5, MEDI4736 was administered every 2 weeks (Q2W) for 13 cycles. Tremelimumab was administered every 4 weeks (Q4W) for the first 6 cycles and then at Cycle 7, 10 and 13 (every 12 weeks (Q12W)).

Per Amendment 5, the study will continue with enrollment into Cohort 3a and possibly Cohort 4a, with the following modifications:

- Cohort 3a: Tremelimumab, 1mg/kg Q4W for 4 four-week cycles; MEDI4736, 3 mg/kg Q2W for 12 four-week cycles.
- Cohort 4a: Tremelimumab, 75 mg Q4W (for subjects > 30 kg) for 4 four-week cycles; MEDI4736, 1500 mg Q4W (for subjects > 30 kg) for 12 four-week cycles. (Note: fixed dosing will be implemented for Cohort 4a. See Section 3.1.7 for details.)
- Cohorts 4 and 5 were removed from the study

The *primary objective* is to determine the MTD and the safety profile of the MEDI4736 / tremelimumab combination. The *secondary objectives* are to evaluate the pharmacokinetics (PK), immunogenicity of MEDI4736 and tremelimumab, and the antitumor activity of the treatment. The *exploratory objective* is to evaluate the biological activity of the MEDI4736 / tremelimumab combination.

Per Amendment 6, optional treatment extension beyond the original 12- or 13-cycle treatment period (Core Study) will be available for subjects who complete the Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator. See Section 8.8 for details.

Sponsor: Ludwig Institute for Cancer Research, Ltd Sponsor representative Signature and Date	**Study Chair:** [redacted] Study Chair Signature and Date

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1 Background Information

1.1 Advanced Solid Tumors and Immunotherapy

In the United States of America, cancer is the second most common cause of death after heart disease, accounting for nearly 1 in every 4 deaths (American Cancer Society, 2011). The 5-year survival rate for all cancers diagnosed between 1999 and 2006 is 68%, which is 18% higher than the rate reported between 1975 and 1977, likely reflecting progress in diagnosing certain cancers earlier and improvements in treatment (American Cancer Society, 2011). Unfortunately, despite this progress, there continues to be an unmet medical need for more effective and less toxic therapies, especially for patients with advanced disease that do not respond to or have become refractory to existing therapies.

Recent advances in immunotherapy offer promise for improving clinical outcomes in patients with advanced solid tumors. It is increasingly appreciated that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors.(1) Studies in mouse models of transplantable tumors have demonstrated that manipulation of costimulatory or coinhibitory signals can amplify T cell responses against tumors.(2) This may be accomplished by blocking coinhibitory molecules such as Cytotoxic T-Lymphocyte-associated Antigen-4 (CTLA-4) or Programmed Death-1 (PD-1) from binding with their ligands, B7 or B7-H1 (PD-L1). Based upon robust preclinical activity in mouse models, antibodies targeting these coinhibitory molecules have been developed for treatment of human cancers. The human CTLA-4 blocking antibody ipilimumab has demonstrated an overall survival benefit in two Phase 3 studies, and was approved by the FDA for the treatment of advanced melanoma in 2011 (3, 4) and approved in Europe for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy. Additionally, clinical activity for PD-1 blocking and PD-L1 blocking antibodies have been reported from Phase 1 studies.(5, 6)

1.2 CTLA-4

CTLA-4, the canonical coinhibitory receptor, was cloned in 1987. (7) However, it took several years to appreciate the unique role of CTLA-4 in attentuating T cell activation (8-10). CTLA-4 engagement on activated T cells inhibits cytokine synthesis and restricts cell proliferation.(8, 10-13) 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.(14-16) On a cellular level, CTLA-4-mediated inhibition of T cell activion 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 (17)).

1.3 PD-1 and PD-L1

Programmed Death-1 (PD-1, CD279) is a member of the immunoglobulin superfamily (IGSF) of molecules involved in regulation of T cell activation. PD-1 acquired its name 'programmed death' when it was identified in 1992 as a gene upregulated in T cell hybridoma undergoing cell death.(18) 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).(19-21) PD-1 has two binding partners: PD-L1 (B7-H1, CD274) and PD-L2 (B7-DC, CD273), distant relatives of the B7-1 and B7-2 molecules. PD-L1, discovered in 1999, is expressed quite broadly, on both hematopoietic and non-hematopoietic lineages.(22, 23) It is found on T cell, B cells, macrophages, NK 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.(9, 24-35) PD-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. PD-L2 was identified in 2001.(36, 37) 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.(23, 38-42) Inhibitory signaling by PD-1 is thought to depend upon the cytosolic ITSM domain, which associates with phosphatases SHP-1 and SHP-2.(43, 44) While CTLA-4 and PD-1 are both inhibitory receptors, they fulfill distinct roles and mediate their effects through distinct mechanisms.(45) 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.(39, 43, 46) Studies of PD-1 -/- knockout and PD-L -/- knockout mice support unique role for PD-1: PD-L interaction in mediating peripheral tolerance and preventing autoimmunity.(27) 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.(47, 48)

PD-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 NSCLC.(9, 24, 25, 29, 30, 34, 49-54) 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.(28, 55-58) Expression of PD-L has been correlated with prognosis in many these malignancies, fueling the hypothesis that PD-L expression is a mechanism for tumor immune evasion.(50, 52, 53, 59) 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.(60-63) Together, these findings suggest that interrupting PD-1: PD-L interaction could be an effective anti-cancer therapy.

1.4 CTLA-4 blocking antibody tremelimumab

Tremelimumab (formerly CP-675,206) is a human immunoglobulin G2 (IgG2) monoclonal antibody (mAb) being investigated as a cancer immunotherapeutic agent. Tremelimumab is specific for human cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), with no cross-reactivity to related human proteins.

Tremelimumab has been administered as single-agent treatment to subjects participating in 9 clinical studies, 1 of which continues to follow subjects. In total, more than 1,300 subjects with a variety of tumor types have been treated in these studies, including over 1,000 subjects treated with tremelimumab. In addition, 116 subjects with a variety of tumor types have received tremelimumab in combination with other anticancer agents in 5 industry sponsored clinical trials.

Across the clinical development program for tremelimumab, and that of the related anti-CTLA-4 antibody ipilimumab, a pattern of efficacy has emerged that 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 months to years even in subjects with aggressive tumors, such as, refractory metastatic melanoma. Some subjects may have had progression of their disease early in their treatment, with a delayed tumor response or disease stabilization. The CTLA-4 blocking antibody ipilimumab has demonstrated a benefit in OS in two Phase 3 studies of subjects with advanced melanoma. Tremelimumab has also been tested in the Phase 3 setting for advanced melanoma, but, at a dose of 15 mg/kg every 3 months, it failed to demonstrate improved overall survival. The present study is testing an alternative dosing schedule, 10 mg/kg monthly that has been tested in a Phase 2 study. The profile of 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, which appears to be confined to subjects with melanoma). Events reported at a frequency of ≥5% and assessed by the investigator as related to treatment (listed in descending order of frequency) were diarrhea, rash, pruritus, fatigue, nausea, vomiting, anorexia, headache, abdominal pain, and colitis. Infusion-related side effects are rare. Age, gender, baseline hepatic or renal function, and body mass index do not appear to influence the number, type, or severity of AEs observed, although older subjects appear to tolerate diarrhea less well. Acute renal failure was seen in subjects who received the combination of tremelimumab and sunitinib in a Phase 1 study; however, acute renal failure has not been an expected AE for tremelimumab as a single agent in other tumors, and was not seen in a Phase 2 study of ipilimumab in RCC. Of the 132 all-causality deaths among tremelimumab-treated subjects that met the reporting criteria for an SAE (120 in single-agent studies, 7 in combination studies, and 5 in investigator-led research studies), 13 (10 in single-agent studies, 2 in combination studies, and 1 in an investigator-led research study) were due to SAEs judged to be related or possibly related to tremelimumab. The treatment-related deaths were attributed to colitis, colonic/intestinal perforation, diverticular perforation/diverticulitis, pulmonary embolism, pneumonia, septic shock, cardiac arrest, electrolyte imbalance, sudden death, and hemorrhage.

1.5 PD-L1 blocking antibody MEDI4736

MEDI4736 is a human monoclonal antibody of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of B7-H1 (PD-L1, cluster of differentiation [CD]274) to programmed death 1 (PD-1; CD279) and CD80 (B7-1). MEDI4736 is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. MEDI4736 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.

Nonclinical data with MEDI4736 suggest that targeting PD-L1 with a biologic agent could be an effective antitumor therapy. MEDI4736 is a human monoclonal antibody that selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and CD80.

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.

Blockade of PD-L1 with MEDI4736 relieved PD-L1-mediated suppression of human T-cell activation in vitro. In a xenograft model, MEDI4736 inhibited human tumor growth via a T-cell-dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy.

The first-time-in-human (FTIH) study, currently being conducted by MedImmune, is a multicenter, open-label study to evaluate the safety, tolerability, and pharmacokinetics of MEDI4736 in subjects with advanced solid tumors. The study includes a standard 3+3 dose-escalation phase followed by an expansion phase in melanoma, CRC, and NSCLC. Dose escalation began enrollment at 0.1 mg/kg administered by intravenous infusion every 2 weeks. Escalation will continue at dose levels of 0.3, 1, 3, and 10 mg/kg or until a maximum tolerated dose (MTD) or optimal biologic dose (OBD) is determined. Once an MTD or OBD is determined, 20 subjects will be enrolled in each expansion cohort to further evaluate the safety and preliminary antitumor activity of MEDI4736.

The dose-escalation schema of 0.1, 0.3, 1, 3, and 10 mg/kg MEDI4736 in the FTIH monotherapy study was designed to achieve dose levels at which clinical activity may be observed while maintaining an adequate safety margin. The starting dose of 0.1 mg/kg is approximately 1/30 of the maximum recommended starting dose (MRSD). The MRSD was determined based on the no-observed adverse-effect-level (NOAEL) of 100 mg/kg in nonclinical studies in cynomolgus monkeys (US FDA, 2005). The MRSD in a 70-kg individual is 3.2 mg/kg, calculated by applying an allometric scaling factor of 3.1 and a safety factor of 10 to the NOAEL (100 mg/kg).

Following intravenous dosing MEDI4736 exhibited multiphasic pharmacokinetics (PK) and exposure that increased supra proportionally with dose from 0.1 to 1 mg/kg. These findings were consistent with the PK observed in preclinical studies in cynomolgus monkeys. Where evaluable, exposures following multiple doses demonstrated exposures and limited accumulation consistent with the half-lives estimated from the first dose in each group (mean

half-lives of 1.8 (SD 0.3), 2.8 (SD 1) and 7.8 (SD 1.5) days in the 0.1, 0.3 and to 1 mg/kg dose groups respectively).

The FTIH trial, Study 1108 (NCT01693562), is the first clinical study with MEDI4736. As of 09Jun2013, a total of 14 subjects have been enrolled in the dose-escalation phase of the study where MEDI4736 is administered Q2W, including 4 subjects in each of the 0.1 and 0.3 mg/kg cohorts and 3 subjects in each of the 1.0 and 3.0 mg/kg cohorts. One subject in the 0.1 mg/kg cohort was replaced after receiving her 2nd infusion of MEDI4736 during the DLT evaluation period over 4 hours rather than the 60 minutes specified per protocol. In addition, one subject in the 0.3 mg/kg cohort was replaced after discontinuing MEDI4736 treatment due to an unrelated intercurrent illness prior to completing the DLT evaluation period.

Overall, subjects have received from 1 to 16 doses of MEDI4736. One subject (0.1 mg/kg cohort) experienced a dosing interruption due to a Grade 2 infusion-related reaction during administration of Dose 1, although the entire dose was ultimately received. Two additional infusion-related reactions were observed for this subject that did not interrupt dosing. Subsequent doses for this subject were administered with corticosteroid prophylaxis and the subject has received 16 doses of MEDI4736 to date with no further infusion-related reactions. Of the 14 subjects enrolled, 12 subjects have reported at least one AE. The most common AEs were diarrhea (4 subjects); cough, fatigue, nausea, pyrexia (3 subjects each); and bronchitis, dizziness, dyspnea, headache, peripheral edema, upper-airway cough syndrome, and vomiting (2 subjects each). All AEs were Grade 1 or 2 in severity with the exception of a Grade 5 disease progression in a subject in the 0.1 mg/kg cohort (see below). Five subjects experienced treatment-related AEs (i.e., infusion-related reaction, rash, diarrhea, nausea, vomiting, fatigue, dizziness, and pruritus). No subject has experienced a dose-limiting toxicity (DLT) as defined by the protocol.

Three subjects have experienced SAEs; these events were disease progression (0.1 mg/kg cohort) in a subject with non-small cell lung cancer, diarrhea and abdominal pain (0.3 mg/kg cohort) in a subject with colorectal cancer, and pyrexia and pneumonia (0.3 mg/kg cohort) in a subject with non-small cell lung cancer, all of which were assessed by the investigator as not related to MEDI4736. One subject in the 0.1 mg/kg cohort died due to disease progression; a white male with non-small cell lung cancer died on 11Nov2012, 18 days after receiving his third dose of MEDI4736. The event was considered not related to investigational product; disease progression was confirmed through radiographic assessment. No other subjects have discontinued treatment due to an AE.

The dose-escalation committee (which includes MedImmune clinical and safety team members and all participating investigators) reviewed all of the safety data and agreed to escalate to the 10.0 mg/kg dose on 06Jun2013.

Updated safety data for MEDI4736 dose of 10 mg/kg will be made available to the investigators prior to starting cohorts at MEDI4736 10 mg/kg dose level in this study.

See updates per Amendment 5 in Section 2.4.

2 Study Rationale

2.1 Rationale for Combining MEDI4736 and tremelimumab

There is sound rationale for evaluating the combination of MEDI4736 and tremelimumab for the treatment of advanced solid tumors in a Phase 1 dose escalation study. Firstly, the mechanisms of activation of known sites for activity for CTLA-4 and PD-1 are non-redundant, suggesting that targeting both pathways may have additive or synergistic activity.(64) Secondly, preclinical data in mouse models of transplantable solid tumors supports the superior anti-tumor activity of combination therapy over monotherapy.(65, 66) 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. In a recently reported study of the combination of similar agents, nivolumab, a PD-1 blocking antibody, with ipilimumab, a CTLA-4 blocking antibody, it was demonstrated that the agents could be combined with a manageable safety profile. Using a dosing schedule of nivolumab and ipilimumab of every 3 weeks for 4 doses followed by every 12 weeks for up to 8 doses, durable tumor regressions were seen. As this was a Phase 1 dose escalation study, doses exceeding the MTD were established (3 mg/kg ipilimumab plus 3 mg/kg nivolumab Q3 weeks x 4 doses, followed by maintenance dosing of both drugs on an alternative schedule). Clinical activity of the concurrent combination appeared to exceed that of published monotherapy data, with rapid and deep tumor responses (≥80% tumor reduction at 12 weeks) in 53% (9/17) of subjects treated at the selected dose of 1 mg/kg nivolumab plus 3 mg/kg ipilimumab and an objective response rate of 40% (21/53) across all dose levels.(67) This regimen is currently studied in an ongoing Phase 3 study (NCT01844505).

As was seen in the combination of nivolumab and ipilimumab, the combination of MEDI4736 and tremelimumab may increase the frequency or severity of toxicities and thus, a Phase 1 dose escalation study in the appropriate setting to explore this combination is indicated.

Tremelimumab has been evaluated in earlier studies and has a well characterized toxicity profile and evidence for clinical activity, as outlined above. The safety, tolerability, pharmacokinetics and antitumor activity of MEDI4736 are being evaluated in an ongoing Phase 1 study as described in Section 1.5.

2.2 Rationale for MEDI4736 dose selection

MEDI4736 dose selection was based upon available clinical, pharmacokinetic, and safety data from the ongoing Phase 1 study of MEDI4736. The range of doses selected was based on predicted PD-L1 suppression. The dose of 0.3 mg/kg is predicted to produce a free PD-L1 level of 5 to 10% at Cmax, with a return to greater than 90% of baseline in approximately 10 days. The dose of 1 mg/kg MEDI4736 is predicted to achieve free PD-L1 of less than 5% at Cmax, while the doses of 10 mg/kg are predicted to achieve free PD-L1 of less than 1% throughout the dosing interval. Safety and tolerability will be established for MEDI4736 monotherapy at each dose level prior to combination dosing with tremelimumab.

The potential of MEDI4736 and tremelimumab to induce cytokine release was tested in a whole blood assay system using whole blood from healthy human donors. In this in vitro study, a positive control (mouse anti-human CD3) induced cytokine release in all donors. However, no cytokine induction was observed with either of the isotype negative controls, MEDI4736 or tremelimumab as single agents or the combination of MEDI4736 and tremelimumab. These results are consistent with the mechanism of action of MEDI4736 and tremelimumab, and the combination is not expected to induce acute cytokine release in humans.

2.3 Rationale for tremelimumab dose selection

The target trough concentration of tremelimumab is estimated to be ~ 30 µg/mL based on enhanced IL-2 release (in vitro) and antitumor activity (in vivo) in preclinical studies. tremelimumab at a dose of 3 mg/kg Q4W is expected to yield a median steady state concentration above the target trough level (~30 µg/mL) for about half of the dosing interval followed by a decrease in PK exposure with a median steady state trough level of ~17 µg/mL at the end of the dosing interval. Using this schedule, tremelimumab concentrations within an individual would be expected to be within the active range, but for a limited period of time, thereby providing both an opportunity to elicit biological activity but also a greater safety margin as a result of reduced PK exposure.

Pharmacokinetic simulations indicate that following tremelimumab at a dose of 10 mg/kg Q4W, approximately 90% of subjects are expected to be above the target concentration of ~ 30 µg/mL compared to ~ 50% with 15 mg/kg Q12W which was used in previous studies.

Therefore, the starting dose of tremelimumab will be 3 mg/kg Q4W and the highest dose was initially chosen as 10 mg/kg Q4W; however, dosing was changed per Amendment 5, as described in Section 2.4.

2.4 Rationale for Study Design

Current treatment options for advanced ovarian cancer, colorectal cancer (CRC), non-triple negative breast cancer, renal cell carcinoma (RCC) and cervical cancer reflect an unmet medical need and additional options for treatment are needed. The current study focuses on evaluating the MTD and safety profile of a novel combination of immunotherapies in subjects with advanced solid tumors that are not eligible for, declined or failed standard treatment. There is a sound rationale to combine MEDI4736 and tremelimumab supported by preclinical evidence for superior antitumor activity in mouse models and clinical data reviewed above. The results from this study will form the basis for decisions for future studies.

Note: Per Protocol Amendment 5, the disease states of NSCLC and head and neck cancer were removed from the study and were replaced by non-triple negative breast cancer. This change was made to avoid redundancy with the MedImmune development program. Cohort sample sizes were increased to 15, for a total of 75 subjects in the expansion phase.

In addition, the dosing regimens for tremelimumab and MEDI4736 were changed according to Amendment 5 in order to align with current recommendations from MedImmune. See Section 3.1.7 for details.

According to MedImmune, the combination dose selection of 1 mg/kg Q4W for tremelimumab and 20 mg/kg Q4W for MEDI4736 was based on the identification of an optimal dose of MEDI4736 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 for Cohort 4a is based on information from MedImmune, which indicates that the dose and schedule of 1500 mg MEDI4736 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 MEDI4736 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 MEDI4736 is equivalent to 10 mg/kg Q2W, 1500 mg Q4W MEDI4736 is equivalent to 20 mg/kg Q4W, and 75 mg Q4W tremelimumab is equivalent to 1 mg/kg Q4W.

3 Experimental Plan

3.1 Study Design

3.1.1 Study Phase

Phase 1 study with a dose-escalation phase followed by an expansion phase.

3.1.2 Enrollment/Randomization

Non-randomized, competitive multicenter, sequential enrollment with central subject registration. Enrollment will be under ongoing review by an internal data safety monitoring panel (see Section 3.1.14, Safety Monitoring and Study Stopping Rules).

For each cohort in the dose-escalation phase, the first study drug administration for the first subject and the second subject will be separated by at least 24 hours. All subjects in a cohort will have their safety data reviewed for DLTs for at least two cycles of treatment before proceeding to a subsequent cohort (see Section 3.1.7).

In the expansion phase, eligible subjects will be enrolled in parallel into each of the disease-specific cohorts.

3.1.3 Blinding/Unblinding

Open label.

3.1.4 Subject Population

For complete subject eligibility criteria, see Section 5.

Prior to Amendment 5, subjects with ovarian cancer, CRC, non-small cell lung cancer, head and neck cancer, RCC and cervical cancer who were not eligible for, declined or failed standard treatment, were included in the study.

Per Amendment 5, the disease states of NSCLC and head and neck cancer were removed from the study and were replaced by non-triple negative breast cancer, for a total of 5 disease-specific cohorts. Cohort sample sizes were increased from 12 to 15, for a total of 75 subjects in the expansion phase.

3.1.5 Number of Sites/Subjects

Up to 10 sites for the dose-escalation phase and up to 10 sites for the expansion phase; up to 105 subjects.

3.1.6 Sample Size Considerations

The dose-escalation phase of the study will enroll 3-6 subjects in each cohort, based on a 3+3 dose-escalation design to assess the MTD level.

The table below gives the probabilities of dose-escalation based on true DLT risk in the 3+3 design.

True DLT rate									
Probability of escalation	10%	20%	30%	40%	50%	60%	70%	80%	90%
	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.01	0.001

The expansion phase sample size of 75 subjects is not based on a formal sample size calculation. Fifteen (15) subjects in each of the 5 disease-specific cohorts are 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. Within each cohort of 15 subjects, the confidence interval of estimating the incidence of AE 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 the table below:

Number of Subjects with Event	Incidence	95% Exact Confidence Interval (Clopper Pearson)
1/15	0.067	(0.002, 0.320)
2/15	0.133	(0.017, 0.405)
3/15	0.200	(0.043, 0.481)
4/15	0.267	(0.078, 0.551)
5/15	0.333	(0.118, 0.616)
6/15	0.400	(0.163, 0.677)

3.1.7 Treatment Cohorts and Treatment Schema

MEDI4736 and tremelimumab will be administered intravenously according to Section 6.

Subjects will be treated for up to 12 months or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, or other reasons to discontinue treatment prematurely occur as defined in Section 3.1.10.

Per Amendment 6, optional treatment extension beyond the Core Study will be available for subjects who complete the Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator. See Section 8.8 for details.

As shown in Figure 1, each cycle consists of 4 weeks.

Prior to Amendment 5, MEDI4736 was administered every 2 weeks (Q2W) for 13 cycles, and tremelimumab was administered every 4 weeks (Q4W) for the first 6 cycles and then at cycle 7, 10 and 13 (every 12 weeks (Q12W)).

Per Amendment 5, the study will continue with enrollment into Cohort 3a and possibly Cohort 4a, with the following modifications:

- Cohort 3a: Tremelimumab, 1mg/kg Q4W for 4 four-week cycles; MEDI4736 3 mg/kg, Q2W for 12 four-week cycles (previously: tremelimumab 1mg/kg Q4W for the first 6 cycles and then Q12W; MEDI4736 3 mg/kg, Q2W for 13 cycles)

- Cohort 4a: Tremelimumab, 75mg Q4W for 4 four-week cycles; MEDI4736 1500 mg Q4W for 12 four-week cycles (previously: tremelimumab 1mg/kg Q4W for the first 6 cycles and then Q12W; MEDI4736 10 mg/kg, Q2W for 13 cycles). (**Note: Per Amendment 5, fixed dosing will be implemented for Cohort 4a.**)
- Cohorts 4 and 5 were removed from the study.

Note: The MEDI4736 and tremelimumab fixed doses are for subjects > 30 kg.

- **MEDI4736 dose: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 Q4W** as long as the body weight remains ≤ 30 kg.
- **Tremelimumab dose: 75 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 **30 mg Q4W** for tremelimumab as long as the body weight remains ≤ 30 kg.

On the days when MEDI4736 and tremelimumab are to be administered, MEDI4736 infusion will start at least 60 minutes after the end of tremelimumab infusion.

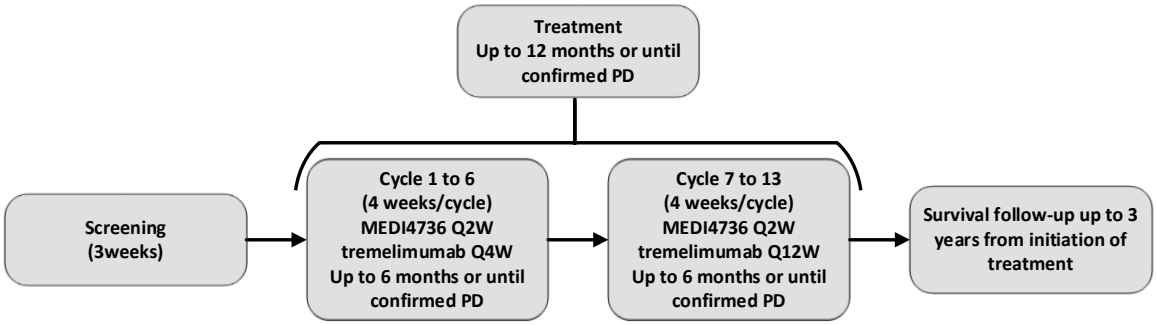

Figure 1: Treatment Schema Prior to-Amendment 5

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 (see Section 3.2).

3.1.7.1 Dose-escalation Phase, 3+3 Design

In each cohort, as a safety precaution, the first study drug administration for the first subject and the second subject will be separated by at least 24 hours. All subjects in a cohort will have their safety data reviewed for DLTs for at least two cycles of treatment before proceeding to a subsequent cohort. Thereafter, the following dose-escalation schema will be applied:

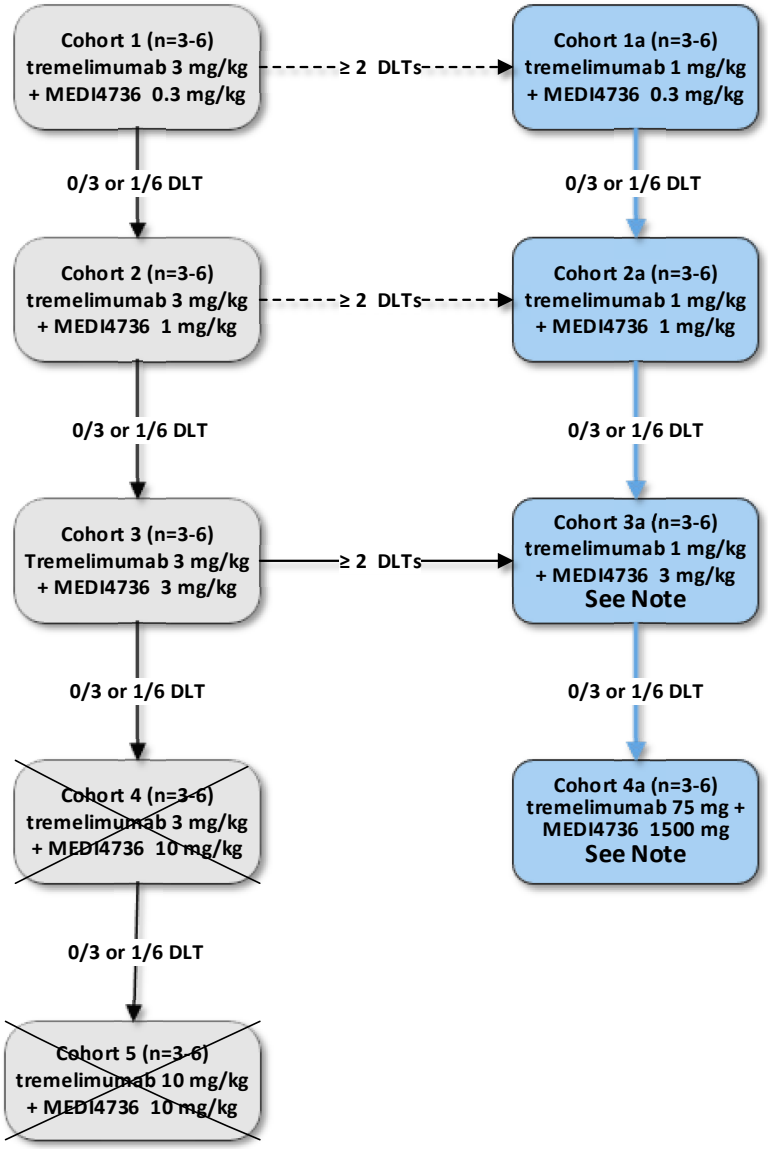

Figure 2: Dose-escalation Schema

Note: Per Amendment 5, dosing regimens for Cohorts 3a and 4a were modified according to Section 3.1.7; Cohorts 4 and 5 were removed from the study and are no longer applicable in the following evaluation.

- If 0 out of the 3 subjects have a DLT, the next dose-escalation cohort may be started.
- If exactly 1 out of the 3 subjects has a DLT, an additional 3 subjects will be enrolled in the same cohort. If none of these 3 additional subjects has a DLT after being observed for at least 2 cycles of treatment, the next dose-escalation cohort may be started.
- If 2 or more subjects in Cohort 1, 2, 3, or 4 develop a DLT, all further subjects will be enrollment in Cohorts 1a, 2a, 3a, or 4a, respectively.
- In Cohort 1a, if 2 or more subjects develop a DLT, enrollment will cease immediately and the study will be halted. No MTD can be determined.

- In Cohort 2a, 3a, and 4a, if 2 or more subjects develop a DLT, enrollment into the cohort will cease immediately, and the previous cohort with fewer than 2 DLTs will be determined as the MTD (Cohort 1 or 1a, 2 or 2a, and 3 or 3a, respectively).
- In Cohort 5, if 2 or more subjects develop a DLT, enrollment into the cohort will cease immediately, and the previous cohort with fewer than 2 DLTs will be determined as the MTD (Cohort 4).
- If fewer than 2 subjects in Cohort 4a or 5 develop a DLT, the respective Cohort 4a or 5 dose level will be declared the MTD level.

Accordingly, the MTD of the combination is defined as the highest dose of tremelimumab and MEDI4736 studied, for which the observed incidence of DLT is less than 33%.

Late onset DLTs that could not be taken into consideration prior to scheduled dose-escalations will be evaluated on a case-by-case basis, and may lead to enrollment of additional subjects in the previous cohort, or to new determination or revision of the MTD.

3.1.7.2 Expansion Phase

Subjects in the expansion phase (Cohorts A to E) will be treated at the MTD level determined in the dose-escalation phase.

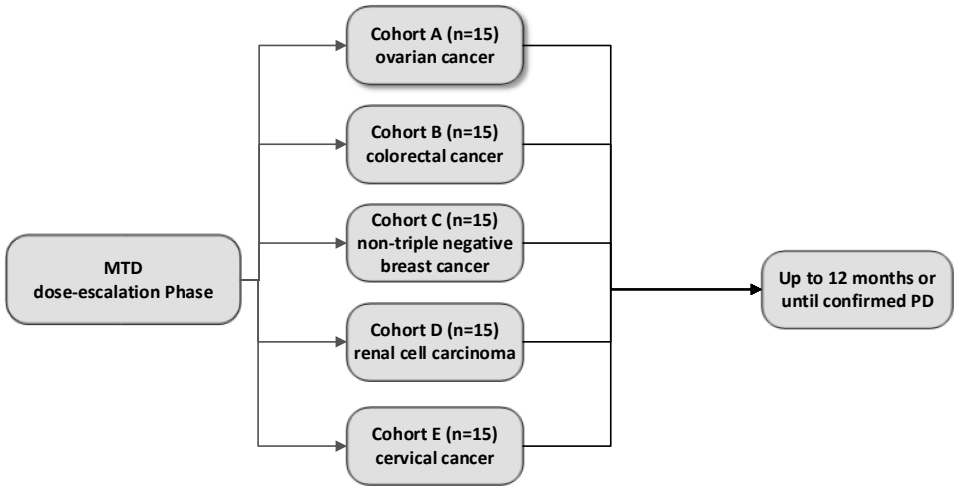

Figure 3: Expansion Phase Schema

NOTE: Per Amendment 5, the disease states of NSCLC and head and neck cancer were removed from the study and were replaced by non-triple negative breast cancer.

Per Amendment 6, optional treatment extension beyond the Core Study will be available for subjects who complete the Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator. See Section 8.8 for details.

3.1.8 Dosing Adjustments, Delays and Discontinuations

3.1.8.1 MEDI4736 and tremelimumab Dose Modification Due to Toxicity

MEDI4736 and tremelimumab administration may be modified or discontinued as a result of toxicities as described in Table 3.1.8-1.

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 MEDI4736 or tremelimumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant.

Table 3.1.8-1 MEDI4736 (M) and Tremelimumab (T) Dose Modification Due to Toxicity

Note: If M and T dosing is held temporarily until resolution of the event as per instructions below, treatment(s) should resume at the next scheduled treatment date.

Immune-related Adverse Events (irAEs)

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 M and T depicted below, **permanently discontinue M and T also for:**

- 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

- In general, no dose modification required.
- For *pneumonitis/interstitial lung disease*, consider holding M and T dosing as clinically appropriate and during diagnostic work-up for other etiologies.

Grade 2

- In general, hold M and T until resolution to ≤ Grade 1 and after the end of any steroid taper, and discontinue M and T permanently if such resolution does not occur within 60 days (30 days for neurotoxicities). Criteria for temporary hold or permanent discontinuation of M and T may differ by event as detailed below.

Table 3.1.8-1 MEDI4736 (M) and Tremelimumab (T) Dose Modification Due to Toxicity

- For *pneumonitis/interstitial lung disease*, the decision to reinitiate M and T upon resolution shall be based upon treating physician's clinical judgment (as long as the event does not meet DLT criteria).
- For *peripheral neuromotor syndromes*, such as *Guillain-Barre* and *Myasthenia Gravis*, follow general instructions above, but always discontinue M and T permanently if there are signs of respiratory insufficiency or autonomic instability.
- For *endocrinopathies*, *other than isolated hypothyroidism*, follow general instructions above, but patients may be retreated if the endocrinopathy is controlled and the patient 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 M and T is at the discretion of the Investigator.
- For *elevated creatinine* or *rash*, M and T should be held until resolution to ≤ Grade 1 or baseline.
- For *vitiligo*, no dose modification required.

Grade 3

- In general, hold M and T until resolution to ≤ Grade 1 and after the end of any steroid taper, and discontinue M and T permanently if such resolution does not occur within 60 days (30 days for neurotoxicities and rash). Criteria for permanent discontinuation of M 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 M and T permanently.
- For *asymptomatic increases of amylase or lipase* levels, hold M and T, and if complete work up shows no evidence of pancreatitis, M and T may be continued.
- For *hepatitis*, discontinue M and T permanently for (1) transaminases or bilirubin not resolving to ≤ Grade 1 or baseline within 14 days, (2) transaminases > 8 × the upper limit of normal (ULN) or bilirubin > 5 × 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 ≤ Grade 1 or baseline.

Grade 4

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

Table 3.1.8-1 MEDI4736 (M) and Tremelimumab (T) Dose Modification Due to Toxicity
Infusion-related Reactions   **Grade 1**   • The infusion rate of M 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.   **Grade 2:**   • **Same as Grade 1**, but consider giving subsequent infusions at 50% of the initial infusion rate; total infusion time not to exceed 4 hours.   **Grade 3 and 4:**   • **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).
All other Adverse Events   **Grade 1**   • No dose modification required.   **Grade 2**   • Hold M and T until resolution to ≤ Grade 1 or baseline, and discontinue M and T permanently if such resolution does not occur within 60 days.   **Grade 3**   • Hold M and T. If AEs downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume M and T administration at next scheduled dose. Otherwise, discontinue M and T permanently.   **Grade 4**   • In general, discontinue M 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.

3.1.8.2 MEDI4736 and Tremelimumab Dose Modification Not Due to Treatment-related Toxicities

MEDI4736 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 10 days for Q2W dosing or no less than 21 days for Q4W dosing. 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 ≤ 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.

3.1.8.3 MEDI4736 and Tremelimumab Discontinuation

Subjects who permanently discontinue treatment as defined in Section 3.1.8.1 and Section 3.1.8.2, and who are **not** withdrawn from study as defined in Section 3.1.10 and/or Section 7.2.7, will proceed to the Post Treatment Follow-up (On Study Follow-up) for 90 days after the last study drug treatment according to Section 3.1.16.

Thereafter, the subjects will be taken off study and they will enter the Post Study Follow-up as per Section 3.1.16.

3.1.9 DLT and MTD

The MTD is defined as the highest dose studied, for which the observed incidence of DLT is less than 33%. Frequencies of toxicities will be tabulated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

A DLT is any event that:

a) occurs during the DLT Evaluation Period (as described in Section 3.1.7.1); and
b) is possibly, probably, or definitely related to the administration of MEDI4736 or tremelimumab; and
c) fulfills any of the following criteria:

    1. Any Grade ≥ 3 colitis, pneumonitis, neurological event, or uveitis
    2. Any Grade 2 pneumonitis, neurological event, or uveitis with the *exception of those that* downgrade to Grade ≤ 1 within 3 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
    3. Any *other* Grade ≥ 3 toxicity, with the *following exceptions*:

        - Grade 3 irAEs that downgrade to Grade ≤ 2 within 3 days, or to Grade ≤ 1 or baseline within 14 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
        - Grade 3 endocrinopathy that becomes asymptomatic when managed with or without systemic corticosteroid therapy and/or hormone replacement therapy.
        - Grade 3 inflammatory reaction attributed to a local antitumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc.).

- Grade 3 fatigue for ≤ 7days.
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.
- Liver transaminase elevation ≤ 8 times upper limit of normal (ULN) that downgrades to Grade ≤ 2 (≤ 5 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
- Total bilirubin ≤ 5 times ULN that downgrades to Grade ≤ 2 (≤ 3 times ULN) within 7 days after onset, whereby maximal supportive care, including systemic corticosteroids, is permitted.
- Grade ≥ 3 neutropenia that (1) is not associated with fever or systemic infection, and (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
- Grade 3 or Grade 4 lymphopenia.
- Grade 3 thrombocytopenia that (1) is not associated with clinically significant bleeding, (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days.
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.
- Any pre-existing laboratory abnormality that deteriorates to Grade 3/4, but where the increment of deterioration is considered not clinically significant by both Investigator and Sponsor.

Immune-related adverse events (irAEs) are defined as 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 the rules for adjudicating DLTs in the context of dose escalation / dose expansion phase are specified above, an AE that is Grade < 3 or listed as exempt above may also be defined as DLT after consultation with the Sponsor and Investigators, based on the emerging safety profiles of MEDI4736 and tremelimumab. 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 be followed as described in Section 3.1.8.3. 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.

The MTD will be determined in accordance with Section 3.1.7.1.

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) Any dose-limiting toxicity as defined in Section 3.1.9.
(4) Confirmation of symptomatic progressive disease or objective progression by Immune-related Response Criteria (irRC).
(5) Significant protocol violation or noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal; e.g., refusal to adhere to study visits.
(6) Development of intercurrent, non-cancer related illness or complications that prevent either continuation of therapy or regular follow up.
(7) Best medical interest of the subject (at the discretion of the Investigator)

See also Section 3.1.8 for subject withdrawal from study treatment due to necessary dosing interruptions or discontinuations.

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 Post Treatment Follow-up (On Study Follow-up) procedures (see Section 3.2) followed by the Post Study Follow-up (see Section 3.1.16).

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 (e.g., start of new treatment)
(2) Initiation of alternative anticancer therapy (marketed or investigational)
(3) Withdrawal of consent for all follow-up
(4) Lost to follow-up
(5) Death

General subject withdrawal criteria are outlined in the Administrative, Legal and Ethical Requirements section of the protocol, Section 7.2.7.

3.1.10.1 Treatment Beyond Progression

Subjects meeting criteria for progression will be allowed to continue on therapy until confirmation of progression if the subject agrees and signs an appropriate informed consent form regarding continuation of treatment and as long as the following criteria are met at the discretion of the Investigator:

a. Absence of symptoms and signs (including worsening of laboratory values) indicating disease progression;
b. No significant decline in ECOG performance status;
c. Absence of rapid progression of disease or of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention.

See Section 8.5 and Section 8.6 regarding tumor response assessment by irRC and RECIST 1.1, respectively.

3.1.11 Per-Protocol Subject Evaluability and Replacement

In the *dose escalation phase*, 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 considered fully evaluable for DLT per Section 4.1.2 will be replaced.

3.1.12 Optional Study Treatment Extension

Optional treatment extension beyond the original 12- or 13-cycle treatment period (Core Study) will be available for subjects who complete the Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator. See Section 8.8 for details.

3.1.13 Interim Analysis

No formal interim analysis is currently planned. Analyses will be performed to assess safety and tolerability in the context of dose-escalations (see Section 3.1.7.1).

3.1.14 Safety Monitoring and Study Stopping Rules

In accordance with the Administrative, Legal and Ethical Requirements section 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 provider of the two study drugs. Additional investigators and staff, or additional Sponsor personnel and consultants, shall participate in reviews as indicated. An Independent Data Monitoring Board will not be utilized for this open label study.

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 MEDI4736 and/or tremelimumab.
(2) Severe anaphylactic reaction to MEDI4736 and/or tremelimumab (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 internal 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 assessed as related to MEDI4736 and/or tremelimumab that, in the opinion of the internal data safety monitoring panel, contraindicates further dosing of study subjects.

General criteria for premature trial termination are outlined in the Administrative, Legal and Ethical Requirements section of the protocol.

3.1.15 Duration of Study

During the dose escalation phase, due to the safety assessments after the first subjects and the end of cohort assessments, 1 cohort is estimated to take 2 months to complete, on average. During the expansion phase, enrollment of 1 subject per site per month is assumed.

Enrollment Period:	38months (24 months dose escalation + 14 months expansion)
Duration of Treatment	12 months See Section 3.1.12 for optional treatment extension.
Length of Study:	50 months (not including long term follow-up)

3.1.16 On Study and Post-Study Follow-up

All subjects, whether they complete treatment as planned, discontinue treatment prematurely as per Section 3.1.8.3, or prematurely withdraw from the study as per Sections 3.1.10 and/or Section 7.2.7, will be followed as per institutional guidelines in accordance with the usual standard of care principles.

Subjects who complete study treatment or discontinue treatment prematurely will enter the Post Treatment Follow-up (On Study Follow-up), which will be conducted for 90 days after the last administration of study drug according to the flowchart in Section 3.2 Refer to Section 7.1.5 for information on collection of adverse events during the Post Treatment Follow-up (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 Post Treatment Follow-up (On Study Follow-up), any assessments required in the first Post Treatment Follow-up (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 Post Treatment Follow-up (On Study Follow-up) visit should not be repeated.

In addition to the Post Treatment Follow-up (On Study Follow-up), there will be a Post Study Follow-up, where clinical outcomes data (dates of progression/relapse, and survival) will be collected at least every 6 months for up to 3 years from the initiation of the 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 this data through review of outside records or communication with the subject or his/her physician.

See Section 3.1.12 for optional study treatment extension.

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 not yet in Post Treatment Follow-up (On Study Follow-up), this End of Study visit will be the first planned visit of the Post Treatment Follow-up (On Study Follow-up). For subjects already in Post Treatment Follow-up (On Study Follow-up), this End of Study visit will be the next planned visit of the Post Treatment Follow-up (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 Flowcharts

Pre Amendment 5 Study Flowchart - Cohorts 3 and earlier (1 of 2)	Screening / Baseline	Treatment													
		Cycle 1 (4 weeks)				Cycle 2 (4 weeks)		Cycle 3 (4 weeks)		Cycle 4 (4 weeks)		Cycle 5 (4 weeks)		Cycle 6 (4 weeks)	
Treatment weeks	-3 to 0	Week 1		Week 2-3		Week 5	Week 7	Week 9	Week 11	Week 13	Week 15	Week 17	Week 19	Week 21	Week 23
Treatment days	-21 to 0	1	2	8±1	15±1	29±3	43±3	57±3	71±3	85±3	99±3	113±3	127±3	141±3	155±3
Study Drugs Administration															
MEDI4736 (pre Amendment 5)		x			x	x	x	x	x	x	x	x	x	x	x
Tremelimumab (pre Amendment 5)		x				x		x		x		x		x	
Tumor & Disease Assessments															
Disease Staging (date/stage at 1st diagnosis & at study entry)	x														
Disease Assessment by RECIST (including appropriate imaging)	x						x			x		x			
Disease Assessment by irRC (including appropriate imaging)	x						x			x		x			
Study Procedures & Examinations															
Eligibility Assessment and Informed Consent[3]	x														
Demographics (incl. DoB; sex; height; race; ethnicity)	x														
Physical Exam (incl. weight and ECOG Perf Status)	x	x		x	x	x		x		x		x		x	
Medical history and Pre-Existing Symptoms	x														
Vital Signs (T, HR, BP, RR) (see Section 6.3)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead ECG	x														
Concomitant Medication (name, indication, dose, route, start & end dates)/ Concomitant Procedures	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Brain MRI repeated as clinically indicated	x														
Adverse Events (starting or worsening after consent)[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Labs															
Blood Hematology (complete blood count with differential, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Mean Corpuscular HGB Concentration, Red Cell Distribution Width, Platelets and Mean Platelet Volume)	-7 to 0	x[2]	x	x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, prot., alb., Tbili., AST, ALT, LDH, ALP, FreeT3, FreeT4, TSH)	-7 to 0	x[2]	x	x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
Chemistry cont. (Amylase, lipase)	-7 to 0	x[2]	x	x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
Serum pregnancy test (urine test only on Day 1)	-7 to 0	x[2]						x[2]				x[2]			
Other Labs & Assays															
Flow cytometry (immune monitoring)	Day -7 to 1 (pre-dose)			x	x[2]	x[2]		x[2]		x[2]		x[2]		x[2]	
PBMC collection (immunodiversity, flow cytometry, functional assays)	Day -7 to 1 (pre-dose)			x	x[2]	x[2]		x[2]		x[2]		x[2]		x[2]	
PAXgene RNA tube		x[2]	x	x		x[2]				x[2]				x[2]	
Archived tumor sample	-7 to 0														
Tumor Biopsy (expansion phase only)	-14 to 0					x									
1 See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.															
2 Collected pre-dose (prior to first drug administration).-Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.															
3 Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart															

Pre Amendment 5 Study Flowchart - Cohorts 3 and earlier (continued - 2 of 2)	Treatment														End of Study Post Treatment Follow-up (On Study Follow-up)				Post Study Follow-up (Done at least every 6 months for up to 3 years from start of treatment)
	Cycle 7 (4 weeks)		Cycle 8 (4 weeks)		Cycle 9 (4 weeks)		Cycle 10 (4 weeks)		Cycle 11 (4 weeks)		Cycle 12 (4 weeks)		Cycle 13 (4 weeks)[4]		Last Study Drug Administration +14±3 days	Last Study Drug Administration +28±3 days	Last Tremelimumab Administration +90±7 days	Last MEDI4736 administration +90±7 days	
Study weeks	Week 25	Week 27	Week 29	Week 31	Week 33	Week 35	Week 37	Week 39	Week 41	Week 43	Week 45	Week 47	Week 49	Week 51	Week 53	Week 55	Week 62	Week 64	
Study days	169±3	183±3	197±3	211±3	225±3	239±3	253±3	267±3	281±3	295±3	309±3	323±3	337±3	351±3	365±3	379±3	428±7	442±7	
Study Drugs Administration																			
MEDI4736 (pre Amendment 5)	x	x	x	x	x	x	x	x	x	x	x	x	x	x					
Tremelimumab (pre Amendment 5)	x						x						x						
Tumor & Disease Assessments																			
Disease Assessment by RECIST (including appropriate imaging)	x				x				x				x		+56 ± 7 days from last disease assessment				
Disease Assessment by irRC (including appropriate imaging)	x				x				x				x		+56 ± 7 days from last disease assessment				
Study Procedures & Examinations																			
Physical Exam (incl. weight and ECOG Perf Status)	x		x		x		x		x		x		x		x	x	x	x	
Vital Signs (T, HR, BP, RR) (see Section 6.3)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant Medication (name, indication, dose, route, start & end dates) /Concomitant Procedures	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse Events (starting or worsening after consent)[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Labs & Assays																			
Blood Hematology (complete blood count with differential, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Mean Corpuscular HGB Concentration, Red Cell Distribution Width, Platelets and Mean Platelet Volume)	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x	x	x	x	
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, prot., alb., Tbili., AST, ALT, LDH, ALP, Free T3, Free T4, TSH)	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x	x	x	x	
Chemistry cont. (Amylase, lipase)	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x	x	x	x	
Serum Pregnancy test	x[2]				x[2]				x[2]				x[2]			x		x	
Other Labs & Assays																			
Flow cytometry (immune monitoring)	x[2]						x[2]						x[2]		x				
PBMC collection (immunodiversity, flow cytometry, functional assays)	x[2]		x[2]		x[2]		x[2]		x[2]		x[2]		x[2]		x	x	x	x	
PAXgene RNA tube	x[2]						x[2]						x[2]		x	x			
Tumor Biopsy (expansion phase only)			x																
Long-Term Follow-up																			
Overall Survival																			x
Progression Free Survival [3]																			x
1 See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.																			
2 Collected pre-dose (prior to first drug administration). Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.																			
3 For subjects who did not experience progression while on study																			
4 Cycle 13 pertains to cohorts 3 and ealier in pre Amendment 5 only																			

Post Amendment 5 Study Flowchart - Cohort 3a (1 of 2)	Screening / Baseline	Treatment													
		Cycle 1 (4 weeks)				Cycle 2 (4 weeks)		Cycle 3 (4 weeks)		Cycle 4 (4 weeks)		Cycle 5 (4 weeks)		Cycle 6 (4 weeks)	
Treatment weeks	**-3 to 0**	**Week 1**		**Week 2-3**		**Week 5**	**Week 7**	**Week 9**	**Week 11**	**Week 13**	**Week 15**	**Week 17**	**Week 19**	**Week 21**	**Week 23**
Treatment days	**-21 to 0**	**1**	**2**	**8±1**	**15±1**	**29±3**	**43±3**	**57±3**	**71±3**	**85±3**	**99±3**	**113±3**	**127±3**	**141±3**	**155±3**
Study Drugs Administration															
MEDI4736 (Post Amendment 5 Cohort 3a)		x			x	x	x	x	x	x	x	x	x	x	x
Tremelimumab (Post Amendment 5 Cohort 3a)		x				x		x		x					
Tumor & Disease Assessments															
Disease Staging (date/stage at 1st diagnosis & at study entry)	x														
Disease Assessment by RECIST (including appropriate imaging)	x						x			x		x			
Disease Assessment by irRC (including appropriate imaging)	x						x			x		x			
Study Procedures & Examinations															
Eligibility Assessment and Informed Consent[3]	x														
Demographics (incl. DoB; sex; height; race; ethnicity)	x														
Physical Exam (incl. weight and ECOG Perf Status)	x	x		x	x	x		x		x		x		x	
Medical history and Pre-Existing Symptoms	x														
Vital Signs (T, HR, BP, RR) (see Section 6.3)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
12-Lead ECG	x														
Concomitant Medication (name, indication, dose, route, start & end dates) / Concomitant Procedures	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Brain MRI repeated as clinically indicated	x														
Adverse Events (starting or worsening after consent)[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Labs															
Blood Hematology (complete blood count with differential, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Mean Corpuscular HGB Concentration, Red Cell Distribution Width, Platelets and Mean Platelet Volume)	-7 to 0	x[2]	x	x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, prot., alb., Tbili., AST, ALT, LDH, ALP, Free T3, Free T4, TSH)	-7 to 0	x[2]	x	x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
Chemistry cont. (Amylase, lipase)	-7 to 0	x[2]	x	x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
Serum pregnancy test (urine test only on Day 1)	-7 to 0	x[2]						x[2]				x[2]			
Other Labs & Assays															
Flow cytometry (immune monitoring)	Day -7 to 1 (pre-dose)		x	x[2]	x[2]		x[2]		x[2]		x[2]		x[2]		
PBMC collection (immunodiversity, flow cytometry, functional assays)	Day -7 to 1 (pre-dose)		x	x[2]	x[2]		x[2]		x[2]		x[2]		x[2]		
PAXgene RNA tube		x[2]	x	x		x[2]				x[2]				x[2]	
Archived tumor sample	-7 to 0														
Tumor Biopsy (expansion phase only)	-14 to 0					x									
1 See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.															
2 Collected pre-dose (prior to first drug administration). Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.															
3 Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart															

Post Amendment 5 Study Flowchart - Cohort 3a (continued 2 of 2)	**Treatment**												**End of Study Post Treatment Follow-up (On Study Follow-up)**			**Post Study Follow-up** (Done at least every 6 months for up to 3 years from start of treatment)
	Cycle 7 (4 weeks)		**Cycle 8 (4 weeks)**		**Cycle 9 (4 weeks)**		**Cycle 10 (4 weeks)**		**Cycle 11 (4 weeks)**		**Cycle 12 (4 weeks)**		**Last Study Drug Administration +14±3 days**	**Last Study Drug Administration +28±3 days**	**Last Study Drug Administration +90±7 days**	
Study weeks	**Week 25**	**Week 27**	**Week 29**	**Week 31**	**Week 33**	**Week 35**	**Week 37**	**Week 39**	**Week 41**	**Week 43**	**Week 45**	**Week 47**	**Week 49**	**Week 51**	**Week 58**	
Study days	**169±3**	**183±3**	**197±3**	**211±3**	**225±3**	**239±3**	**253±3**	**267±3**	**281±3**	**295±3**	**309±3**	**323±3**	**337±3**	**351±3**	**399±7**	
Study Drugs Administration																
MEDI4736 (Post Amendment 5 Cohort 3a)	x	x	x	x	x	x	x	x	x	x	x	x				
Tremelimumab (Post Amendment 5 Cohort 3a)																
Tumor & Disease Assessments																
Disease Assessment by RECIST (including appropriate imaging)	x				x				x				+56 ± 7 days from last disease assessment			
Disease Assessment by irRC (including appropriate imaging)	x				x				x				+56 ± 7 days from last disease assessment			
Study Procedures & Examinations																
Physical Exam (incl. weight and ECOG Perf Status)	x		x		x		x		x		x		x	x	x	
Vital Signs (T, HR, BP, RR) (see Section 6.3)	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Concomitant Medication (name, indication, dose, route, start & end dates) /Concomitant Procedures	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Adverse Events (starting or worsening after consent)[1]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
Labs & Assays																
Blood Hematology (complete blood count with differential, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Mean Corpuscular HGB Concentration, Red Cell Distribution Width, Platelets and Mean Platelet Volume)	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x	x	x	
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, prot., alb., Tbili., AST, ALT, LDH, ALP, Free T3, Free T4, TSH)	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x	x	x	
Chemistry cont. (Amylase, lipase)	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x	x	x	
Serum Pregnancy test	x[2]				x[2]				x[2]				x		x	
Other Labs & Assays																
Flow cytometry (immune monitoring)	x[2]						x[2]						x			
PBMC collection (immunodiversity, flow cytometry, functional assays)	x[2]		x[2]		x[2]		x[2]		x[2]		x[2]		x	x	x	
PAXgene RNA tube	x[2]						x[2]						x	x		
Tumor Biopsy (expansion phase only)			x													
Long-Term Follow-up																
Overall Survival																x
Progression Free Survival[3]																x

1 See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.

2 Collected pre-dose (prior to first drug administration). Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.

3 For subjects who did not experience progression while on study

Post Amendment 5 Study Flowchart - Cohort 4a (1 of 2)	Screening / Baseline	Treatment								
		Cycle 1 (4 weeks)				Cycle 2 (4 weeks)	Cycle 3 (4 weeks)	Cycle 4 (4 weeks)	Cycle 5 (4 weeks)	Cycle 6 (4 weeks)
Treatment weeks	**-3 to 0**	**Week 1**		**Week 2-3**		**Week 5**	**Week 9**	**Week 13**	**Week 17**	**Week 21**
Treatment days	**-21 to 0**	**1**	**2**	**8±1**	**15±1**	**29±3**	**57±3**	**85±3**	**113±3**	**141±3**
Study Drugs Administration										
MEDI4736 (Post Amendment 5 Cohort 4a)		x				x	x	x	x	x
Tremelimumab (Post Amendment 5 Cohort 4a)		x				x	x	x		
Tumor & Disease Assessments										
Disease Staging (date/stage at 1st diagnosis & at study entry)	x									
Disease Assessment by RECIST (including appropriate imaging)	x						x	x	x	
Disease Assessment by irRC (including appropriate imaging)	x						x	x	x	
Study Procedures & Examinations										
Eligibility Assessment and Informed Consent[3]	x									
Demographics (incl. DoB; sex; height; race; ethnicity)	x									
Physical Exam (incl. weight and ECOG Perf Status)	x	x		x	x	x	x	x	x	x
Medical history and Pre-Existing Symptoms	x									
Vital Signs (T, HR, BP, RR) (see Section 6.3)	x	x	x	x	x	x	x	x	x	x
12-Lead ECG	x									
Concomitant Medication (name, indication, dose, route, start & end dates) /Concomitant Procedures	x	x	x	x	x	x	x	x	x	x
Brain MRI repeated as clinically indicated	x									
Adverse Events (starting or worsening after consent)[1]	x	x	x	x	x	x	x	x	x	x
Labs										
Blood Hematology (complete blood count with differential, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Mean Corpuscular HGB Concentration, Red Cell Distribution Width, Platelets and Mean Platelet Volume)	-7 to 0	x[2]	x	x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, prot., alb., Tbili., AST, ALT, LDH, ALP, Free T3, Free T4, TSH)	-7 to 0	x[2]	x	x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
Chemistry cont. (Amylase, lipase)	-7 to 0	x[2]	x	x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
Serum pregnancy test (urine test only on Day 1)	-7 to 0	x[2]					x[2]		x[2]	
Other Labs & Assays										
Flow cytometry (immune monitoring)	Day -7 to 1 (pre-dose)			x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
PBMC collection (immunodiversity, flow cytometry, functional assays)	Day -7 to 1 (pre-dose)			x	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]
PAXgene RNA tube		x[2]	x	x		x[2]		x[2]		x[2]
Archived tumor sample	-7 to 0									
Tumor Biopsy (expansion phase only)	-14 to 0					x				

1 See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.

2 Collected pre-dose (prior to first drug administration). Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.

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

Post Amendment 5 Study Flowchart - Cohort 4a (continued - 2 of 2)	Treatment						End of Study Post Treatment Follow-up (On Study Follow-up)			Post Study Follow-up (Done at least every 6 months for up to 3 years from start of treatment)
	Cycle 7 (4 weeks)	Cycle 8 (4 weeks)	Cycle 9 (4 weeks)	Cycle 10 (4 weeks)	Cycle 11 (4 weeks)	Cycle 12 (4 weeks)	Last Study Drug Administration +28±3 days	Last Study Drug Administration +56±3 days	Last Study Drug Administration +90±7 days	
Study weeks	Week 25	Week 29	Week 33	Week 37	Week 41	Week 45	Week 49	Week 53	Week 58	
Study days	169±3	197±3	225±3	253±3	281±3	309±3	337±3	365±3	399±7	
Study Drugs Administration										
MEDI4736 (Post Amendment 5 Cohort 4a)	x	x	x	x	x	x				
Tremelimumab (Post Amendment 5 Cohort 4a)										
Tumor & Disease Assessments										
Disease Assessment by RECIST (including appropriate imaging)	x		x		x		+56 ± 7 days from last disease assessment			
Disease Assessment by irRC (including appropriate imaging)	x		x		x		+56 ± 7 days from last disease assessment			
Study Procedures & Examinations										
Physical Exam (incl. weight and ECOG Perf Status)	x	x	x	x	x	x	x	x	x	
Vital Signs (T, HR, BP, RR) (see Section 6.3)	x	x	x	x	x	x	x	x	x	
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 consent)[1]	x	x	x	x	x	x	x	x	x	
Labs & Assays										
Blood Hematology (complete blood count with differential, Mean Corpuscular Hemoglobin, Mean Corpuscular Volume, Mean Corpuscular HGB Concentration, Red Cell Distribution Width, Platelets and Mean Platelet Volume)	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x	x	x	
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, prot., alb., Tbili., AST, ALT, LDH, ALP, Free T3, Free T4, TSH)	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x	x	x	
Chemistry cont. (Amylase, lipase)	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x	x	x	
Serum Pregnancy test	x[2]		x[2]		x[2]		x		x	
Other Labs & Assays										
Flow cytometry (immune monitoring)	x[2]			x[2]			x			
PBMC collection (immunodiversity, flow cytometry, functional assays)	x[2]	x[2]	x[2]	x[2]	x[2]	x[2]	x	x	x	
PAXgene RNA tube	x[2]			x[2]			x	x		
Tumor Biopsy (expansion phase only)		x								
Long-Term Follow-up										
Overall Survival										x
Progression Free Survival [3]										x

1 See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.

2 Collected pre-dose (prior to first drug administration). Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.

3 For subjects who did not experience progression while on study

4 Study Objectives and Endpoints

Primary Objectives	Safety/Tolerability (Endpoint: MTD, CTCAE version 4.03)
Secondary Objectives	Pharmacokinetics and immunogenicity (MEDI4736/tremelimumab) Clinical efficacy (Tumor Response by RECIST and irRC, progression-free survival and overall survival)
Exploratory objective	Biological activity of MEDI4736/tremelimumab Combination

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 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.

4.1.1 Endpoints & Assessment Methods

Laboratory tests, vital sign measurements, physical exams and subject interviews will be performed to detect new abnormalities and deteriorations of any pre-existing conditions. All "treatment-emergent" clinically significant abnormalities and deteriorations that begin or worsen in severity after initial administration of MEDI4736 and/or tremelimumab should be recorded in the Case Report Forms as Adverse Events and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.

4.1.2 Subject Evaluation and Statistics

All subjects who receive at least the first two cycles of treatment (i.e., DLT evaluation period; approx. 8 weeks) and respective safety assessments, as well as, all subjects who discontinue the study prematurely due to DLT are considered fully evaluable per protocol for DLT (see Section 3.1.11 for subject replacement). Subjects must also have received at least 75% of the planned dose during the DLT evaluation period (except for subjects who discontinued prematurely due to DLT) to be evaluable for DLT.

All subjects who received at least one dose of MEDI4736 and/or tremelimumab will be evaluated for safety and tolerability. Appropriate summaries of AEs, laboratory data and vital sign data will be presented. AEs 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.

The MTD will be determined in accordance with Section 3.1.9.

4.2 MEDI4736 and tremelimumab pharmacokinetics

4.2.1 Endpoints and Assessment Methods

A validated enzyme-linked immunosorbent assay (ELISA) will be used for the quantitative determination of tremelimumab in human serum. A validated electrochemiluminescence assay (ECLA) using a Meso Scale Discovery (MSD) platform will be used for the quantitative determination of MEDI4736 in human serum.

NOTE: Per Amendment 6, samples will no longer be collected for analysis of MEDI4736 and tremelimumab pharmacokinetics, as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2.

4.2.2 Subject Evaluation and Statistics

Only subjects, who received at least one dose of MEDI4736 and tremelimumab and provided the baseline and at least one post-treatment sample, will be evaluated. The PK of MEDI4736 and tremelimumab will be assessed using parameters including peak concentration (Cmax), trough concentration (Cmin) and time to peak concentration (Tmax) and area under the concentration-time curve (AUC) after the first dose. MEDI4736 and tremelimumab steady-state PK parameters including peak concentration (Cmax,ss), trough concentration (Cmin,ss), and time to peak concentration (Tmax,ss) will be estimated. All PK parameters will be estimated by non-compartmental analysis. Accumulation to steady state will be assessed as the ratio of Cmax,ss:Cmax and Cmin,ss:Cmin.

4.3 MEDI4736 and tremelimumab Immunogenicity

4.3.1 Endpoints and Assessment Methods

Validated electrochemiluminescence assays using the MSD platform will be used for the detection of anti-tremelimumab and anti-MEDI4736 antibodies in human serum.

NOTE: Per Amendment 6, samples will no longer be collected for the assessment of anti-tremelimumab and anti-MEDI4736 anti-drug antibodies (ADA), as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2.

4.3.2 Subject Evaluation and Statistics

Only subjects who received at least one dose of both MEDI4736 and tremelimumab, and provided the baseline and at least one post-treatment sample, will be evaluated. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-MEDI4736 or tremelimumab antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-MEDI4736 or tremelimumab antibodies.

4.4 Clinical Efficacy

Clinical efficacy evaluation will include tumor response assessed by irRC and RECIST, Progression-free Survival and overall survival.

4.4.1 Tumor Response Assessment by irRC

Tumor Response will be assessed by the Immune-related Response Criteria (irRC) as published by Wolchok et al., 2009.(68) Tumor Response by irRC is defined as irPR or irCR over a period of at least 4 weeks. Disease Control by irRC is defined as irSD or irPR or irCR. Disease control by irRC will be used to determine eligibility for the maintenance treatment phase (see Section 3.1.7).

4.4.2 Tumor Response Assessment by RECIST

Tumor Response will also be evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) Committee. Tumor Response by RECIST is defined as PR or CR over a period of at least 4 weeks. Disease Control by RECIST is defined as SD or PR or CR.

4.4.3 Progression-free survival (PFS)

Progression-free Survival will be determined for each subject with time origin at the start of the treatment (Day 1) until the first occurrence of confirmed progression by irRC or date of death if the subject dies from any causes before progression. Every effort will be made to follow subjects for progression after they discontinue the study.

4.4.4 Overall Survival (OS)

Overall survival (OS) will be measured for each subject with time origin at the start of the treatment (Day 1) until recorded date of death. Every effort will be made to follow subjects for overall survival after they discontinue the study.

4.4.5 Subject Evaluation and Statistics

All subjects who received at least one dose of MEDI4736 and/or tremelimumab, as well as baseline and at least one post-baseline disease assessments, will be evaluated for clinical efficacy. Tumor Responses by irRC and RECIST, progression free survival and overall survival will be summarized and analyzed descriptively.

4.5 Biological activity of MEDI4736/tremelimumab Combination

4.5.1 Endpoints and Assessment Methods

Samples for exploratory pharmacodynamic assessments at each visit and time points as noted in Section 3.2).

Exploratory pharmacodynamic assessments may include but not be limited to:

- Serum sPD-L1 levels before and after treatment.
- PBMCs will be collected to assess immune cell phenotypes that may include T cell phenotype and activation markers, B cells, myeloid derived suppressor cells and/or immune diversity.
- Levels of Circulating soluble factors (cytokine profiling)
- Flow cytometry (immune monitoring)
- Circulating Tumor Cell (CRC, ovarian cancer, and SCCHN)
- Immunologic changes in the tumor microenvironment
- mRNA/miRNA profiling

NOTE: Per Amendment 6, samples will no longer be collected for analysis of sPD-L1, circulating soluble factors, and circulating tumor cells (CTC), as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2.

4.5.2 Subject Evaluation and Statistics

Only subjects who received at least one dose of both MEDI4736 and tremelimumab, 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 tumor microenvironment will include the correlation between clinical activity and the expression level of PD-L1 and tumor-infiltrating lymphocytes (TILs) changes in biopsies pre and post treatment. Subjects will be classified as responders or non-responders based on irRC. Within each response group, subject tumors will be assessed as positive or negative for PD-L1 expression. For the purpose of this exploratory analysis, and to maximize power, the 5 disease-specific cohorts will be combined and a Cochran-Mantel-Haenszel test stratified by cohort will be used to test whether there is a significant association between responder-status and PD-L1 expression. Assuming tumor biopsies are available for at least 48 subjects and approximately equal numbers of responders and non-responders, if there are 80% and 40% of subjects with positive PD-L1 expression in the two groups, respectively, there will be at least 80% power to detect a significant difference. The association between response and PD-L1 expression within each disease-specific cohort will be assessed descriptively. 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.

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- or cytologically-confirmed ovarian cancer, colorectal cancer, non-triple negative breast cancer, renal cell carcinoma and cervical cancer, with at least one lesion measurable by irRC not previously irradiated. **NOTE: Per Amendment 5, the disease states of non-small cell lung cancer and head and neck cancer were removed from the study and were replaced by non-triple negative breast cancer**.
2.	Failed to respond to or relapsed following standard treatment, or declined or was not eligible for standard treatment.
3.	ECOG performance status of 0-2.
4.	Anticipated lifespan greater than 6 month.
5.	At the time of day 1 of the study, subjects with brain metastases must be asymptomatic for at least 4 weeks and: • at least 8 weeks without tumor progression after any whole brain radiotherapy • at least 4 weeks since craniotomy and resection or stereotactic radiosurgery • at least 3 weeks without new brain metastases as evidenced by MRI/CT
6.	Adequate organ and marrow function, as defined below: • Hemoglobin ≥ 9 g/dL • Absolute Neutrophil Count ≥ 1500/mm3 • Platelet count ≥ 100,000/mm3 • Total bilirubin within normal ranges unless associated with hepatobiliary metastases or Gilbert syndrome, then total bilirubin ≤ 2 x ULN • Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 2.5 x ULN unless associated with hepatic metastases, then ALT and AST ≤ 5 x ULN • Creatinine ≤ 2.0 mg/dL
7.	Have been informed of other treatment options.
8.	Age ≥18 years.
9.	Able and willing to give valid written informed consent.
10.	Able and willing to give valid written consent for archival tumor samples
11.	Able and willing to give valid written consent for biopsy samples (subjects with biopsiable tumors, and if clinically appropriate, in the expansion phase only).

5.2 Exclusion Criteria

*Subjects **<u>may not</u>** enter the study if they fulfill any of the following criteria:*

1.	Prior exposure to tremelimumab or MEDI4736 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 or vitiligo.
4.	Any prior Grade ≥ 3 immune-related adverse event (irAE) or any prior corticosteroid-refractory irAE.
5.	Known active or chronic viral hepatitis or history of any type of hepatitis within the last 6 months.
6.	History of sarcoidosis syndrome.
7.	Active or history of inflammatory bowel disease (colitis, Crohn's), diverticulitis, irritable bowel disease, celiac disease, or other serious, chronic, gastrointestinal conditions associated with diarrhea. Active or history of systemic lupus erythematosus or Wegener's granulomatosis.
8.	Metastatic disease to the central nervous system for which other therapeutic options, including radiotherapy, may be available.
9.	Known immunodeficiency or active HIV.
10.	Other active serious illnesses (e.g., serious infections requiring antibiotics).
11.	If a subject previously received investigational treatment, the last dose of investigational treatment was administered within 4 weeks of Day 1 of the study or adverse event(s) attributable to investigational treatment have not resolved to Grade 1 or better.
12.	Major surgical procedure (as defined by the investigator) within 30 days prior to Day 1 or still recovering from prior surgery.
13.	Mental impairment that may compromise the ability to give informed consent and comply with the requirements of the study.
14.	Lack of availability for immunological and clinical follow-up assessments.
15.	Women who are breast feeding or pregnant as evidenced by positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG)
16.	**Females subjects of childbearing potential** who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (see table below) from the time of screening, and must agree to continue using such precautions for 90 days after last dose of MEDI4736 or for 6 months after the final dose of MEDI4736 + 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.

	Female subjects should also refrain from breastfeeding throughout the period described above. Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal 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: • 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. **Non-sterilized 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 MEDI4736 or through 6 months after receipt of the final dose of MEDI4736 + tremelimumab (whichever is longer). Female partners (of childbearing potential) of a male subject must use a highly effective method of contraception (see table below) 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 contraception. Male subjects should refrain from sperm donation throughout the period described above. Highly effective 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 not 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 [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills). Acceptable highly effective methods of contraception are described in the following table:

	Highly Effective[a] Methods of Contraception **Barrier/Intrauterine Methods** • Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (e.g., Mirena®)[b] **Hormonal Methods** • "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® [a] Highly effective (i.e. failure rate of <1% per year) [b] This is also considered a hormonal method [c] Cerazette® is currently the only highly effective progesterone based pill
17.	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.
18.	Subjects must not donate blood while on study and for at least 90 days following the last MEDI4736 treatment or 6 months after the last tremelimumab treatment, whichever is longer.

5.3 Restrictions on Concomitant Therapies

5.3.1 Non-Permitted Concomitant Therapies

*Subjects **<u>may not</u>** 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 1.
2.	Other cancer therapy (chemotherapy, radiation or immunotherapy). Wash-out period: 4 weeks or 5 half-lives (whichever is shorter) prior to Day 1; 6 weeks for nitrosoureas.
3.	Live/attenuated vaccines 1 month prior to Day 1 and for at least 6 months after the last dose of treatment.
4.	Sunitinib within 3 months after the last dose of tremelimumab.
5.	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 **<u>may</u>** 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 (< 5% of body surface area) dermatitis.
2.	NSAIDs, acetylsalicylic acid and specific COX-2 inhibitors.
3.	Antihistamines and other non-steroidal anti-allergy medication.
4.	Hormone or hormone-related anti-cancer therapy.
5.	**At the discretion of the investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, <u>including high dose corticosteroids and</u>** TNF-α inhibitors **<u>to treat adverse reactions</u>.**
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.	

6 Study Drugs

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

When MEDI4736 and tremelimumab are to be administered on the same day, MEDI4736 infusion will start at least 60 minutes after the end of tremelimumab infusion.

6.1 MEDI4736

6.1.1 Study Drug Information for MEDI4736

Manufacturer	MedImmune		
Expiration/Retest Date	*Expiration/retest dates are documented on the Certificate of Analysis and/or stability certification or in the in the QA Disposition of Investigational Medicinal Product (IMP) Report.*		
Container Description	*Type:* Single use vial	*Material:*	*Size:*
Formulation	Lyophilized powder containing 200 mg MEDI4736. When reconstituted with 4 mL of water for injection (WFI), the solution contains 50 mg/mL MEDI4736, 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (weight/volume [w/v]) polysorbate 80, at pH 6.0.		
Active Ingredient Content	*Mass/Weight:* 200 mg	*Volume:* n/a	*Concentration:* n/a
Storage Conditions	+2°C to +8°C		
Stability after reconstitution	24h at 2 to 8°C and 4h at 25°C/ambient		
Labeling	Product name, lot number, route of administration, and storage conditions		

6.1.2 MEDI4736 Preparation

Each vial of MEDI4736 selected for dose preparation should be inspected. If there are any defects noted with the investigational product (IP), the Investigator, Site Monitor, and Sponsor should be notified immediately.

Preparation of MEDI4736 and preparation of the intravenous (IV) bag are to be performed by the IP Manager or designated personnel using aseptic technique. . No incompatibilities between MEDI4736 and polyvinylchloride or polyolefin copolymers have been observed.

MEDI4736 does not contain preservatives and any unused portion must be discarded.

MEDI4736 requires reconstitution prior to use. The reconstitution should be performed with 4 mL sterile water for injection (WFI) for each vial with the liquid added gently to the side of the vial to minimize product foaming. The vial should be gently rotated or swirled for 5 minutes or until dissolution is complete. The vial should not be shaken or vigorously agitated. Reconstituted MEDI4736 should stand undisturbed at room temperature for a minimum of 5

minutes or until the solution clarifies. The reconstituted solution should appear clear or slightly opalescent. A thin layer of bubbles on the liquid surface is considered normal.

6.1.2.1 Preparation of 0.3 mg/kg dose for administration with a syringe

For an IV dose equal to 0.3 mg/kg, administration will be performed using a polypropylene syringe and IV administration set. Each dose will be administered as an admixture of MEDI4736 and 0.9% (w/v) saline prepared to a set volume. The delivery volume for the dose level of 0.3 mg/kg is 12 mL. The preparation volume will include additional volume of admixture to allow for purging the lines of the administration set.

The dose preparation procedure is as follows:

1. Calculate the amount of admixture to prepare using the formula below:

Preparation Volume (mL)	=	Delivery Volume (mL)	+	Hold-up Volume of Administration Set (mL)

2. Calculate the concentration of MEDI4736 in the admixture using the formula below:

Final Dose Concentration (mg/mL)	=	Dose (mg/kg)	X	Subject Weight (kg)	÷	Delivery Volume (mL)

3. Determine the volume of reconstituted MEDI4736 (mL) to be prepared in 0.9% (w/v) saline required for the calculated concentration:

Volume of MEDI4736 to be Diluted (mL)	=	Final Dose Concentration (mg/mL)	X	Preparation Volume (mL)	÷	Drug Product Concentration (nominal 50 mg/mL)

4. Determine the volume of 0.9% (w/v) saline (mL) used to dilute MEDI4736:

Volume of 0.9% (w/v) Saline (mL)	=	Preparation Volume (mL)	-	Volume of MEDI4836 to be Diluted (mL)

The admixture should be prepared in a separate sterile container. Following preparation, the admixture must be mixed by gentle swirling or inversion. The admixture should then be inspected to ensure the solution is clear and then drawn up into the syringe. Intravenous lines are then purged and the specified delivery volume is administered, using a 0.2-µm in-line filter. Subjects will receive the infusion over 60 minutes (± 5 minutes) in duration. Disconnect the IV line when the correct volume has been delivered. See Section 6.1.3 for details regarding administration of MEDI4736.

Example:

1. The administration lines to be used have a hold-up volume of approximately 10 mL. The volume of admixture to prepare is 22 mL (12 mL + 10 mL)
2. The Final Dose Concentration of MEDI4736 for a subject weighing 100 kg and dosed at 0.3 mg/kg will be 2.5 mg/mL. (0.3 mg/kg × 100 kg ÷ 12 mL)
3. The volume of reconstituted MEDI4736 required will be 1.1 mL. (2.5 mg/mL × 22 mL ÷ 50 mg/mL)

4. The volume of 0.9% (w/v) saline required to dilute MEDI4736 will be 20.9 mL. (22 mL - 1.1 mL). After gentle mixing the admixture in the syringe by gentle inversion the lines are purged and 12 mL is administered over the specified infusion time.

6.1.2.2 Preparation of 1 mg/kg, 3 mg/kg and 10 mg/kg dose for administration with an IV bag

Doses greater than or equal to 1 mg/kg 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 volume of reconstituted MEDI4736 to add to the IV bag is calculated as follows:

Volume of MEDI4736 (mL)	=	Dose (mg/kg)	X	Subject Weight (kg)	÷	MEDI4736 Concentration (nominal 50 mg/mL)

A volume of diluent equal to the calculated volume of MEDI4736 to be added to the IV bag must be removed from the bag prior to addition of MEDI4736. The calculated volume of MEDI4736 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 subject weighing 80 kg and dosed at 10 mg/kg, 16 mL [10 mg/kg × 80 kg divided by 50 mg/mL] of MEDI4736 is to be diluted in a 250 mL IV bag . First, 16.0 mL of diluent is removed from the IV bag, and then 16 mL of MEDI4736 is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted MEDI4736 is administered as described below.

NOTE: Per Amendment 5, Fixed dosing will be used for Cohort 4a (See Section 6.1.2.3). Per Amendment 6, fixed dosing will be used for the optional study treatment extension as described in Section 3.1.12 and Section 8.8.

6.1.2.3 Preparation of 1500 mg dose for administration with an IV bag (Amendment 5 Cohort 4a subjects and for optional study treatment extension)

Beginning with Amendment 5, subjects enrolled to Cohort 4a will receive a fixed dose of MEDI4736: 1500 mg Q4W for subjects > 30 kg.

Beginning with Amendment 6, subjects who receive optional study treatment extension per Section 3.1.12 will receive a fixed dose of MEDI4736 (1500 mg Q4W for subjects > 30 kg), unless a lower dose is agreed upon by Investigator and Sponsor.

NOTE: If a subject's body weight drops to ≤ 30 kg while on the study, the subject will be dosed at 600 mg Q4W for MEDI4736 as long as the body weight remains ≤ 30 kg.

The volume of reconstituted MEDI4736 required for 1500 mg is 30 mL (see calculation below). This will require approximately 8 vials of MEDI4736, depending on the extractable volume from the vials.

Volume of MEDI4736 (mL)	=	Dose (1500 mg)	÷	MEDI4736 Concentration (nominal 50 mg/mL)

Doses 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 30 mL diluent must be removed from the bag, and then, the 30 mL reconstituted MEDI4736 is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted MEDI4736 is administered as described below.

6.1.3 Administration of MEDI4736

Following preparation of the dose, MEDI4736 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.
- Prior to the start of the infusion, the IV contents must be at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
- MEDI4736 must not be administered via IV push or bolus, but as an IV infusion.
- MEDI4736 solution should not be infused with other solutions or medications.
- MEDI4736 must be administered at room temperature by controlled infusion into a peripheral vein or central line.
- Subjects will receive the dose of MEDI4736 as an IV infusion over 60 (± 5) minutes. **An infusion time of less than 55 minutes is considered a deviation.**
- When a syringe is used for the infusion, the syringe should be disconnected when the correct volume has been infused. See Section 6.1.2.1 for details.
- When an IV bag is used for the infusion, the entire contents of the IV bag should be administered as an IV infusion, using a 0.2- or 0.22-µm in-line filter.
- 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, the infusion will be completed according to institutional policy to ensure the full dose is administered. If the line was not flushed, documentation is required.
- The total time between reconstitution of MEDI4736 to 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 MEDI4736 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 6.3.
- See Section 3.1.8.1 for guidelines for infusion-related reactions.

6.2 Tremelimumab

6.2.1 Study Drug Information for Tremelimumab

Manufacturer	MedImmune		
Expiration/Retest Date	*Expiration/retest dates are documented on the Certificate of Analysis and/or stability certification or in the QA Disposition of Investigational Medicinal Product (IMP) Report*		
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 Preparation

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.

The dose of tremelimumab for administration must be prepared by the IP manager or designated personnel using aseptic technique. No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed. However, administration sets containing cellulose-based filters should not be used with tremelimumab.

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

Dose Calculation:
Subject weight measurements can be taken in street clothes without shoes and a calibrated scale must be used for all measurements.

The dose will be calculated at each dosing visit using the following formula:

Tremelimumab Dose (mL)	=	subject weight (kg)	X	dose level (mg/kg)	÷	Tremelimumab concentration (20 mg/mL)

The corresponding volume of investigational product should be rounded according to institutional practice. Each vial contains a small amount of overage and the overage should be utilized as much as possible before using another vial.

The number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

Number of vials	=	Tremelimumab Dose (mL)	÷	20 (mL/vial)

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. To prepare the IV bag:

- First, calculate the dose volume of tremelimumab required.
- Second, remove the volume of IV diluent equivalent to the calculated dose volume of tremelimumab from the IV bag.
- Lastly, add the calculated dose volume of tremelimumab to the IV bag.
- Gently mix the solution in the bag by inverting up and down. Avoid shaking the IV bag to prevent foaming.

Example for a 10 mg/kg dose: A subject weighing 85 kg will require 42.5 mL (3 vials) of tremelimumab. Remove 42.5 mL of diluent from the IV bag. Add the 42.5 mL of tremelimumab to the IV bag and gently mix by inverting up and down.

NOTE: Per Amendment 5, Fixed dosing will be used for Cohort 4a (See Section 6.2.2.1).

6.2.2.1 Preparation of 75 mg dose (Amendment 5, Cohort 4a subjects)

Dose Calculation:
Beginning with Amendment 5, subjects enrolled to Cohort 4a will receive a fixed dose of tremelimumab: 75 mg for subjects > 30 kg.

Note: If a subject's body weight drops to ≤ 30 kg while on the study, the subject will be dosed at 30 mg for tremelimumab as long as the body weight remains ≤ 30 kg.

The volume of tremelimumab required for a 75 mg dose is 3.75 mL (see calculation below).

Tremelimumab Dose (mL)	=	dose level (75 mg)	÷	Tremelimumab concentration (20 mg/mL)

The corresponding volume of tremelimumab should be rounded according to institutional practice.

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. To prepare the IV bag (for a 75 mg dose), remove 3.75 mL of diluent. Then, add 3.75 mL of tremelimumab to the IV bag. Gently mix the solution in the bag by inverting up and down. Avoid shaking the IV bag to prevent foaming.

6.2.3 Administration of Tremelimumab

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

- 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.
- 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.
- Tremelimumab must not be administered via IV push or bolus but as a controlled IV infusion.
- Tremelimumab solution should not be infused with other solutions or medications.
- Tremelimumab must be administered at room temperature by controlled infusion into a peripheral vein or central line.
- The entire contents of the IV bag should be administered by IV infusion over 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, 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 will be monitored before, during and after infusion with assessment of vital signs according to Section 6.3.
- See Section 3.1.8.1 for guidelines for infusion-related reactions.

6.3 Assessment of Vital Signs during Administration of Study Drugs

Subjects will be monitored before, during and after tremelimumab and MEDI4736 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		
MEDI4736	X	Every 15 (± 5) minutes	X	X	x

Note: When MEDI4736 and tremelimumab are to be administered on the same day, MEDI4736 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 MEDI4736 (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)				
Drug	**Pre Dose**	**During Infusion**	**End of Infusion (± 5 minutes)**	**15 (± 5) Minutes Post Infusion**
MEDI4736	X	Every 30 (± 5) minutes	X	X

6.4 Estimated Study Requirements

Drug	***Required Quantity***
MEDI4736	9200 vials
Additional MEDI4736 for optional study treatment extension per Section 3.1.12	1000 vials
tremelimumab	1550 vials

6.5 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 MEDI4736 or tremelimumab. Any overdoses with these drugs should be managed symptomatically and reported, with or without associated AEs/SAEs, according to Section 7.1.5 and Section 7.1.6.

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 that 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 LICR studies to include any events, intercurrent diseases and accidents observed while the patient/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 patient/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 patient/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.

7.1.2 Additional SAE Definitions for this Study

For the purpose of this study, the following events are considered medically important conditions and must be treated as SAEs:

1. Pregnancy
2. Overdose (as defined in Section 6.5)

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 adverse events to the investigational agent(s) will be determined by the Investigator on the basis of their 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)
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 Section7.1.4. 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 as per Sections 7.1.1 and 7.1.2, 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. This should be done using the "Initial Serious Adverse Event Report Form," provided by the Sponsor, or, if Medidata RAVE data capture is utilized, using the respective Adverse Event and Safety Case Summary eCRFs (and indicated as an SAE). This includes any deaths that occur after the off-study date, but within 30 days of last study drug administration. Note: If an SAE cannot be reported through the "Initial Serious Adverse Event Report Form" or through Medidata RAVE 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 by an "Initial Serious Adverse Event Report Form" or through Medidata RAVE 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 Sponsor Contact, as specified in "Sponsor Information", Section 8.4. Studies utilizing the Medidata "Safety Gateway", built into the eCRF, and respective SAE reporting procedures, do not require reporting by fax or email. Questions related to "Safety Gateway" procedures should be directed to the Drug Safety Contact or Primary Sponsor Contact.

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

Serious adverse events must also be reported by the Principal Investigator to the respective Institutional Review Board after being assigned a serious adverse event tracking number by the Sponsor. Institutional Review Boards may have specific rules on which Adverse Events need to be reported expeditiously, as well as, the time frames for such reporting.

SAE 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 AstraZeneca/Medimmune 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, using the "SAE Follow-up Report form", provided by the Sponsor.

7.1.8 Adverse Events of Special Interest (AESIs)

An AESI is an event of scientific and medical interest specific to the understanding of the investigational product(s) 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 product(s).

AESIs for MEDI4736 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 MEDI4736 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 MEDI4736 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 MEDI4736 and tremelimumab Investigator Brochures. Guidelines for the management of subjects experiencing the toxicities listed below can be found in Section 3.1.8.1 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)."***.

7.1.8.1 Hepatic Function Abnormality

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 disease (e.g., 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 ≥ 3 x ULN **or** total bilirubin ≥ 2 x 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.

7.1.8.2 Pneumonitis

Adverse events of pneumonitis are also of interest for the Sponsor, as pneumonitis has been observed with anti-PD-1, anti-PD-L1, and anti-CTLA-4 antibodies.(69) Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

7.1.8.3 Infusion Reactions

Adverse events of infusion reactions (also termed infusion-related reactions) are of special interest to the sponsor and are defined, for the purpose of this protocol, as all AEs occurring from the start of the study treatment infusion up to 48 hours after the infusion start time. For all infusion reactions, the eCRF should be completed as described above, and all SAEs should be reported to the Sponsor as described in Section 7.1.6.

7.1.8.4 Hypersensitivity Reactions

Hypersensitivity reactions have been reported with anti-PD-L1 and anti-PD-1 therapy.(69) As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of 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.

7.1.8.5 Gastrointestinal Disorders

Diarrhea and colitis are the most commonly observed treatment-emergent SAEs. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed.

7.1.8.6 Neurotoxicity (Neuropathy/Neuromuscular toxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis.

7.1.8.7 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.

7.1.8.8 Dermatitis/Rash

Prompt treatment with steroids (topical or systemic based on severity) is important as per current established toxicity management guidelines.

7.1.8.9 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.

7.1.8.10 Pancreatic Disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis (or labs suggestive of pancreatitis); increased serum lipase, increased serum amylase).

7.1.8.11 Uveitis

Uveitis is among the clinically significant, immune-mediated adverse reactions that occurred in less than 1% of subjects treated with agents targeting the PD-1 / PD-L1 pathway. Physicians should initiate ophthalmologic evaluation should symptoms develop.

7.2 Administrative Sponsor Requirements

7.2.1 Pre-Study Requirements

The following are required before study drug can be shipped to the study site:

- Satisfactory Site Validation (conducted by Sponsor, if applicable)
- Signed Statement of Investigator
- Regulatory Approval (e.g., active IND or IMPD)
- Institutional Review Board approval of Protocol and Informed Consent Form
- Executed Clinical Trial Agreement (if applicable)

7.2.2 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.

7.2.3 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.

7.2.4 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.

7.2.5 Monitoring

The Sponsor will oversee the conduct of the study and perform clinical monitoring visits for site validation, 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 case report forms at regular intervals throughout the trial to verify adherence to the protocol, the completeness, accuracy and consistency of the data, and adherence to Good Clinical Practice guidelines. The Clinical Monitor should have access to patient charts, laboratory reports and other patient records needed to verify the entries on the case report forms ("source data verification").

7.2.6 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 an 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.

7.2.7 Premature Subject Withdrawal from Treatment or from Study

A subject may withdraw from 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, all efforts will be made to complete the required study procedures and report the treatment observations as thoroughly as possible.

A complete final evaluation should be made at the time of the subject's withdrawal from treatment or from the study. 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.

7.2.8 Early Trial Termination

Sponsor and Investigator have the right to terminate the study early. Specific study stopping rules are listed in Section 3.1.14. 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.

7.2.9 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
- 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-off 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 Serious Adverse Events (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.

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 case report forms 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.

7.3.5 Inclusion of Women and Minorities

Both men and women and members of all ethnic groups are eligible for this trial. The expected distribution of men and women enrolled is based on the experience with other clinical trials at the study sites included in this study. The anticipated study population will be about 50% male and 50% female.

8 Appendices

8.1 Protocol Version History

Version 000 **Issue date: 27-June-2013** **Summary of Changes:** n/a
Version 001 (Amendment 001) **Issue Date: 26-July-2013** **Summary of Changes:** Following FDA comments, updates for this amendment are outlined below: • Section 3.1.9, DLT and MTD: second bullet: all Grade 4 irAEs are now considered as DLTs. • Section 3.1.14 Safety Monitoring and Study Stopping Rules: reason (3) was updated to include specific toxicities. • Section 5.1 Inclusion Criteria 6: adequate marrow function is now defined as hemoglobin ≥ 9 g/dl absolute neutrophil ≥ 1500/m3
Version 002 (Amendment 002) **Issue Date: 06-September-2013** **Summary of Changes:** Following Roswell Park Cancer Center SRC review, Dana-Farber Cancer Institute SRC pre-review and Memorial Sloan-Kettering Cancer Center Medicine Steering review, updates for this amendment are outlined below: • Section 3.1.6 Sample Size Considerations was updated to include confidence intervals indicating the degree of precision that can be expected when estimating AE of special interest incidence rates within each cohort • Section 3.1.7 Treatment Cohorts and Treatment Schema & section 6 Study Drugs, MEDI4736 and tremelimumab administration was updated to a 60 minutes (± 10 minutes) infusion. • Section 3.1.8.1 MEDI4736 and tremelimumab Dose Modification Due to Toxicity, footnote c was added to define maximum allowable time for decrease or interruption of MEDI4736 or tremelimumab infusion rate • Section 3.1.9: the definition of a DLT was clarified • Section 3.1.11 Per-Protocol Subject Evaluability and Replacement was updated to confirm that patient in the dose-escalation phase not evaluable for DLT will be replaced as defined as defined in Section 4.1.2 • Section 3.2 Study Flowchart was updated to specify that “other Labs and Assays” should be performed at screening only if patient is deemed eligible. Tumor biopsies time points were updated to ensure consistency with section 8.7.7.2 Tumor Biopsies

- Section 4 Study Objectives and Endpoints sections were re-ordered to ensure consistency across the document
- Section 5.1 Inclusion Criteria, Inclusion criterion 5 was updated to correct creatinine unit.
- Section 6 Study Drugs and Section 8.5 Study Drug Information were merged.
- Section 6 Study Drugs:
    - Formatting was updated
    - MEDI4736 and tremelimumab stability after reconstitution were added
    - Maximum allowable time for decrease or interruption of MEDI4736 or tremelimumab infusion rate was added
    - Rounding rules for tremelimumab dose calculation were updated
    - Specifications for tremelimumab via a central line were added
- Section 8.2 Participating Study Sites, Investigators and Staff Patrick Ott, MD, PhD replace Stephen Hodi, MD as principal investigator
- 8.7.7.2 Tumor Biopsies was updated to state that tumor biopsies will be obtained for all biopsiable tumors in the expansion phase

Version 003 (Amendment 003)
Issue Date : 11-October-2013
Summary of Changes:

Following Dana-Farber Cancer Institute IRB comments updates for this amendment are outlined below:

- Section 3.1.8.1 MEDI4736 and tremelimumab Dose Modification Due to Toxicity was updated to mention that MEDI4736 and tremelimumab should not be held for dermatologic irAEs
- Section 4.5.2 Subject Evaluation and Statistics and Section 8.7.7.2 Tumor Biopsies were updated to clarify collection of biopsiable tumors in the expansion phase and include a statistical justification for the sample size

Version 004 (Amendment 004)
Issue Date: 18-February-2015
Summary of Changes:

Based on updated information from Medimmune and to provide clarifications for the protocol, updates for this amendment are outlined below. Due to the extent of changes made in this amendment, a separate document (Amendment 4 Summary of Changes) was generated. Outline of changes:

- Section 3.1.8.1 (MEDI4736 and tremelimumab Dose Modification Due to Toxicity): Table 3.1.8-1 was modified and replaced with an updated table based on the most recent recommendations from Medimmune. The 2 guidelines from Medimmune for management of toxicity and for management of diarrhea and colitis were referenced in Section 3.1.8.1.
- Section 3.1.9 (DLT and MTD): The DLT definition and criteria were updated to be consistent with Medimmune recommendations

- Section 3.1.10 (Patient Withdrawal): Item 3 was updated to indicate that either objective progression, per irRC, or symptomatic progressions is sufficient cause for patient withdrawal.
- Section 3.1.14 (Safety Monitoring and Study Stopping Rules): Item 2 was changed to add clarification that anaphylactic reaction refers to severe reactions such as those associated with respiratory and cardiovascular failure.
- Section 3.1.16 (Post Study Follow-up): Clarification was added regarding the distinction between Post Treatment Follow-up and Post Study Follow-up (which will be done at least every 6 months for up to 3 years from the initiation of the treatment)
- Section 3.2.1: Changes were made to flowchart to add pregnancy tests to Weeks 9, 17, 33. 41 and 49
- Section 3.2.1and Section 3.2.2:
    - Clarifications for hematology testing and addition of free T3 and free T4 to blood chemistry panel were added to flowcharts.
    - Clarification was added regarding the distinction between Post Treatment Follow-up and Post Study Follow-up (which will be done at least every 6 months for up to 3 years from the initiation of the treatment).
- Section 4.1.2 (Patient Evaluation and Statistics) was modified to clarify that patients will be considered evaluable for a DLT if they receive at least75% of the planned dose during the DLT evaluation period (except for patients who discontinued prematurely due to DLT)
- Section 5.2 (Exclusion criteria): Number 16 was modified to provide more detailed guidance regarding contraception use.
- Section 6.5 (Drug Overdose Management) was modified to provide clarification on what is considered an overdose as well as treatment and reporting procedures.
- Section 7.1 (Documentation and Reporting of AEs):
    - A new section was added as Section 7.1.2, Additional SAE Definitions for this Study: Pregnancy and Overdose
    - Other sections were re-numbered as appropriate
    - Section 7.1.4 (General Reporting Requirements) was re-numbered to Section 7.1.5.
    - Section 7.1.8 (Adverse Events of Special Interest) was added.
- Section 8.3 (Participating Laboratories): the address for Quintiles Laboratories was changed.
- Section 8.4 was updated to include the new Project Manager for this study.
- Section 8.5 (Tumor Response Assessment by irRC): The antitumor response based on total measurable tumor burden was updated to define a minimum size requirement for considering lesions measurable.
- Section 8.7.7.1 (Archival Tumor Samples) was revised to define the availability, quantity and quality of archival tumor samples during the screening period. The section was also updated to allow patients who are otherwise eligible to obtain fresh biopsies prior to start of study drug.

Amendment 005
Issue Date: 27-OCT-2015
Summary of Changes

In order to align the protocol with current recommendations from MedImmune, the following changes were made:

- Synopsis, Sections 2.4, 3.1.2, 3.1.4, 3.1.7.2, and 5.1 and Figure 3 were changed (or notes were added) to indicate:
    - Disease states of non-small cell lung cancer and head and neck cancer were removed from the study and were replaced by non-triple negative breast cancer, for a total of 5 expansion cohorts. Cohort sample sizes were increased to 15, for a total of 75 subjects in the expansion phase.
- Synopsis, Sections 2.3, 2.4, 3.1.7, Figure 1, and Figure 2: Dosing for Cohorts 3a and 4a were changed (or notes were added):
    - Cohort 3a: Tremelimumab, 1mg/kg Q4W for 4 cycles; MEDI4736 3 mg/kg, Q2W for 12 four-week cycles (previously: tremelimumab 1mg/kg Q4W for the first 6 cycles and then Q12W; MEDI4736 3 mg/kg, Q2W for 13 cycles)
    - Cohort 4a: Tremelimumab, 75 mg Q4W for 4 cycles; MEDI4736 1500 mg, Q4W for 12 four-week cycles (previously: tremelimumab 1mg/kg Q4W for the first 6 cycles and then Q12W; MEDI4736 10 mg/kg, Q2W for 13 cycles). Fixed dosing was added for Cohort 4a.
    - Cohorts 4 and 5 were removed from the study
- Section 3.1.5: Number of sites and subjects were updated
- Section 3.1.6: Sample size considerations were updated to reflect change in sample size of 15 per disease cohort, with a total of 75 subjects in the expansion phase.
- Section 3.1.7.1: clarification was added for review of DLTs
- Section 3.1.8.1:
    - Added references for Yervoy™, Opdivo®, and Keytruda® to provide additional guidance for dose modifications.
    - For Table 3.1.8-1, the Note for temporary hold of MEDI4736 and tremelimumab until resolution of event was moved from the irAE section to the top of the table to indicate that the note refers to all sections.
    - Table 3.1.8-1 was updated based on the most recent dose modification guidelines from Medimmune. The following additions were made:
        - In addition to the criteria for permanent discontinuation of M and T depicted below, permanently discontinue M and T also for: 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; and recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.
        - Under irAE Grade 2: For *pneumonitis/interstitial lung disease*, the decision to reinitiate M and T upon resolution shall be based upon treating physician's clinical judgment (as long as the event does not meet DLT criteria)
        - Under irAE Grade 3: recommendations were provided for elevated serum creatinine and asymptomatic increases in amylase or lipase

- Under irAE Grade 4: recommendations were provided for asymptomatic increases in amylase or lipase

- Section 3.1.8.2 (MEDI4736 and tremelimumab Discontinuation) was re-numbered as Section 3.1.8.3; and a new Section 3.1.8.2 (MEDI4736 and Tremelimumab Dose Modification Not Due to Toxicities) was added. Cross references were updated as needed.
- Section 3.1.8.3: clarification was provided to indicate that the Follow up every 8 weeks, not to exceed week 64, would start 8 weeks after the Last Study Drug +90 day visit.
- Section 3.1.9
  - #3, 2nd bullet: "Grade 3 asymptomatic endocrinopathy" was changed to "Grade 3 endocrinopathy that becomes asymptomatic."
  - #3, 8th bullet: Grade ≥ 3 neutropenia was clarified to indicate that (1) is not associated with fever or systemic infection, and (2) does not require medical intervention, and (3) improves to Grade 2 within 7 days (changed from 3 days).
  - #3, 10th bullet: for thrombocytopenia, the criterion for improvement to Grade 2 was changed from 3 to 7 days.
  - The rules for adjudicating DLTs were clarified and expanded
  - A sentence was added to indicate that subjects who experience a DLT will be discontinued from study treatment and will be followed as described in Section 3.1.8.3. 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.
- Section 3.1.10:
  - Section was clarified to indicate reasons for withdrawal from treatment vs. withdrawal from study.
  - The withdrawal criteria from Section 7.2.7 were deleted and combined with those in Section 3.1.10.
  - Additional cross reference to Section 3.1.8 was added regarding patient withdrawal due to necessary dosing interruptions or discontinuations
- Section 3.1.15: duration of study was updated based on changes of Amendment 5.
- Section 3.1.16: additional clarification was added for Post Treatment Follow-up (On Study Follow-up) versus Post Study Follow-up.
- Section3.2 1:
  - Updated flowchart to show pre and post Amendment 5 dosing for MEDI4736 and tremelimunab.
  - Created flowcharts specific for pre Amendment 5, Cohort 3a Post Amendment 5, and Cohort 4a Post Amendment 5; additional flowcharts were included to provide details specific to Cohorts 3a and 4a as a result of Amendment 5.
  - Cycle 13 was deleted for Cohorts 3a and 4a
  - Clarified that ECG is 12-lead ECG
  - Footnote was added to clarify that all AEs will be reported for 90 days following last study drug dose.
  - For Cohorts 3a and 4a, SCCHN was removed from CTC assessment
  - For Cohorts 3a and 4a, tremelimumab PK assessment was removed from Cycle 10 and from Post Treatment Follow-up; and total volume blood drawn was adjusted accordingly.

    - For Cohort 4a, disease assessment by RECIST and irRC were moved from Week 7 to Week 9 to coincide with Study visit for new dosing schedule in Amendment 5. All other assessments for Weeks 7, 11, 15, 19, 23, 27, 31, 35, 39, 43 and 47 were removed.
- Section 3.2.2: Flowchart for subjects who discontinue treatment per Section 3.1.8.3:
    - Clarification was provided to flowchart to indicate that the 8 week follow-up for up to 64 weeks is part of the On Study Follow-up.
    - Additional flowcharts were included to provide details specific to Cohorts 3a and 4a as a result of Amendment 5; created flowcharts specific for pre Amend 5, Cohort 3a Post Ament 5, and Cohort 4a Post Amend 5.
    - Footnote was added to clarify that all AEs will be reported for 90 days following last study drug dose or until subject enters the Post Study Follow-up.
    - For Cohorts 3a and 4a, SCCHN was removed from CTC assessment
- Section 4.1.2: Clarification was added (see bold). All subjects who receive at least the **first two** cycles of treatment **(i.e., approx. 8 weeks)** and respective safety assessments, as well as, all subjects who discontinue the study prematurely due to DLT are considered fully evaluable per protocol for DLT.
- Section 5.2
    - #11: Clarification was provided to indicate "If a patient previously received investigational treatment, the last dose of investigational treatment was administered within 4 weeks of Day 1 of the study or adverse event(s) attributable to investigational treatment have not resolved to Grade 1 or better."
    - #16: For females of childbearing potential and non sterilized males, the period for continuation of contraception after final dose of investigational product was changed from 90 days to 6 months. This is a requirement for tremelimumab.
- Section 6.1.2.3: Additional section was added for instructions on the preparation of the fixed dose of 1500 mg MEDI4736.
- Section 6.2.2: In the calculation example, clarification was added that the example is for a 10mg/kg dose.
- Section 6.2.2.1; Additional section was added for instructions on the preparation of the fixed dose of 75 mg tremelimumab
- Section 6.3: estimated study requirements were updated.
- Section 7.1.6: additional detail and clarification were added regarding reporting of SAEs to the Sponsor within 24 hours**.**
- Section 7.1.8: clarification was added regarding recording of AESIs. Expedited reporting by the Investigator to the Sponsor within 24 hours is not required.
- Section 7.1.8.6, Uveitis, was added.
- Section 7.2.7: Section was updated to be aligned with Section 3.1.10. Study Status Outcome form was changed to the "appropriate form."
- Section 8.1 (Protocol Version History):
    - The format of the table was changed to allow more space for recording the Summary of Changes.
    - The Issue date for Amendment 4 was corrected to 18-February-2015 (previously 06-February-2015)
- Section 8.4: Primary Sponsor Contact was changed from [redacted], who was already listed in this section as the Clinical Project Manager.

- Section 8.7.7.2: for tumor biopsy collections, added "(or Cycles 8 to 12 post Amendment 5)".
- Administrative Changes
    - The term "patient(s) was changed to "subjects(s)" throughout the document, where appropriate.
    - General spelling and capitalization changes, as needed
    - Added IND # and signature line to Synopsis page
    - Updated abbreviations list
    - Updated footer and synopsis page with new protocol format and logo

Amendment 006
Issue Date: 04-JUN-2016
Summary of Changes:

- Synopsis: The following statement was added: "**Per Amendment 6**, optional treatment extension beyond the original 12- or 13-cycle treatment period (Core Study) will be available for subjects who complete the Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator. See Section 8.8 for details.
- Sections for Participating Study Sites and Participating Laboratories were deleted from the Synopsis, as these sections are not included in the current protocol template.
- Section 3.1.7. The infusion time for MEDI4736 and tremelimumab was changed from 60 (± 10) minutes to 60 (± 5) minutes, and the following statement was added: **"**An infusion of less than 55 minutes is considered a deviation." In addition, the following change was made (change in bold): "On the days when MEDI4736 and tremelimumab are to be administered, MEDI4736 infusion will start **at least** 60 **~~(±10)~~** minutes after the end of tremelimumab infusion."
- Section 3.1.8.1:
    - The statement, which referenced guidelines for ipilimumab, nivolumab, and pembrolizumab was deleted.
    - The reference to tremelimumab guideline was deleted, as this guideline is now included in Medimmune's Dosing Modification and Toxicity Management Guidelines (also referenced in this section).
    - MEDI4736 and Tremelimumab Dose Modifications due to toxicity were updated according to current recommendations from MedImmune/AstraZeneca (Dated 02-OCT-2015).
- Section3.1.8.2:
    - For Point 2, "7 days or less" was changed to "≤ half the planned dosing interval."
    - For Point 3, "7 days" was changed to "half the planned dosing interval."
- Section 3.1.8.3: The section was changed **FROM**: "Subjects who permanently discontinue treatment as defined in Section 3.1.8.1 and Section 3.1.8.2, and who are **not** withdrawn from study as defined in Section 3.1.10 and/or Section 7.2.7, will remain on study on a modified/reduced study schedule without study drug administrations as per Section 3.2.2 for the remainder of the planned study or until withdrawn from study as per Section 3.1.10 and/or Section 7.2.7. For example, if a subject permanently discontinues treatment due to toxicity, then the subject will be followed on study according to the

schedule defined in Section 3.2.2 until disease progression or initiation of alternative anticancer therapy including another investigational product. Under the modified/reduced study schedule as per Section 3.2.2 subjects will be followed up for up to 64 weeks according to the following assessments:

- Disease assessments (including appropriate imaging), as per the original schedule (see Section 3.2.1), up to Week 64.
- End of Study Post treatment Follow-up (On Study Follow-up) scheduled to match the required time frames from the last study drug administrations (Section 3.2.2).
- Follow up every 8 weeks, not to exceed week 64, starting 8 weeks after the Last Study Drug +90 day visit (Section 3.2.2).

Thereafter, the subjects will be taken off study and they will enter the Post Study Follow-up as per Section 3.1.16."

TO: "Subjects who permanently discontinue treatment as defined in Section 3.1.8.1 and Section 3.1.8.2, and who are **not** withdrawn from study as defined in Section 3.1.10 and/or Section 7.2.7, will proceed to the Post Treatment Follow-up (On Study Follow-up) for 90 days after the last study drug treatment according to Section 3.1.16. Thereafter, the subjects will be taken off study and they will enter the Post Study Follow-up as per Section 3.1.16."

- Section 3.1.10:
  - Treatment withdrawal criterion #6 "Initiation of alternative anti-cancer therapy including another investigational agent" was moved to Study withdrawal criterion #2 and changed to "Initiation of alternative anti-cancer therapy (marketed or investigational)."
  - The following paragraph was changed **FROM**: "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 procedures according to Section 3.1.8.3." **TO: "**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 Post Treatment Follow-up (On Study Follow-up) procedures (see Section 3.2) followed by the Post Study Follow-up (see Section 3.1.16)."
- Section 3.1.11 was changed **FROM:** "Subjects who are not considered fully evaluable per protocol for the primary objective of safety and tolerability per Section 4.1.2 may be replaced. In the dose-escalation phase, subjects who are not evaluable for DLT will be replaced." **TO**: "In the *dose escalation phase*, 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 considered fully evaluable for DLT per Section 4.1.2 will be replaced."
- Section 3.1.12 was updated to indicate that optional treatment extension beyond initial study is permitted. The following statement was added: "Optional treatment extension beyond the original 12- or 13-cycle treatment period (Core Study) will be available for subjects who complete the Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator. See Section 8.8 for details."

- Section 3.1.13: “No formal interim analysis will be performed” was changed to “No formal interim analysis is currently planned.”
- Section 3.1.15 and Section 3.1.16: reference was provided to Section 3.1.12 regarding optional study treatment extension.
- Section 3.1.16:
    - Paragraph 2 was changed **FROM:** “Post Treatment Follow-up (On Study Follow-up) will be conducted according to Section 3.2.1 (for subjects who complete the study) and Section 3.2.2 (for subjects who discontinue treatment prematurely according to Section 3.1.8.3.” **TO**: “Subjects who complete study treatment or discontinue treatment prematurely will enter the Post Treatment Follow-up (On Study Follow-up), which will be conducted for 90 days after the last administration of study drug according to the flowchart in Section 3.2 Refer to Section 7.1.5 for information on collection of adverse events during the Post Treatment Follow-up (On Study Follow-up).”
    - The following was added: “If the determination is made to remove a subject from treatment at a visit that coincides with the first visit of the Post Treatment Follow-up (On Study Follow-up) Period, any assessments required in the post-last treatment visit that are not covered as part of the 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 visit and the post-last treatment visit should not be repeated.”
    - The following correction was made (change in bold): In addition to the Post Treatment Follow-up (On Study Follow-up), there will be a Post Study Follow-up, where clinical outcomes data (dates of progression/relapse, **~~subsequent therapy~~**, and survival) will be collected at least every 6 months for up to 3 years from the initiation of the treatment.
    - The following was added: “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.”
- Section 3.2
    - For each of the 3 major flowcharts in Section 3.2.1, parts 1 and 2 were consolidated into one section and parts 3 and 4 were consolidated into a second section.
    - Deleted the flowcharts related to “Subjects discontinuing treatment per Section 3.1.8.3” to provide alignment with update to Section 3.1.8.3
    - Footnote related to PK collections was deleted and other footnotes were re-numbered as appropriate.
    - Added a Note to Indicate “It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.”
    - ECOG Perf Status was deleted as a single assessment at baseline and added to Physical Exam assessments.
    - For the Cohorts 3 and earlier flowchart, pregnancy test was added to Last study drug +28 days On Study Follow-up Visit

- Added the footnote: “Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart.”
- Added (or clarified) the AE footnote: “See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.” The footnote was re-numbered as appropriate for each flowchart.
- Added amylase and lipase assessments to Chem cont., as these are required for monitoring pancreatitis.
- Deleted MEDI4736 and tremelimumab PK, sPD-L1, ADA, circulating soluble factors, and CTC sample collections. Medimmune has determined that they have adequate data, and samples are no longer needed.
- Deleted blood volume for blood collections, as this information is provided in the Lab Manual.
- Added concomitant procedures to concomitant medications line in flowchart
- Added reference to Section 6.3 for vital signs assessment.
- Disease assessment during Post Treatment Follow-up (On Study Follow-up) was changed from a specific study visit to “'+56 ± 7 days from last disease assessment.” This allows the frequency of disease assessments to remain constant for subjects who complete the study as well as those who discontinue early.
- Collection for flow cytometry and PBMC at baseline and Day 1 were merged as “Day -7 to 1 (pre-dose)”
- Updated formatting, as appropriate

- Section 4.2.1: the following statements were added: “NOTE: Per Amendment 6, samples will no longer be collected for analysis of MEDI4736 and tremelimumab pharmacokinetics, as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2.”
- Section 4.3.1: the following statements were added: “NOTE: Per Amendment 6, samples will no longer be collected for the assessment of anti-tremelimumab and anti-MEDI4736 anti-drug antibodies (ADA), as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2.”
- Section 4.5.1: the following statements were added: “NOTE: Per Amendment 6, samples will no longer be collected for analysis of sPD-L1, circulating soluble factors, and circulating tumor cells (CTC), as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2.”
- Section 4.5.2: “6 disease-specific cohorts” was changed to “5 disease-specific cohorts” to align with other changes made in Amendment 5.
- 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.”
- Section 5.1: Criterion #11 was changed **FROM**: “Able and willing to give valid written consent for biopsy samples (subjects in the expansion phase only).”
  TO: “Able and willing to give valid written consent for biopsy samples (subjects **with biopsiable tumors, and if clinically appropriate**, in the expansion phase only).”

- Section 5.2: contraception requirements were changed from 6 months after last dose of drug to "90 days after last dose of MEDI4736 or 6 months after the final dose of tremelimumab (whichever is longer)."
- Section 5.3.1:
    - Added bold phrase: "Wash-out period: 4 weeks **or 5 half-lives (whichever is shorter)** prior to day 1; 6 weeks for nitrosoureas."
    - Added the following as #5: "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."
- Section 5.3.2: The last statement was modified as follows (changes in bold: "All non-drug therapies must be recorded in the respective sections of the case report form, ~~**or as adverse events**~~".
- Section 6: second paragraph was changed **FROM**: "On the days when MEDI4736 and tremelimumab are to be administered (first day of Cycles 1-7, 10, and 13), MEDI4736 infusion will start 60 minutes after the end of tremelimumab infusion." **TO:** "When MEDI4736 and tremelimumab are to be administered on the same day, MEDI4736 infusion will start at least 60 minutes after the end of tremelimumab infusion."
- Section 6.1, Medi4736:
    - MEDI4736 Preparation and Administration sections were re-organized to remove redundancy and to improve clarity.
    - The following statements were added:
        - Each vial of MEDI4736 selected for dose preparation should be inspected. If there are any defects noted with the investigational product, the Investigator, Site Monitor, and Sponsor should be notified immediately.
        - Preparation of MEDI4736 is to be performed aseptically.
        - Per Amendment 6, fixed dosing will be used for the optional study treatment extension as described in Section 3.1.12 and Section 8.8.
        - Beginning with Amendment 6, subjects who receive optional study treatment extension per Section 3.1.12 will receive a fixed dose of 1500 mg MEDI4736, regardless of weight, unless a lower dose is agreed upon by Investigator and Sponsor.
        - Each dose of investigational product should be administered using 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. Investigational product(s) must not be administered via IV push or bolus but as an IV infusion.
        - Investigational product(s) must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein or central line. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
        - Total in-use storage time from reconstitution of MEDI4736 to start of administration should not exceed 4 hours at room temperature or 24

hours at 2-8°C. If administration time exceeds these limits, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives and any unused portion must be discarded.
        - Subjects will be monitored before, during and after infusion with assessment of vital signs according to Section 6.3.
    - Infusion time window was changed from 60 ±10 minutes to 60 ± 5 minutes, and the following statement was added: **"An infusion of less than 55 minutes is considered a deviation**."
- Section 6.2, Tremelimumab: The following statements were added
    - Each vial of tremelimumab selected for dose preparation should be inspected. If there are any defects noted with the investigational product, the Investigator and Sponsor should be notified immediately.
    - The infusion should be administered by IV infusion over 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.**
    - Subjects will be monitored before, during and after infusion with assessment of vital signs according to Section 6.3.
- Section 6.3 was added to replace Table 3.2-1 for the assessment of vital signs during study drug administration; a second table was added to provide assessment vital signs frequency that may be used if a subject tolerates treatment well for the first 4 doses of MEDI4736 (i.e., no infusion reactions). Other sections were re-numbered accordingly. The following note was added: "Note: When MEDI4736 and tremelimumab are to be administered on the same day, MEDI4736 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."
- Section 6.4: Additional estimated MEDI4736 requirements (1000 vials) for optional study treatment extension was added.
- Section 7.1.5: language for documenting AEs was changed

  FROM: "Documentation of serious and non-serious adverse events 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 adverse events 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."

  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)."

- Section 7.1.6: The following phrase was added to the beginning of the second paragraph: "If the Initial Serious Adverse Event Report Form" is being used..."
- Section 7.2.3: 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."
- Sections 8.2 and 8.3: Tables for Participating Study Sites and Participating Laboratories, respectively, were deleted. The following statement was added: "This information is provided in the Clinical Study File."
- Section 8.7.1: The following statement was added: "NOTE: Per Amendment 6, samples will no longer be collected for analysis of sPD-L1, as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2."
- Section 8.7.4: The following statement was added: "NOTE: Per Amendment 6, samples will no longer be collected for analysis of circulating soluble factors, as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2."
- Section 8.7.5: the following statement was added: "NOTE: Per Amendment 6, samples will no longer be collected for analysis of CTC, as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2."
- Section 8.8 was added to provide additional details and flowchart for subjects who receive optional treatment extension according to Section 3.1.12.
- Administrative:
    - Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.
    - Monitor and Study Monitor were standardized as "Clinical Monitor" in Sections 7.25 and 7.2.9.
    - Updated abbreviation list

Amendment 7
Issue Date: 02-FEB-2017
Summary of Changes:

1. Synopsis: Clarification was provided that fixed dosing of 1500 mg for MED4737 and 75 mg for tremelimumab is for subjects >30 kg.
2. Section 3.1.7, Treatment Cohorts and Treatment Schema:
   a. Clarification was provided regarding administration of MEDI4736 and tremelimumab (reference to Section 6 was provided).
   b. Clarification was also added that, per Amendment 6, optional treatment extension beyond the Core Study is available.
   c. The following text was added:
      Note: The MEDI4736 and tremelimumab fixed doses are for subjects > 30 kg.
      - **MEDI4736 dose: 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 Q4W** as long as the body weight remains ≤ 30 kg.
      - **Tremelimumab dose: 75 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 **30 mg Q4W** for tremelimumab as long as the body weight remains ≤ 30 kg.
3. Section 3.1.8.1, MEDI4736 and tremelimumab Toxicity Management Guidelines: Section was updated to correspond with current Medimmune/AZ guidelines (19August2016).
4. Section 3.1.8.2, MEDI4736 and Tremelimumab Dose Modification Not Due to Treatment-related Toxicities: Section was changed **FROM:** MEDI4736 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 ≤ half the planned dosing interval, the originally planned drug administration should be given. Any respective protocol deviation should be documented, if applicable; 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.
   TO: MEDI4736 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 10 days for Q2W dosing or no less than 21 days for Q4W dosing. 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 ≤ 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. Section 3.1.10.1, Treatment Beyond Progression, was added.
6. Section 3.1.16.1, End of Study Visit, was added.
7. Section 5.2, Exclusion Criteria:

a. #16: Requirements for Contraception: updated entire section for agreement with current Medimmune guidelines.
b. #18 was added: “Subjects must not donate blood while on study and for at least 90 days following the last MEDI4736 treatment or 6 months after the last tremelimumab treatment, whichever is longer.”

8. Section 6.1 (MEDI4736) and Section 6.2 (Tremelimumab): the entire sections were updated and reorganized according to current language from Medimmune/AstraZeneca.
   a. Dextrose was added as an option to be used as a diluent.
   b. Infusion pump requirement was deleted
   c. Weight restriction for fixed doses of MEDI4736 and tremelimumab were added
   d. The following statement was added “See Section 3.1.8.1 for guidelines for infusion-related reactions.”
   e. The following statement was clarified for MEDI4736: ”The total time between reconstitution of MEDI4736 to 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.”
   f. The following statement was clarified for tremelimumab: “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.”
   g. The following statement was added for tremelimumab: “No incompatibilities between tremelimumab and polyvinylchloride or polyolefin have been observed. However, administration sets containing cellulose-based filters should not be used with tremelimumab.”
9. Section 7.1.6: The following statement was added; “Serious adverse event reporting to AstraZeneca/Medimmune is described in a separate agreement.”
10. Section 7.1.8 (AESIs). Additional information was added to the description of the AESIs per the updated guidelines provided by Medimmune/AstraZeneca. The following AESIs were added: neurotoxicity, endocrine disorders (including Type 1 diabetes mellitus), dermatitis/rash, nephritis, and pancreatic disorders.
11. Section 8.8, Details for Subjects Who Continue Treatment Beyond Core Study: Weight restriction for fixed dose of MEDI4736 was added
12. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable. Sections were numbered as appropriate when additional sections were added.

Amendment 8 **Issue Date: 08-JAN-2019** **Summary of Changes:** Section 8.8.2, Reinduction with MEDI4736 and Tremelimumab for Subjects With Confirmed Progression, was added.

8.2 Participating Study Sites, Investigators and Staff

This information is provided in the Clinical Study File.

8.3 Participating Laboratories

This information is provided in the Clinical Study File

8.4 Sponsor Information

Ludwig Institute for Cancer Research 666 3rd Ave 28th Floor New York, New York 10017 Tel: 212-450-1500	*Drug Safety Contact:* [redacted] Assistant Director, Drug Safety Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave 28th Floor New York, New York 10017 [redacted] godonnell@licr.org *Primary Sponsor Contact:* [redacted] Senior Clinical Project Manager Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave 28th Floor New York, New York 10017 [redacted]

8.5 Tumor Response Assessment by irRC

Tumor Response will be assessed by the Immune-related Response Criteria (irRC) as published by Wolchok et al.(68) Response is defined as irCR, irPR or irSD over a period of at least 4 weeks. A condensed/abbreviated summary of the irRC is provided is provided below:

Antitumor response based on total measurable tumor burden:
Only index and measurable new lesions are taken into account when evaluating total measurable tumor burden. The longest diameter and longest perpendicular diameter should be recorded in millimeters (mm). At the baseline tumor assessment, the sum of the products of the two largest perpendicular diameters (SPD) of all index lesions (≥ 10 x 10 mm; five lesions per organ, up to 10 visceral lesions and five cutaneous index lesions) is calculated. At each subsequent tumor assessment, the SPD of the index lesions and of new, measurable lesions (≥ 5 × 5 mm; up to 5 new lesions per organ: 5 new cutaneous lesions and 10 visceral lesions) are added together to provide the total tumor burden.

Time-point response assessment:
Percentage changes in tumor burden per assessment time point describe the size and growth kinetics of both conventional and new, measurable lesions as they appear. At each tumor assessment, the response in index and new, measurable lesions is defined based on the change in tumor burden (after ruling out irPD). Decreases in tumor burden must be assessed relative to baseline measurements (i.e., the SPD of all index lesions at screening).

irCR	Disappearance of all lesions in two consecutive observations not less than 4 weeks apart.
irPR	≥50% decrease in tumor burden compared with baseline in two observations at least 4 weeks apart.
irSD	50% decrease in tumor burden compared with baseline cannot be established nor 25% increase compared with nadir.
irPD	At least 25% increase in tumor burden compared with nadir (at any single time point) in two consecutive observations at least 4 weeks apart.

Overall response assessment:

The overall response is derived from time-point response assessments (based on tumor burden) as follows:

Index and new Measurable Lesions (Tumor Burden)	**Non-index Non-measurable Lesions**	**New Non-measurable Lesions**	**Overall Response**
100%	Absent	Absent	irCR
100%	Stable	Any	irPR
100%	Unequivocal Progression	Any	irPR
≥50%	Absent/Stable	Any	irPR
≥50%	Unequivocal Progression	Any	irPR
<50% TO <25%	Absent/Stable	Any	irSD
<50% TO <25%	Unequivocal Progression	Any	irSD
≥25%	Any	Any	irPD

8.6 Tumor Response Assessment by RECIST

Response and progression will be evaluated using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) Committee.(70)

Objective responses will be measured by serial CT scans of the chest, abdomen, pelvis, and brain MRI if malignant brain lesion(s) were present at time of pre-treatment evaluation. Overall tumor response, based on CT scan results, will be based on observation of measurable and non-measurable disease as compared to baseline in target and non-target lesions every 4 to 12 weeks.

8.7 Laboratory procedures

8.7.1 sPD-L1

The association of sPD-L1 with response to treatment and clinical outcome will be evaluated.

NOTE: Per Amendment 6, samples will no longer be collected for analysis of sPD-L1, as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2.

8.7.2 Flow Cytometry

Samples will be collected for analyses at time points designated in the study flowchart (Section 3.2).

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

8.7.3 PBMC Banking

Peripheral Blood Mononuclear Cells (PBMCs) will be isolated and banked as described below at time points designated in the study flowchart (Section 3.2)

These samples may be used to address several key questions:

- The diversity of the immune cell repertoire may be assessed in PBMCs 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.

8.7.4 Circulating soluble factors

Analyses of circulating levels of soluble factors such as CRP, cytokines and chemokines 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, cancer biomarkers (AFP, CEA, CA125, PSA), granzyme B, IFN, LARGE, CXCL10, SOCS3, APRIL, BAFF, IGF-1, IGF-2, and autoantibodies to host and tumor antigens and exploration of their association with tremelimumab treatment and clinical outcome.

NOTE: Per Amendment 6, samples will no longer be collected for analysis of circulating soluble factors, as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2.

8.7.5 CTC

Samples for Circulating Tumor Cell (CTC) analysis will only be collected from subjects with CRC, ovarian cancer and SCCHN.

CTC numbers and the PD-L1-expressing CTC subset will be examined in subjects with CRC, ovarian cancer, and SCCHN to explore their relationship to treatment effects with MEDI4736 and tremelimumab.

NOTE: Per Amendment 6, samples will no longer be collected for analysis of CTC, as sufficient samples have already been collected. The collection time points for these assays have been removed from the flowchart in Section 3.2.

8.7.6 mRNA/miRNA profiling

Whole blood samples (pre- and post- MEDI4736/tremelimumab treatment) will be collected and preserved in PAXgene tubes to prepare miRNA/mRNA samples for future analyses of transcript and/or miRNA expression mRNA levels of selected inflammatory/immune and cytokine pathways which may include but are not limited to IL-6, IL-8, TIMP1, FCRG2B, LIF, IFN, LARGE, CXCL10, SOCS3 may be measured, as well as their association with tremelimumab/MEDI-4736 treatment outcome. RNA analyses may be conducted to generate hypotheses associated with the mechanisms of action of immunotherapy and/or to identify subsets of subjects responsive to MEDI4736 and tremelimumab.

8.7.7 Archival Tumor Samples and Tumor Biopsies

Consent for archival tumor samples is mandatory (all subjects) and consent for tumor biopsies is mandatory in the expansion phase for all subjects with biopsiable tumors (if clinically appropriate).

Tumor samples will be examined to evaluate biomarkers by immunohistochemistry (IHC) and mRNA/miRNA expression profiling. This may include but is not limited to, the expression level and localization of immunosuppressive proteins such as PD-L1 on tumor cells, 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 with MEDI4736 and tremelimumab will be evaluated. Additionally, analyses of tumor mutations and polymorphisms using archival tumor tissue may be performed through relevant methodologies in order to assess genetic alterations and their potential relationships with treatment outcome to MEDI4736 and tremelimumab. Further, selected gene sequencing of samples may be employed to evaluate genetic alterations and relationships with treatment outcome with MEDI4736 and tremelimumab.

8.7.7.1 Archival Tumor Samples

Archival tumor samples are required for all subjects and must be deemed available during the screening period. If the availability, quantity (25 unstained slides: 12 slides with tissue sections of 4 microns thick and 13 slides with tissue sections of 10 microns thick), and quality of archival tumor samples during screening period cannot be confirmed, then baseline fresh tumor biopsies will be obtained prior to Day 1. Formalin-fixed paraffin-embedded tumor samples will be collected for immunohistochemistry (IHC) and additional correlative markers.

8.7.7.2 Tumor Biopsies

In the expansion phase, tumor biopsy samples are required for all subjects with biopsiable tumors (if clinically appropriate). Tumor biopsy samples will be examined to evaluate the correlation between clinical activity and the expression level of PD-L1 and tumor-infiltrating lymphocytes changes in biopsies pre and post treatment (Section 4.5.2).

Tumor biopsy will be performed according to institutional practice during screening, 30 to 60 days after initiation of treatment (if clinically appropriate), and during Cycles 8 to 13 (or Cycles 8 to 12 post Amendment 5) or time of progression (if clinically appropriate) for subjects in the expansion phase of the study (Section 3.2).

Tumor lesions planned for biopsy must not be used as index lesions for assessment of disease and tumor response. Excisional biopsies are preferred where clinically appropriate. Otherwise, subjects will undergo 4 core biopsies (18 g or larger, if clinically appropriate). Two tissue cores will be placed in formalin and processed to FFPE. The remaining 2 cores will be immediately frozen in liquid nitrogen and then stored at -80°C. Additional details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

8.7.8 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. Patients who declined consent to participate in additional translational studies will have their samples 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.

8.8 Details for Subjects who Continue Treatment beyond the Core Study

According to Section 3.1.12, optional treatment extension with MEDI4736 beyond the Core Study is available for subjects who complete the Core Study with Stable Disease or better; the optional treatment extension will be permitted upon agreement with subject, Sponsor and Investigator.

Subjects who receive optional study treatment extension will receive the currently recommended fixed dose of 1500 mg MEDI4736, unless a lower dose is agreed upon by Investigator and Sponsor.

Note: the fixed dose of MEDI4736 of 1500 mg Q4W is 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 Q4W for MEDI4736 as long as the body weight remains ≤ 30 kg.

The following procedures will be implemented for subjects who receive optional study treatment:

1. Fixed dose of 1500 mg MEDI4736 will be used; preparation details are provided in Section 6.1.2.3.
2. Administration of MEDI4736 will proceed according to Section 6.1.3.
3. Subjects will be monitored by assessment of vital signs before, during and after each MEDI4736 dose administration according to Section 6.3.
4. First MEDI4736 dose during optional treatment extension will be administered as follows:
    a. Last dose in Core Study + 2 weeks (± 3 days) for subjects on Q2W regimen in Core Study, OR
    b. Last dose in Core Study + 4 weeks (± 3 days) for subjects on Q4W regimen in Core Study
5. After first dose, MEDI4736 dosing will continue Q4W.
6. The flowchart for optional treatment extension, which is provided in Section 8.8.1 will be followed.

8.8.1 Study Flowchart for Subjects who Continue Treatment beyond the Core Study

Study Flowchart for Subjects who Continue Optional Study Treatment after Core Study	Optional Study Treatment[1,2] (Q4W following first optional study treatment dose)	On Study Follow-up[5]			Post Study Follow-up (Done at least every 6 months for up to 3 years from start of treatment)
		Last Study Drug Administration +28 (± 3) days	Last Study Drug Administration +56 (± 5) days	Last Study Drug Administration +90 (± 7) days	
Treatment					
MEDI4736	1500 mg				
Tumor & Disease Assessments					
Disease Assessment by RECIST (including appropriate imaging)	SOC	+56 ± 7 days from last disease assessment			
Disease Assessment by irRC (including appropriate imaging)	SOC	+56 ± 7 days from last disease assessment			
Study Procedures & Examinations					
Physical Exam (incl. weight and ECOG Perf Status)	X	X	X	X	
Vital Signs (T, HR, BP, RR)[4]	X	X	X	X	
Concomitant Medications and Procedures	X	X	X	X	
Adverse Events (starting or worsening after consent)[5]	X	X	X	X	
Laboratory Assessments					
Blood Hematology (CBC, differential, platelets)	x[3]	X	X	X	
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO_2, prot., alb., Tbili., AST, ALT, LDH, ALP, Free T3, Free T4, TSH)	x[3]	X	X	X	
Chemistry cont. (Amylase, lipase)	x[3]	X	X	X	
Serum pregnancy test	at first optional study treatment visit, then Q8W[3]	x		x	
Long-Term Follow-up					
Overall Survival					x
Progression Free Survival					x

Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SOC = Standard of Care

1 - First MEDI4736 dose during optional treatment extension will be administered:

a) Last dose in Core Study + 2 weeks (± 3 days) for subjects on Q2W regimen in Core Study OR

b) Last dose in Core Study + 4 weeks (± 3 days) for subjects on Q4W regimen in Core Study

2 - After first dose, MEDI4736 dosing will continue Q4W

3 - Collected pre-dose. Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing.

4 - See Section 6.3 for assessment of vital signs before, during and after administration of MEDI4736 dose.

5 - See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration.

8.8.2 Reinduction with MEDI4736 and Tremelimumab for Subjects With Confirmed Progression

Upon agreement between the Investigator and the Sponsor and if the subject agrees and signs an appropriate informed consent form, a subject with confirmed progression may be reinduced with MEDI4736 and tremelimumab. The reinduction will consist of 4 doses (Q4W) of 75 mg tremelimumab and 1500 mg MEDI4736 (Q4W). There should be no other intervening therapy prior to reinduction with MED4736 and tremelimumab. Reinduction is permitted only once.

The following procedures will be implemented for reinduction:

1. Fixed doses of 1500 mg MEDI4736 and 75 mg trememlimumab will be used; preparation details are provided in Sections 6.1.2.3 and 6.2.2.1, respectively.
   NOTE: the MEDI4736 dose of 1500 mg Q4W is for subjects > 30 kg. If a subject's body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing as described in Section 6.1.2.3. When tremelimumab 75 mg is given with MEDI4736 1500 mg Q4W, if a subject's body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing for both drugs as described in Sections 6.1.2.3 and 6.2.2.1, respectively.
2. Administration of MEDI4736 and tremelimumab will proceed according to Sections 6.1.3 and 6.2.3, respectively.
   NOTE: When MEDI4736 and tremelimumab are to be administered on the same day, MEDI4736 infusion will start at least 60 minutes after the end of tremelimumab infusion.
3. Subjects will be monitored by assessment of vital signs before, during and after each MEDI4736 and tremelimumab dose administration according to Section 6.3.
4. The assessments and procedures identified in the Flowchart in Section 8.8.1 will be followed during the reinduction period.

After reinduction, MEDI4736 dosing may be continued as outlined in the flowchart in Section 8.8.1.

8.9 List of Abbreviations

ADA	Anti-drug antibodies
AE	Adverse event
AESI	adverse event of special interest
ALT	alanine transaminase
AST	aspartate transaminase
CBC	Complete Blood Chemistry
CRC	Colorectal Cancer
CTLA-4	Cytotoxic T-Lymphocyte-associated Antigen-4
CTCAE	Common Terminology Criteria for Adverse Events
DLT	Dose-limiting Toxicity
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FFPE	Formalin-fixed paraffin-embedded
GCP	Good Clinical Practice
HLA	Human Leukocyte Antigen
IB	Investigator's Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IHC	Immunohistochemistry
IMP	Investigational medicinal product
IP	Investigational product
IRB	Institutional Review Board
irCR	Immune-Related Complete Response
irPD	Immune-Related Progressive Disease
irPR	Immune-Related Partial Response
irRC	Immune-Related Response Criteria
irSD	Immune-Related Stable Disease
LICR	Ludwig Institute for Cancer Research
MedDRA	Medical Dictionary for Regulatory Activities
MSKCC	Memorial Sloan Kettering Cancer Center
MTD	Maximum Tolerated Dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NSCLC	Non-Small Cell Lung Cancer
PD-1	Programmed Death-1
Q2W	Every 2 weeks
RCC	Renal Cell Carcinoma
RECIST	Response Evaluation Criteria In Solid Tumors

SAE	Serious Adverse Event
SD	Standard Deviation
SPD	Sum of Perpendicular Diameters
sPD-L1	soluble programmed death ligand 1
WFI	Water for Injection

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