LUDWIG CANCER RESEARCH	**Study Protocol**	**LUD2014-001**	**US-IND# 125040** **NCT02431559**
	Amendment 4	**Final**	**08-SEP-2017**

Protocol Title
A Phase 1/2 Study of Chemo-immunotherapy with Toll-like Receptor 8 Agonist Motolimod (VTX-2337) and anti-PD-L1 Antibody MEDI4736 in Subjects with Recurrent, Platinum-Resistant Ovarian Cancer for Whom Pegylated Liposomal Doxorubicin (PLD) is Indicated.

Objectives and Synopsis

This is an open-label, non-randomized, multicenter Phase 1/2 study of motolimod and MEDI4736 in subjects with recurrent, platinum-resistant ovarian cancer, scheduled to receive pegylated liposomal doxorubicin (PLD).

Subjects will be treated during each 28-day cycle according to the following schedules.

PER Amendment 2, motolimod dosing will be discontinued for all subjects. At the time of Amendment 2, Phase 1 is completed, and Phase 2 will be initiated at the +1 dose level (PLD 40 mg/m^2, MEDI4736 1500 mg Q4W). Subjects who initiated treatment during Phase 1 will continue the trial at their respective doses levels for PLD and MEDI4736; however, motolimod will be discontinued.

PER Amendment 2, the treatment schedule for the cohort at dose level 0a will be:

Day	CYCLES 1 – 12
1	Pegylated liposomal doxorubicin (IV)
3	MEDI4736 (IV)
17	MEDI4736 (IV)

PER Amendment 2, the treatment schedule for all subjects EXCEPT the cohort at dose level 0a will be:

Day	Cycles 1 – 12
1	Pegylated liposomal doxorubicin (IV)
3	MEDI4736 (IV)

Pre Amendment 2 Treatment Schedule for cohort at dose level 0a only (see note below):

Day	CYCLES 1 – 3	CYCLES 4 – 12
1	Pegylated liposomal doxorubicin (IV)	Pegylated liposomal doxorubicin (IV)
3	MEDI4736 (IV) + Motolimod (SC)	MEDI4736 (IV) + Motolimod (SC)
10	Motolimod (SC)	n/a
17	MEDI4736 (IV) + Motolimod (SC)	MEDI4736 (IV) + Motolimod (SC)

Pre Amendment 2 (and Per Amendment 1) Treatment Schedule for all subjects except cohort at dose level 0a:

Day	Cycles 1 – 3	Cycles 4 – 12
1	Pegylated liposomal doxorubicin (IV)	Pegylated liposomal doxorubicin (IV)
3	MEDI4736 (IV) + Motolimod (SC)	MEDI4736 (IV) + Motolimod (SC)
10	Motolimod (SC)	n/a
17	Motolimod (SC)	n/a

Phase 1 Cohorts: Dose escalations and de-escalations for the determination of the MTD (or highest tolerable dose tested) via assessment of DLTs will be performed based on the available dose levels and respective standard 3 + 3 rules, as per table below:

Dose Level	Pegylated liposomal doxorubicin [mg/m² IV]	MEDI4736 [IV]	Motolimod [mg/m² SC] Pre Amendment 2 only*
-1	40	450 mg Q4W	2.0
0a (Starting Level)	***40***	***3 mg/kg Q2W (equivalent to 450 mg Q4W)***	***2.5***
0b	40	1500 mg **Q4W****	2.0
+1	40	1500 mg Q4W**	2.5

Q2W = every 2 weeks; Q4W = every 4 weeks
*PER Amendment 2, motolimod dosing will be discontinued for all subjects
**Note for fixed dose of 1500 mg MEDI4736: If a subject's body weight drops to ≤ 30 kg while on the study, the MEDI4736 dose will be weight based as long as the body weight remains ≤ 30 kg (see Section 6.3.3.2)

Note: Per Amendment 1, dose level 0 was renamed as 0a, and dose level 0b was added to Phase 1. Depending on the timing of Amendment 1, dose level 0b cohort could be running concurrently with the cohort at dose level 0a, -1, or +1. The dosing for the cohort in dose level 0a will continue per the protocol prior to Amendment 1 (i.e., MEDI4736 at 3 mg/kg Q2W); however, escalation or de-escalation dosing will be according to Amendment 1.

The *primary objective* is to determine the Maximum Tolerated Dose (MTD) and the safety profile of the combination. *Secondary objective* is the evaluation of clinical efficacy as measured by the Progression Free Survival (PFS) rate at 6 months.

Phase 2 Cohort: The Phase 1 Cohort treated at the MTD (n=6) will become the Phase 2 Cohort and expanded to a total of 41 evaluable subjects. The *primary objective* is the evaluation of clinical efficacy as measured by the Progression Free Survival (PFS) rate at 6 months.

All Phase 1 and 2 Cohorts: *Secondary objectives* are the evaluation of clinical efficacy as measured by overall response rate, progression-free survival rate at 12 months, overall survival and biological activity defined as immunological responses.

Safety will be assessed by CTCAE v4.03 and clinical efficacy by RECIST 1.1 and irRECIST.

Per Amendment 3, optional MEDI4736 treatment extension beyond the initial 12-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, and it may continue until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See Section 8.9 for details regarding treatment extension and collection/reporting of adverse events during this period.

Sponsor: Ludwig Institute for Cancer Research, New York, NY **Sponsor Representative Signature & Date**	**Study Chair:** [redacted] **Study Chair Signature & Date**
Local Sponsor for Switzerland: Ludwig Institute for Cancer Research Ltd, Zurich, Switzerland L**ocal Sponsor for Switzerland Signature & Date**	**US Study Chair**: [redacted] **US Study Chair Signature & Date**

Confidentiality Statement

Table of Contents

1 Background 8
1.1 Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer 8
1.2 PEGylated Liposomal Doxorubicin (PLD) 8
1.3 Motolimod (VTX-2337) 8
1.4 PD-1 and PD-L1 9
1.4.1 MEDI4736 (Durvalumab) 10
2 Study Rationale 11
2.1 Rationale for Amendment 1 12
3 Experimental Plan 14
3.1 Study Design 14
3.1.1 Study Phase 14
3.1.2 Enrollment/Randomization 14
3.1.3 Blinding/Unblinding 14
3.1.4 Subject Population 14
3.1.5 No. of Sites/Subjects 14
3.1.6 Sample Size and Statistical Considerations 15
3.1.7 Treatment Arms and Treatment Schema 15
3.1.8 Dosing Adjustments, Delays and Discontinuations 17
3.1.9 DLT and MTD 18
3.1.10 Subject Withdrawal from Treatment or Study 19
3.1.10.1 Treatment beyond Progression 20
3.1.11 Subject Evaluability and Replacements 20
3.1.12 Optional Study Treatment Extension 20
3.1.13 Interim Analysis 21
3.1.14 Safety Monitoring and Study Stopping Rules 21
3.1.15 Duration of Study 21
3.1.16 On Study and Post Study Follow-up 21
3.1.16.1 End of Study Visit 22
3.2 Study Flowchart 23
4 Study Objectives & Endpoints 27
4.1 Clinical Efficacy 27
4.1.1 Endpoints & Assessment Methods 27
4.1.1.1 Progression-free Survival Rate 27
4.1.1.2 Progression-free Survival Time 27
4.1.1.3 Overall Response Rate 28
4.1.1.4 Overall Disease Control Rate 28
4.1.1.5 Overall Survival Time 28
4.1.2 Subject Evaluation & Statistics 28
4.2 Safety and Tolerability 28
4.2.1 Endpoints & Assessment Methods 29

4.2.2 Subject Evaluation & Statistics 29
4.3 Biological Activity 30
4.3.1 Endpoints & Assessment Methods 30
4.3.2 Subject Evaluation & Statistics 30
5 Subject Eligibility 31
5.1 Inclusion Criteria 31
5.2 Exclusion Criteria 32
5.3 Restrictions on Concomitant Therapies 35
5.3.1 Non-Permitted Concomitant Therapies 35
5.3.2 Permitted Concomitant Therapies 35
6 Study Drug Preparation and Administration 36
6.1 Pegylated Liposomal Doxorubicin (PLD) 36
6.2 Motolimod 36
6.2.1 Motolimod Study Drug Information 36
6.2.2 Motolimod Preparation 36
6.2.3 Motolimod Administration 37
6.3 MEDI4736 38
6.3.1 MEDI4736 Study Drug Information 38
6.3.2 MEDI4736 Investigational Product Inspection 38
6.3.3 MEDI4736 Preparation 38
6.3.3.1 MEDI4736 Preparation for Cohort at Dose Level 0a 39
6.3.3.2 MEDI4736 Preparation for all Subjects except Cohort at Dose Level 0a and for Treatment Extension 39
6.3.4 MEDI4736 Administration 40
6.3.5 Monitoring of MEDI4736 Dose Administration 41
6.4 Estimated Study Drug Requirements for Motolimod and MEDI4736 42
6.5 Drug Overdose Management 42
7 Administrative, Legal & Ethical Requirements 43
7.1 Documentation and Reporting of Adverse Events 43
7.1.1 General AE/SAE Definitions per ICH Guidelines 43
7.1.2 Additional Expedited Reporting Requirements for this Study 44
7.1.2.1 Pregnancy 44
7.1.2.2 Overdose 44
7.1.2.3 Hepatic Function Abnormality 45
7.1.3 Severity of an Adverse Event 45
7.1.4 Relationship of Adverse Events to Study Drug 45
7.1.5 General Reporting Requirements 45
7.1.6 Expedited Serious Adverse Event (SAE) Reporting Requirements 46
7.1.7 Serious Adverse Event (SAE) Follow-up Requirements 47
7.1.8 Adverse Events of Special Interest (AESIs) 47
7.1.8.1 Additional AESIs for this Study 49
7.2 Administrative Sponsor Requirements 50
7.2.1 Study Master Files 50
7.2.2 Case Report Form Data Collection 50

7.2.3 Language 50
7.2.4 Monitoring 51
7.2.5 Protocol Amendments 51
7.2.6 Premature Subject Withdrawal 51
7.2.7 Early Trial Termination 52
7.2.8 Study Drug Shipments & Accountability 52
7.3 Regulatory, Legal & Ethical Requirements 52
7.3.1 Good Clinical Practice (GCP), Laws and Regulations 52
7.3.2 Informed Consent 52
7.3.3 Institutional Review Board 53
7.3.4 Subject Confidentiality 53
8 Appendices 54
8.1 Protocol Version History 54
8.2 Pegylated Liposomal Doxorubicin (PLD) Dose Delays and Adjustments 68
8.2.1 Hematological Toxicity 68
8.2.2 Hand Foot Syndrome (HFS) 68
8.2.3 Stomatitis 69
8.2.4 Subjects with Impaired Hepatic Function 69
8.3 Motolimod Toxicity Management and Dose Adjustments 70
8.3.1 Management of Injection Site Reactions 70
8.3.2 Management of Systemic Toxicities 70
8.3.3 Motolimod Dose Modifications due to Toxicities 71
8.3.3.1 Cytokine Release Syndrome 71
8.3.3.2 Injection Site Reaction 71
8.3.3.3 Non-Hematologic Drug-Related AEs 71
8.3.3.4 Hematologic Drug-Related AEs 71
8.4 MEDI4736 Toxicity Management and Dose Adjustments 72
8.4.1 Management of MEDI4736-related Toxicities 72
8.4.2 MEDI4736 Dose Modifications due to Toxicities 72
8.4.2.1 Immune-related Adverse Events (irAEs) 73
8.4.2.2 Infusion-related Reactions 74
8.4.2.3 All other Adverse Events 75
8.4.3 MEDI4736 Dose Modifications Not Due to Toxicities 75
8.5 RECIST 1.1 Guidelines 76
8.5.1 Disease Parameters 76
8.5.2 Methods for Evaluation of Measurable Disease 77
8.5.3 Response Criteria 79
8.5.3.1 Evaluation of Target Lesions 79
8.5.3.2 Evaluation of Non-Target Lesions 79
8.5.3.3 Evaluation of Best Overall Response 79
8.5.3.4 Duration of Response 80
8.6 irRECIST Guidelines 81
8.6.1 Response in Measurable Lesions 81
8.6.2 Response in Non-measurable Lesions 81
8.6.3 Evaluation of Biomarkers 82

8.6.4 Overall Response 82
8.6.5 Duration of Response 83
8.7 Exploratory Assessment of Correlative Immunologic Research 84
8.7.1 Phenotypic Analysis of PBMCs 84
8.7.2 Myeloid Derived Suppressor Cells (MDSC) 84
8.7.3 Quantification of Tumor-specific T-cell Responses 84
8.7.4 Baseline Immune Responsiveness to TLR8 activation 85
8.7.5 Immune Landscape: TILs and Tumor Microenvironment 85
8.7.6 TCR sequencing 86
8.7.7 Immune biomarkers 86
8.7.8 Pharmacogenomics 86
8.7.9 BRCA status of tumors 87
8.7.10 MEDI4736 PK and Immunogenicity for Anti-drug Antibodies (ADA) 87
8.7.11 sPD-L1 87
8.7.12 Circulating soluble factors 87
8.7.13 Additional translational and exploratory studies 87
8.7.14 mRNA/miRNA Profiling 88
8.8 ECOG Performance Status 89
8.9 Details for Subjects Who Continue Optional MEDI4736 Treatment beyond the Core Study 90
8.9.1 Study Flowchart for Subjects Who Continue Optional MEDI4736 Treatment beyond the Core Study 91
8.10 Abbreviations 92
9 References 94

1 Background

1.1 Epithelial Ovarian, Fallopian Tube or Primary Peritoneal Cancer

Approximately 24,000 new cases are diagnosed and 15,000 women die of ovarian cancer annually in the US, and approximately ten times as many worldwide. No significant advances have been made in chemotherapy over the past three decades, and no molecular drugs appear promising. Initial response rates of advanced ovarian cancer to standard upfront paclitaxel / carboplatin approach 75%, with complete clinical response rates near 55%.

Unfortunately, over 80% of patients progress, and response rates to second line chemotherapy for platinum-resistant patients are significantly lower, usually 15-20%. Once ovarian cancer has recurred, it is incurable with available therapies. These facts elucidate the enormous unmet need for the development of alternate therapies in ovarian cancer.

1.2 PEGylated Liposomal Doxorubicin (PLD)

PEGylated liposomal doxorubicin (PLD, known commercially as Doxil, Caelyx or Lipodox) is a formulation of doxorubicin encapsulated in polyethylene-glycol (PEG)-coated liposomes, which leads to dramatic improvement in pharmacokinetics, characterized by a prolonged circulation time, reduced clearance, and a small volume of distribution.(1) It is approved for the treatment of ovarian cancer after failure of platinum-based chemotherapy and is considered standard of care for these patients.

The approved clinical dose of PLD is 50 mg/m^2. However, based on an improved tolerability profile without a perceived loss of efficacy, 40 mg/m^2 of PLD has become the community standard dose and will thus be used in this study.(2)

Refer to the current PLD (Doxil, Caelyx, Lipodox) prescribing information for complete and current information.

1.3 Motolimod (VTX-2337)

PER Amendment 2, motolimod dosing will be discontinued for all subjects.

Motolimod (VTX-2337) is briefly described in this section below. Refer to the current motolimod Investigator's Brochure for complete and current information.

Motolimod is a small molecule agonist of TLR8 that stimulates specific immune cell populations. TLR8 is primarily expressed by monocytes, myeloid dendritic cells (mDCs), and NK cells. Engagement of TLR8 with single-stranded RNA (its natural ligand) or a pharmacologic agonist, such as motolimod, stimulates an inflammatory immune response, in part, via the activation of NF-κB pathway. In vivo, TLR8 stimulation induces the production of multiple cytokines and chemokines including: G-CSF, MCP-1, MDC, MIP-1β, TNFα, IL-1α, IL-8, IL-6, IL-12, IL-18 and IFNγ. Production of these mediators is hypothesized to enhance the efficacy of standard-of-care (SOC) chemotherapy and monoclonal antibody therapy in the oncology setting via modulation of the tumor microenvironment and augmentation of both innate and adaptive immune responses.

Motolimod has been evaluated in **4 open-label trials**: as monotherapy in a Phase 1 dose escalation study (3) and in Phase 1b trials of combination regimens utilizing cytotoxic

chemotherapy (PLD and paclitaxel) (4) and two studies in combination with the monoclonal antibody cetuximab.(5) Across these trials, 79 subjects have received motolimod, which has been shown to be safe and well tolerated as a single agent or in combination, with no significant drug-related hematologic, gastrointestinal, neurologic, or cardiac toxicities observed.

Motolimod is currently being evaluated in **2 double-blind, randomized Phase 2 studies**: in combination with PLD in women with recurrent ovarian cancer and in combination with the EXTREME regimen (platinum chemotherapy + 5-flourouracil + cetuximab) in subjects with recurrent or metastatic squamous cell carcinoma of the head and neck (SCCHN). A total of 297 subjects with ovarian cancer and 195 subjects with SCCHN have been enrolled as of 02 December 2015. Preliminary blinded safety data indicate that the combinations appear to be safe and well tolerated.

1.4 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.(6) 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).(7-9) 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.(10-12) It is found on T-cells, B cells, macrophages, NK cells, DCs, and mast cells (13). 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.(13-24) PD-L1 is constitutively expressed on many hematopoietic cells, but may be upregulated in hematopoietic and non-hematopoietic cells.(25) Regulation of PD-L1 is mediated, in part, by type I and type II interferons. PD-L2 was identified in 2001.(26, 27) Its expression is far more restricted and is confined to hematopoietic cells.(28)

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.(29-33) Inhibitory signaling by PD-1 is thought to depend upon the cytosolic ITSM domain, which associates with phosphatases SHP-1 and SHP-2.(34, 35)

Tumors employ the programmed cell death 1 (PD-1) inhibitory pathway to paralyze the antitumor immune response. PD-1 is expressed by activated T-cells, but not by resting T-cells. PD-1 binds two ligands, PD-L1 and PD-L2, also called B7-H1 (CD274) and B7-DC (CD273), respectively. Upregulation of PD-L1 occurs in most ovarian cancers, suggesting that cancer cells utilize the PD-1/PD-L1 inhibitory pathway to escape the host immune response. Thus, although anti-tumor immunity can be elicited against ovarian cancer through *in situ* vaccination, it could be counterbalanced by immunosuppressive factors in the tumor microenvironment. In fact, recent studies showed that tumor-infiltrating T-cells express PD-1 in ovarian cancer, and survival in ovarian cancer patients inversely correlates with PD-L1 expression.(15, 36) PD-1 blockade could enhance the reactivity and cytokine response of NY-ESO-1 specific tumor-derived T-cells from ovarian cancers.(37) PD-L1 blockade in mice bearing intraperitoneal ID8 ovarian cancer tumors (which express PD-L1) can restore antitumor immunity and synergize with

whole tumor antigen vaccine (GVAX) to produce tumor rejections. Vaccine alone was completely ineffective, while PD-L1 antibody monotherapy produced half the cure rate than GVAX plus PD-L1 blockade combination.(38)

1.4.1 MEDI4736 (Durvalumab)

MEDI4736 is briefly described in this section below. Refer to the current Investigator's Brochure (IB) for complete and current information.

MEDI4736 is a human immunoglobulin G1 kappa monoclonal antibody (MAb) directed against human PD-L1. MEDI4736 has an overall molecular weight of approximately 149 kDa, including N-linked oligosaccharides. The antibody is composed of 2 identical heavy chains of approximately 49,670 Da each, and 2 identical light chains of approximately 23,390 Da each. The fragment crystallizable (Fc) domain of MEDI4736 contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fcm receptors, responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC).(39) Subsequent to this triple mutation, the anticipated lack of MEDI4736-mediated ADCC and complement-dependent cytotoxicity were confirmed using cell based functional assays. MEDI4736 is selective for recombinant PD-L1 and blocks the binding of recombinant PD-L1 to the PD-1 and cluster of differentiation (CD) 80 receptors.

As of the data cutoff dates in the IB (15Apr2015 to 12Jul2015), a total of 1,883 subjects have been enrolled and treated in 30 ongoing MEDI4736 clinical studies, including 20 sponsored (6 monotherapy and 14 combination therapy) and 10 collaborative studies. Of the 1,883 subjects, 1,279 received MEDI4736 monotherapy, 440 received MEDI4736 in combination with tremelimumab or other anticancer agents, 14 received other agents (1 gefitinib, 13 MEDI6383), and 150 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

The safety profile of MEDI4736 as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with MEDI4736 and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy / neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with MEDI4736 and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols.

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

2 Study Rationale

It is evident that ovarian tumors are spontaneously recognized and controlled by the immune system in some patients. For example, in ovarian cancer, CD8+ tumor infiltrating lymphocytes (TIL) are associated with favorable prognosis,(40) while, conversely, tumor infiltrating T regulatory (T reg) cells predict for reduced survival.(41) Research also suggests that natural immune surveillance can be associated with a lower risk of developing ovarian cancer.(42) The finding of spontaneous antitumor immune responses in some patients with ovarian cancer suggests that immunotherapy, if delivered in the right context, could produce substantial clinical benefit.

Nevertheless, for the most part, immunotherapy trials have been unsuccessful in ovarian cancer patients, suggesting that there are potent immune suppressing mechanisms at play in the majority of patients. It is notable that PD-1/PD-L1 inhibitor therapy has not demonstrated significant single agent activity in ovarian cancer despite reports of PD-L1 expression on ovarian tumor cells. There are a variety of potential reasons for this diminished immune activity, including defects in T-cell access to tumors (T-cell-poor tumors), the presence of potent immune suppressive cells such as T reg and myeloid derived suppressor cells (MDSC) in the tumor microenvironment, and defects in the generation of activated cancer-specific T-cells.(43-45)

Motolimod and PLD have been combined safely (without dose limiting toxicities) in Phase 1, and a Phase 2 study is ongoing in subjects with recurrent ovarian cancer without significant toxicities. Given the background above, there is strong rationale for adding a PD-L1 inhibitor to this combination.

Based on its mechanism of action, the administration of motolimod and PLD may have in situ vaccination effects, which may be enhanced with the addition of MEDI4736. Motolimod stimulation of the innate immune system may alter the tumor microenvironment to drive T-cell infiltration into T-cell-poor tumors, and create an inflamed microenvironment poised for anti-tumor immunity. Stimulation of the TLR8 receptor on immunosuppressive MDSCs may promote their differentiation into non-suppressive mDCs and macrophages (unpublished data and (26, 46)). The novel tumor antigens exposed on tumor cells that are immunogenically killed by PLD may then be captured and processed by motolimod-stimulated mDCs. These mature mDCs have the capacity to cross-present a large repertoire of potential tumor rejection antigens to CD8+ and CD4+ T-cells, both in the tumor and in draining lymph nodes. The summation of these steps may result in an increase in the population of PD-1 expressing activated CD8+ effector cells, infiltrating tumors that will destroy cognate antigen expressing tumor cells not expressing PD-L1, and will be unleashed by the PD-L1 inhibitor to destroy antigen expressing tumor cells that do express PD-L1.

NOTE: PER Amendment 2, motolimod dosing will be discontinued for all subjects. This decision was based upon the results from a Phase 2 study of motolimod and PLD (GOG-3003) that was being conducted by VentiRx. Although the combination of motolimod with PLD was safe and well-tolerated in GOG-3003, the combination did not significantly improve overall survival or progression free survival (as determined using irRECIST) in the ITT population compared to PLD alone.

At the time of Amendment 2, Phase 1 is completed, and Phase 2 will be initiated at the +1 dose level (PLD 40 mg/m^2, MEDI4736 1500 mg Q4W). Subjects who initiated treatment during

Phase 1 will continue the trial at their respective doses levels for PLD and MEDI4736; however, motolimod will be discontinued.

2.1 Rationale for Amendment 1

Per Amendment 1, the following changes will be implemented (refer to Section 8.1 for a complete description of all changes):

1. The starting dose level cohort was renamed as dose level 0a. The dosing for the cohort in dose level 0a will continue per the protocol prior to Amendment 1 (i.e., MEDI4736 at 3 mg/kg Q2W); however, escalation or de-escalation dosing will be conducted according to Amendment 1.

2. Dose level 0b was added to Phase 1. See table below:

Dose Level	PLD [mg/m² IV]	MEDI4736 [IV]	Motolimod [mg/m² SC]
-1	40	450 mg Q4W	2.0
0a (Starting Level)	***40***	***3 mg/kg Q2W (equivalent to 450 mg Q4W)***	***2.5***
0b	40	1500 mg **Q4W**	2.0
+1	40	1500 mg Q4W	2.5

3. A fixed dosing schedule for MEDI4736 was added for all subjects except for those in the cohort that was already started prior to Amendment 1 (i.e., dose level 0a).

Rationale for fixed dosing of MEDI4736:

Currently, the recommended dosing schedule for MEDI4736 is 20 mg/kg every 4 weeks (Q4W). The fixed dosing in this protocol for MEDI4736 (1500 mg Q4W for the +1 and 0b dose levels) is based on data from PK models. Using population PK models, simulations indicated that both body weight-based and fixed dosing regimens of MEDI4736 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, it is considered feasible to switch to fixed dosing regimens. Based on an average body weight of 75 kg, a fixed dose of 1500 mg Q4W MEDI4736 is equivalent to 20 mg/kg Q4W or 10 mg/kg Q2W.

The 1500 mg dosing of MEDI4736 is recommended only for subjects with > 30 kg body weight due to endotoxin exposure. Subjects with a body weight ≤ 30 kg are not eligible for enrollment in the current study. If a subject's body weight drops to ≤ 30 kg while on the study, the MEDI4736 dose will be weight based as long as the body weight remains ≤ 30 kg (see Section 6.3.3.2).

Rationale for addition of dose level 0b:

If the starting dose level 0a does not clear and dosing de-escalates to -1, dose level 0b will continue to accrue subjects according to the 3 + 3 design (in addition to the cohort at the dose level -1) because it represents a de-escalation of motolimod from 2.5 to 2.0 mg/m^2. The 1500 mg of MEDI4736 is supported by the fact that there is no dose response for toxicity for anti-PD-1 and anti-PD-L1 antibodies, and even half the clinical dose of MEDI4736 would be above

saturation of the receptor. Therefore, it would be safe to reduce the motolimod dose (from 2.5 to 2.0) but maintain the currently recommended 1500 mg dose for MEDI4736.

If dose level 0a does clear and dosing escalates to +1, dose level 0b will also continue to accrue subjects according to the 3 + 3 design (in addition to the cohort at the dose level +1).

Depending on the timing of Amendment 1, dose level 0b cohort could be running concurrently with the cohort at dose level 0a, -1, or +1. Thus, subject enrollment will occur as follows:

a) when only 1 cohort is open: sequential enrollment;
b) when 2 parallel cohorts are open: preferential sequential enrollment into the cohort with the higher motolimod dose level or into the cohort with the higher MEDI4736 dose level if both cohorts have the same motolimod dose level.

3 Experimental Plan

3.1 Study Design

3.1.1 Study Phase

Phase 1/2.

3.1.2 Enrollment/Randomization

Subjects will be enrolled in a non-randomized, competitive multicenter, sequential enrollment manner with central subject registration. Subject enrollment and the safety of the combination regimen will be reviewed on an ongoing basis by an internal data safety monitoring panel (see Section 3.1.14, Safety Monitoring and Study Stopping Rules).

For each cohort in Phase 1, the start of the Cycle 1 Day 3 study drug administration (MEDI4736 + motolimod) for the first and second subject will be separated by at least 24 hours. All subjects in a cohort will have their safety data reviewed for DLTs as per Section 3.1.9, before proceeding with a cohort expansion or to a dose-escalated/de-escalated cohort (see section 3.1.7).

Per Amendment 1, the cohort at dose level 0b will be added to Phase 1. Depending on the timing of Amendment 1, dose level 0b cohort could be running concurrently with the cohort at dose level 0a, -1, or +1. Thus, subject enrollment will occur as follows:

a) when only 1 cohort is open: sequential enrollment;
b) when 2 parallel cohorts are open: preferential sequential enrollment into the cohort with the higher motolimod dose level or into the cohort with the higher MEDI4736 dose level if both cohorts have the same motolimod dose level.

PER Amendment 2, motolimod dosing will be discontinued for all subjects.

Subject enrollment will be centrally administered.

Enrollment in Phase 2 will begin after the MTD has been established in Phase 1.

3.1.3 Blinding/Unblinding

This is an open label study.

3.1.4 Subject Population

Subjects must have recurrent or persistent epithelial ovarian, fallopian tube, or primary peritoneal carcinoma with measureable disease (as defined by RECIST 1.1.) after first or second line platinum-based chemotherapy, for which treatment with PLD is indicated.

See Section 5 for complete eligibility criteria.

3.1.5 No. of Sites/Subjects

Approximately 6 to 9 sites; and 6 to 53 evaluable subjects are estimated for this study.

Phase 1: 6-18 evaluable subjects will be needed to identify the MTD.

Phase 2: 41 evaluable subjects, including the 6 subjects treated in Phase 1 at the MTD.

3.1.6 Sample Size and Statistical Considerations

Phase 1 of this trial will employ the 3+3 design as described in Section 3.1.7. The maximum tolerated dose (MTD) is defined as the highest dose for which fewer than 33% of subjects experience a dose-limiting toxicity (DLT).

Phase 2 of this trial will expand the Phase 1 cohort that was treated at the MTD. For the subject population to be enrolled, standard of care treatment with PLD alone has been reported to result in a 25% 6-months PFS rate.(47-50) A true 6-months PFS rate of ≥45% in the current study, using motolimod + MEDI4736 with standard of care, would be of interest and represent a clinically meaningful improvement, while ≤25% would be of no interest. Therefore, the study will test the hypotheses H0: p≤0.25 versus H1: p≥0.45, with p being the proportion of subjects who have survived and not progressed at 6 months, based on RECIST v1.1 criteria. Expansion of the Phase 1 MTD cohort to 41 evaluable subjects will yield 80% power to test the null hypothesis of 6-months PFS rate of ≤25% against the alternative hypothesis of a PFS rate of ≥45% at an alpha level of 0.05 (one-sided) based on exact test for single proportion.

PER Amendment 2, motolimod dosing will be discontinued for all subjects.

3.1.7 Treatment Arms and Treatment Schema

All subjects will be treated with pegylated liposomal doxorubicin (PLD) intravenously, MEDI4736 intravenously and motolimod (pre Amendment 2 only) subcutaneously during each 28-day cycle according to the treatment schedule below. On days with concurrent motolimod and MEDI4736 dosing, motolimod administration will occur 30-60 minutes after the end of the MEDI4736 infusion (pre Amendment 2 only).

PER Amendment 2, motolimod dosing will be discontinued for all subjects. At the time of Amendment 2, Phase 1 is completed, and Phase 2 will be initiated at the +1 dose level (PLD 40 mg/m^2, MEDI4736 1500 mg Q4W). Subjects who initiated treatment during Phase 1 will continue the trial at their respective doses levels for PLD and MEDI4736; however, motolimod will be discontinued.

PER Amendment 2 Treatment Schedule for Cohort at Dose Level 0a only	
DAY	**CYCLES 1 – 12**
1	Pegylated liposomal doxorubicin (IV)
3	MEDI4736 (IV)
17	MEDI4736 (IV)

PER Amendment 2 Treatment Schedule for all Subjects Except Cohort at Dose Level 0a	
DAY	**CYCLES 1 – 12**
1	Pegylated liposomal doxorubicin (IV)
3	MEDI4736 (IV)

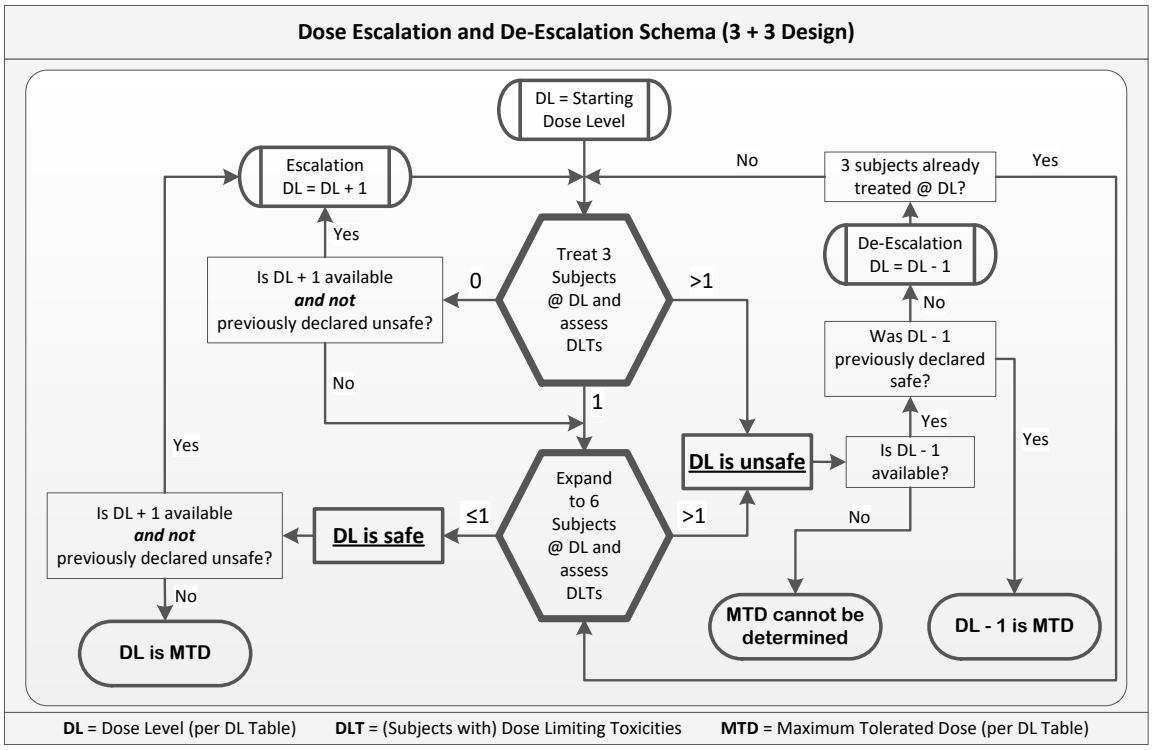
Pre Amendment 2 Treatment Schedule for Cohort at Dose Level 0a only (see note below)		
DAY	**CYCLES 1 – 3**	**CYCLES 4 – 12**
1	Pegylated liposomal doxorubicin (IV)	Pegylated liposomal doxorubicin (IV)
3	MEDI4736 (IV) + Motolimod (SC)	MEDI4736 (IV) + Motolimod (SC)
10	Motolimod (SC)	n/a
17	MEDI4736 (IV) + Motolimod (SC)	MEDI4736 (IV) + Motolimod (SC)

Pre Amendment 2 Treatment Schedule for all Subjects Except Cohort at Dose Level 0a		
DAY	**CYCLES 1 – 3**	**CYCLES 4 – 12**
1	Pegylated liposomal doxorubicin (IV)	Pegylated liposomal doxorubicin (IV)
3	MEDI4736 (IV) + Motolimod (SC)	MEDI4736 (IV) + Motolimod (SC)
10	Motolimod (SC)	n/a
17	Motolimod (SC)	n/a

Phase 1 Dose escalations and de-escalations for the determination of the MTD (or highest tolerable dose tested) will be performed based on the available dose levels and the respective rules for a standard 3 + 3 study design, as per Dose Level Table and Schema below:

Dose Level Table			
Dose Level	Pegylated liposomal doxorubicin **[mg/m² IV]**	**MEDI4736 [IV]**	**Motolimod [mg/m² SC] Pre Amendment 2 only***
-1	40	450 mg Q4W	2.0
0a (Starting Level)	***40***	***3 mg/kg Q2W (equivalent to 450 mg Q4W)***	***2.5***
0b	40	1500 mg Q4W**	2.0
+1	40	1500 mg Q4W**	2.5
Q2W = every 2 weeks; Q4W = every 4 weeks **Note for fixed dose of 1500 mg MEDI4736: If a subject's body weight drops to ≤ 30 kg while on the study, the MEDI4736 dose will be weight based as long as the subject's body weight remains ≤ 30 kg. See Section 6.3.3.2. ***PER Amendment 2, motolimod dosing will be discontinued for all subjects**			

Note: Per Amendment 1, dose level 0 was renamed as 0a, and dose level 0b was added to Phase 1. Depending on the timing of Amendment 1, dose level 0b cohort could be running concurrently with the cohort at dose level 0a, -1, or +1. The dosing for the cohort in dose level 0a will continue per the protocol prior to Amendment 1 (i.e., MEDI4736 at 3 mg/kg Q2W); however, escalation or de-escalation dosing will be conducted according to Amendment 1.



For detailed definitions of DLT and MTD see Section 3.1.9.

Phase 2 subjects will be treated at the MTD level determined in Phase 1. See Sections 3.1.5 and 3.1.6 for the number of subjects to be enrolled.

Subjects will be followed on study for 90 days after the last drug administration and off-study every 3 months thereafter for 3 years from initiation of treatment (see Section 3.1.16).

3.1.8 Dosing Adjustments, Delays and Discontinuations

PER Amendment 2, motolimod dosing will be discontinued for all subjects.

Dose adjustment and management guidelines for toxicity related to the standard PLD regimen, motolimod, and MEDI4736 are outlined in Sections 8.2, 8.3, 8.4, respectively.

In the event of a delay in PLD dosing due to drug-related toxicity, doses of motolimod and MEDI4736 should also be delayed, so that the relative timing of the administration of each drug within each cycle is not altered. That is, the administration of PLD always constitutes cycle Day 1, and the dose dates of motolimod and MEDI4736 are determined relative to this date (see Section 3.1.7). Note that delays in the dosing of motolimod or MEDI4736 due to drug-related toxicity should not delay the 28-day dosing cycle of PLD, if possible. Likewise, any delay in MEDI4736 should not delay the administration of motolimod, and vice versa.

If PLD has to be discontinued due to PLD-related toxicities, the treatment with motolimod and/or MEDI4736 may continue, provided that the subject had received at least 2 doses of PLD (i.e., 2 cycles).

Irrespective of delay(s) in the dosing of the combination treatment, the disease assessments (CT, MRI) should not be delayed and must be conducted on the days originally scheduled, as calculated from the first study dose of PLD (Cycle 1 Day 1).

If a toxicity occurs that requires toxicity management in accordance with the toxicity management guidelines referenced above, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed.

3.1.9 DLT and MTD

PER Amendment 2, motolimod dosing will be discontinued for all subjects.

DLTs will be observed over a period of the first cycle including the pre-dose assessment for Cycle 2, defined as the "DLT Evaluation Period". The decisions for dose escalations, de-escalations and MTD, as described in Section 3.1.7, will primarily be based on the number of subjects with DLTs occurring during the DLT Evaluation Period. DLTs occurring outside the DLT Evaluation Period will also be evaluated and may impact such decisions.

DLTs are defined as any adverse events that are possibly, probably, or definitely related to the administration of MEDI4736, motolimod or PLD, and fulfill 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 *following exception*:
   - Grade 2 pneumonitis, neurological event, or uveitis that downgrades 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 PLD-related toxicities, manageable according to the dose modification instructions in the package insert/product information (see Section 8.2.)
   - Grade 3 irAEs (see definition below) 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 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, (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 AEs (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 rules for adjudicating DLTs 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 motolimod, and in combination with PLD. 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 therapy and will enter the On Study Follow-up phase of the study (see Sections 3.1.16 and 3.2). 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 of combination treatment is defined as the highest dose of MEDI4736 + motolimod + PLD studied, for which the observed incidence of DLT is less than 33% (based on n=6).

3.1.10 Subject Withdrawal from Treatment or Study

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

1. Withdrawal of consent for further treatment.
2. Pregnancy or intent to become pregnant.
3. Dose-limiting toxicity at any time (see Section 3.1.9 for definition of DLT and permitted continuation).
4. Confirmation of progressive disease by irRECIST criteria requiring alternative treatment.
5. Significant protocol violation or noncompliance that, in the opinion of the Investigator or Sponsor, warrants withdrawal.
6. Development of intercurrent, non-cancer related illnesses 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)

Discontinuation from receiving study treatment does not mean that the subject is withdrawn from the study. If feasible, subjects who are withdrawn from study treatment should enter the On Study Follow-Up, followed by the Post Study Follow-up (see Sections 3.1.16 and 3.2).

Subjects who begin other anti-cancer therapy should immediately be considered off-study and proceed to 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.
2. Initiation of alternative anti-cancer therapy including marketed or another investigational agent.
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 (see Section 7.2.6).

See also Sections 8.2, 8.3, and 8.4 for subject withdrawal from treatment due to necessary dosing interruptions or discontinuations.

3.1.10.1 Treatment beyond Progression

Subjects meeting criteria for progression by RECIST 1.1 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 for additional information regarding RECIST 1.1.

3.1.11 Subject Evaluability and Replacements

Phase 1: Subjects are fully evaluable for DLT if they fulfill the criteria for the Per-Protocol Population for DLT Assessment as defined in Section 4.2.2.

Subjects who are not fully evaluable for DLT *will* be replaced.

Phase 2: Subjects are fully evaluable for the primary endpoint of clinical efficacy, if they fulfill the criteria for the Per-Protocol Population (as defined in Section 4.1.2). Subjects who are not fully evaluable per protocol *may* be replaced.

3.1.12 Optional Study Treatment Extension

Optional MEDI4736 treatment extension beyond the initial 12-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, and it may continue until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met. See

Section 8.9 for details regarding treatment extension and collection / reporting of adverse events during this period.

3.1.13 Interim Analysis

Interim safety reviews will be performed to assess DLTs in Phase 1 (see Section 3.1.7). Interim analyses may be performed to analyze the endpoints of progression free survival at 6 and 12 months and/or as specified in the statistical analysis plan.

3.1.14 Safety Monitoring and Study Stopping Rules

In accordance with the Administrative, Legal and Ethical Requirements section of the protocol (see Section 7), 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 and VentiRx, providers of the study drugs. Additional investigators and staff, or additional sponsor personnel and consultants, shall participate in reviews as indicated. An Independent Data Monitoring Board (IDMB) will not be utilized for this open label study.

PER Amendment 2, motolimod dosing will be discontinued for all subjects.

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

1. A death that is unexpected and at least probably related to MEDI4736, motolimod, or to the combination of MEDI4736 and motolimod and PLD.
2. Severe anaphylactic reaction (i.e., with respiratory and cardiovascular failure) to MEDI4736 or motolimod.
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 Grade ≥3 neurological toxicity.
4. Any other safety finding assessed as related to MEDI4736 or motolimod that, in the opinion of the internal data safety monitoring panel, contraindicates further dosing of study subjects.
5. Any interim findings that, in the opinion of the Investigators and the Sponsor, suggest that the study treatment has no clinical benefit for the subjects.

3.1.15 Duration of Study

Duration of Treatment:	Up to 12 months for individual subjects See Section 3.1.12 for optional treatment extension.
Duration of On Study Follow-up	3 months
Enrollment Period:	24 months
Length of Study:	39 months
Post Study Follow-up	3 years from initiation of treatment

3.1.16 On Study and Post Study Follow-up

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

For all subjects who complete study treatment or discontinue treatment prematurely, there will be an On Study Follow-up Period (see Section 3.2) for 90 days after the last study drug administration, which will include collection of AE data (see Section 7.1.5 for details on collection of AEs).

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

Following the 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 every 3 months for 3 years from initiation of treatment.

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

For subjects who do not continue Post Study Follow-up at one of the study sites after the end of study, the Principal Investigator, 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 On Study Follow-up, this End of Study visit will be the first planned visit of the On Study Follow-up. For subjects already in On Study Follow-up, this End of Study visit will be the next planned visit of the On Study Follow-up. However, any procedures/assessments that were done within 7 days of the End of Study visit need not be repeated. All subjects of childbearing potential who withdraw from study must have a serum pregnancy test done at the End of Study visit, unless it was done within 7 days prior to the End of Study visit.

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

3.2 Study Flowchart

Study Flowchart for Subjects in Dose Level 0a Cohort Only	Screening / Baseline	Treatment																	
		Cycle 1			Cycle 2			Cycle 3			Cycle 4			Cycle 5			Cycle 6		
Cycle week		1		3	1		3	1		3	1		3	1		3	1		3
Visit Day per Cycle	-28 to -1	1	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2	1±3	3±1	17±2
Target Cumulative Visit Day		1	3	17	29	31	45	57	59	73	85	87	101	113	115	129	141	143	157
Phase 1 & 2 STUDY DRUG ADMINISTRATION																			
Pegylated liposomal doxorubicin - PLD (IV)		X			X			X			X			X			X		
MEDI4736 (IV)			X	X		X	X		X	X		X	X		X	X		X	X
Tumor & Disease Assessments																			
Disease Staging (date/stage at 1st diagnosis and at study entry)	X																		
Disease Assessment by RECIST 1.1 and irRECIST (including appropriate imaging)	-14 to -1										X								
Study Procedures & Examinations																			
Eligibility Assessment and Informed Consent (IC)[i]	X																		
Demographics (incl. DoB; sex; race; ethnicity)	X																		
Medical history	X																		
Physical Exam (incl. weight and ECOG Perf Status)	X	X			X			X			X			X			X		
Height	X																		
Vital Signs (T, HR, BP, RR)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[a]	X				X			X			X			X			X		
Echocardiogram or MUGA	X									X									X
Concomitant Medication / Procedure	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (starting or worsening after IC)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Specimens for Laboratory Procedures																			
Blood Hematology (complete blood count, differential, platelets)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, PO4, Mg, prot., alb., Tbili., AST, ALT, ALP, LDH)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry cont. (Amylase and lipase)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry cont. (Free T3, Free T4, TSH)[a]	X	X		X	X		X	X		X	X		X	X		X	X		X
Serum pregnancy test[a,f]	-7 to -1							X						X					
CA-125[a]	-14 to -1				X			X			X			X			X		
Urine Pregnancy Test[a,f]		X[a]																	
Specimens for Correlative Assessments																			
PBMC/Plasma Collection & Banking[a,g]	X				X			X											
MDSC (Serametrix)[a,g] (US sites only)	X							X											
Tumor Biopsy (Tumor microenvironment, PD-L1 expression, TCR sequencing)[e]	X				X	X (at disease progression: optional)													
Pharmacogenomics (including BRCA1 and BRCA2 tumor status)[c]	X[g]																		
PAX RNA[a,g]	X				X	X (at disease progression: optional)													

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

b - See Section 6.3.5 for assessment of vital signs before/during/after MEDI4736 infusion

c - An aliquot of the PBMC and/or Tumor Biopsy/Archival Tissue will be used for pharmacogenomics – a separate sampling is not needed

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

e - Biopsy is optional for Phase 1. Refer to Criterion 4 in Section 5.1. Archival tissue will be requested for all subjects, preferably from primary tumor site prior to cancer treatment; however, archival tissue is not a requirement for study entry.

f - Pregnancy tests are not required for subjects who are not of child-bearing potential as defined in Section 5.2, #17

g- Screening/Baseline specimens for correlative assessments may be collected up to Cycle 1/Day 1 prior to the PLD dose.

h - See Section 3.1.16 regarding assessments scheduled for both the last on treatment visit and the first post-last treatment visit.

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

Study Flowchart for Subjects in Dose Level 0a Cohort Only (Cont)	Treatment																		On Study Follow-up			Post Study Follow-Up
	Cycle 7			Cycle 8			Cycle 9			Cycle 10			Cycle 11			Cycle 12			Last Study Drug Administration	Last Study Drug Administration	Last Study Drug Administration	
Cycle week	1		3	1		3	1		3	1		3	1		3	1		3				
Visit Day per Cycle	1±3	3±1	17±2	1 ±3	3 ±1	17 ±2	1 ±3	3 ±1	17 ±2	1 ±3	3 ±1	17 ±2	1 ±3	3±1	17 ±2	1 ±3	3 ±1	17 ±2	+14 ±3 days[h]	+42 ±7 days	+90 ±7 days End of Study	
Target Cumulative Visit Day	169	171	185	197	199	213	225	227	241	253	255	269	281	283	297	309	311	325				
Phase 1 & 2 STUDY DRUG ADMINISTRATION																						
Pegylated liposomal doxorubicin - PLD (IV)	X			X			X			X			X			X						
MEDI4736 (IV)		X	X		X	X		X	X		X	X		X	X		X	X				
Tumor & Disease Assessments																						
Disease Staging (date/stage at 1st diagnosis and at study entry)																						
Disease Assessment by RECIST and irRECIST (including appropriate imaging)	X									X									+84 ±7 days from last disease assessment			
Study Procedures & Examinations																						
Eligibility Assessment and Informed Consent (IC)[i]																						
Demographics (incl. DoB; sex; race; ethnicity)																						
Medical history																						
Physical Exam (incl. weight and ECOG Perf Status)	X			X			X			X			X			X			X	X	X	
Height																						
Vital Signs (T, HR, BP, RR)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[a]	X			X			X			X			X			X			X			
Echocardiogram or MUGA									X										X			
Concomitant Medication / Procedure (name, indication, dose, route, start & end dates)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events (starting or worsening after IC)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Specimens for Laboratory Procedures																						
Blood Hematology (complete blood count, differential, platelets)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, PO4, Mg, prot., alb., Tbili., AST, ALT, ALP,LDH)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry cont. (Amylase and lipase)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry cont. (Free T3, Free T4, TSH)[a]	X		X	X		X	X		X	X		X	X		X	X		X	X	X	X	
Serum pregnancy test[a,f]	X						X						X						X		X	
CA-125[a]	X			X			X			X			X			X			X			
Urine Pregnancy Test[a,f]																						
Specimens for Correlative Assessments																						
PBMC/Plasma Collection & Banking[a,g]	X																		X		X	
MDSC (Serametrix)[a,g] (US sites only)	X																		X			
Tumor Biopsy (Tumor microenvironment, PD-L1 expression, TCR sequencing)[e]	X (at disease progression: optional)																					
Pharmacogenomics (including BRCA1 and BRCA2 tumor status)[c]																						
PAX RNA[a,g]	X (at disease progression: optional)																					

Every 3 months for 3 years from initiation of treatment.
Clinical outcomes data (dates of progression/relapse and survival) will be recorded (See Section 3.1.16).

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

b - See Section 6.3.5 for assessment of vital signs before/during/after MEDI4736 infusion

c –An aliquot of the PBMC and/or Tumor Biopsy/Archival Tissue will be used for pharmacogenomics – a separate sampling is not needed

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

e - Biopsy is optional for Phase 1. Refer to Criterion 4 in Section 5.1. Archival tissue will be requested for all subjects, preferably from primary tumor site prior to cancer treatment; however, archival tissue is not a requirement for study entry.

f - Pregnancy tests are not required for subjects who are not of child-bearing potential as defined in Section 5.2, # 17

g- Screening/Baseline specimens for correlative assessments may be collected up to Cycle 1/Day 1 prior to the PLD dose.

h - See Section 3.1.16 regarding assessments scheduled for both the last on treatment visit and the first post-last treatment visit.

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

Study Flowchart for All Subjects Except Dose Level 0a Cohort	**Screening / Baseline**	**Treatment**											
		Cycle 1		**Cycle 2**		**Cycle 3**		**Cycle 4**		**Cycle 5**		**Cycle 6**	
Cycle week		**1**		**1**		**1**		**1**		**1**		**1**	
Visit Day per Cycle	-28 to -1	1	3±1	1±3	3±1	1±3	3±1	1±3	3±1	1±3	3±1	1±3	3±1
Target Cumulative Visit Day		1	3	29	31	57	59	85	87	113	115	141	143
Phase 1 & 2 STUDY DRUG ADMINISTRATION													
Pegylated liposomal doxorubicin - PLD (IV)		X		X		X		X		X		X	
MEDI4736 (IV)			X		X		X		X		X		X
Tumor & Disease Assessments													
Disease Staging (date/stage at 1st diagnosis and at study entry)	X												
Disease Assessment by RECIST 1.1 and irRECIST (including appropriate imaging)	-14 to -1							X					
Study Procedures & Examinations													
Eligibility Assessment and Informed Consent (IC)[i]	X												
Demographics (incl. DoB; sex; race; ethnicity)	X												
Medical history	X												
Physical Exam (incl. weight and ECOG Perf Status)	X	X		X		X		X		X		X	
Height	X												
Vital Signs (T, HR, BP, RR)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X
12-Lead ECG[a]	X			X		X		X		X		X	
Echocardiogram or MUGA	X								X				X
Concomitant Medication / Procedure	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse Events (starting or worsening after IC)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X
Specimens for Laboratory Procedures													
Blood Hematology (complete blood count, differential, platelets)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, PO4, Mg, prot., alb., Tbili., AST, ALT, ALP, LDH)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry cont. (Amylase and lipase)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistry cont. (Free T3, Free T4, TSH)[a]	X	X		X		X		X		X		X	
Serum pregnancy test[a,f]	-7 to -1					X				X			
CA-125[a]	-14 to -1			X		X		X		X		X	
Urine Pregnancy Test[a,f]		X[a]											
Specimens for Correlative Assessments													
PBMC/Plasma Collection & Banking[a,g]	X			X		X							
MDSC (Serametrix)[a,g] (US sites only)	X					X							
Tumor Biopsy (Tumor microenvironment, PD-L1 expression, TCR sequencing)[e]	X			X		**X (at disease progression: optional)**							
Pharmacogenomics (including BRCA1 and BRCA2 tumor status)[c]	X[g]												
PAX RNA[a,g]	X			X		**X (at disease progression: optional)**							

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

b - See Section 6.3.5 for assessment of vital signs before/during/after MEDI4736 infusion

c - An aliquot of the PBMC and/or Tumor Biopsy/Archival Tissue will be used for pharmacogenomics – a separate sampling is not needed

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

e - Biopsy is optional for Phase 1. Refer to Criterion 4 in Section 5.1. Archival tissue will be requested for all subjects, preferably from primary tumor site prior to cancer treatment; however, archival tissue is not a requirement for study entry.

f - Pregnancy tests are not required for subjects who are not of child-bearing potential as defined in Section 5.2, #17

g- Screening/Baseline specimens for correlative assessments may be collected up to Cycle 1/Day 1 prior to the PLD dose.

h - See Section 3.1.16 regarding assessments scheduled for both the last on treatment visit and the first post-last treatment visit.

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

Study Flowchart for All Subjects Except Dose Level 0a Cohort (Cont)	Treatment												On Study Follow-up			Post Study Follow-Up
	Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12		Last Study Drug Administration +28 ±3 days[h]	Last Study Drug Administration +56 ±7 days	Last Study Drug Administration +90 ±7 days End of Study	
Cycle week	1		1		1		1		1		1					
Visit Day per Cycle	1±3	3±1	1 ±3	3 ±1	1 ±3	3 ±1	1 ±3	3 ±1	1 ±3	3±1	1 ±3	3 ±1				
Target Cumulative Visit Day	169	171	197	199	225	227	253	255	281	283	309	311				
Phase 1 & 2 STUDY DRUG ADMINISTRATION																
Pegylated liposomal doxorubicin - PLD (IV)	X		X		X		X		X		X					
MEDI4736 (IV)		X		X		X		X		X		X				
Tumor & Disease Assessments																
Disease Staging (date/stage at 1st diagnosis and at study entry)																
Disease Assessment by RECIST and irRECIST (including appropriate imaging)	X						X						+84 ± 7 days from last disease assessment			
Study Procedures & Examinations																
Eligibility Assessment and Informed Consent (IC)[i]																
Demographics (incl. DoB; sex; race; ethnicity)																
Medical history																
Physical Exam (incl. weight and ECOG Perf Status)	X		X		X		X		X		X		X	X	X	
Height																
Vital Signs (T, HR, BP, RR)[b]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
12-Lead ECG[a]	X		X		X		X		X		X		X			
Echocardiogram or MUGA						X							X			
Concomitant Medication / Procedure (name, indication, dose, route, start & end dates)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Events (starting or worsening after IC)[d]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Specimens for Laboratory Procedures																
Blood Hematology (complete blood count, differential, platelets)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO2, PO4, Mg, prot., alb., Tbili., AST, ALT, ALP,LDH)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry cont. (Amylase and lipase)[a]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Chemistry cont. (Free T3, Free T4, TSH)[a]	X		X		X		X		X		X		X	X	X	
Serum pregnancy test[a,f]	X				X				X				X		X	
CA-125[a]	X		X		X		X		X		X		X			
Urine Pregnancy Test[a,f]																
Specimens for Correlative Assessments																
PBMC/Plasma Collection & Banking[a,g]	X												X		X	
MDSC (Serametrix)[a,g] (US sites only)	X												X			
Tumor Biopsy (Tumor microenvironment, PD-L1 expression, TCR sequencing)[e]	X (at disease progression: optional)															
Pharmacogenomics (including BRCA1 and BRCA2 tumor status)[c]																
PAX RNA[a,g]	X (at disease progression: optional)															

Every 3 months for 3 years from initiation of treatment.
Clinical outcomes data (dates of progression/relapse and survival) will be recorded (See Section 3.1.16).

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

b - See Section 6.3.5 for assessment of vital signs before/during/after MEDI4736 infusion

c -An aliquot of the PBMC and/or Tumor Biopsy/Archival Tissue will be used for pharmacogenomics – a separate sampling is not needed

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

e - Biopsy is optional for Phase 1. Refer to Criterion 4 in Section 5.1. Archival tissue will be requested for all subjects, preferably from primary tumor site prior to cancer treatment; however, archival tissue is not a requirement for study entry.

f - Pregnancy tests are not required for subjects who are not of child-bearing potential as defined in Section 5.2, #17

g- Screening/Baseline specimens for correlative assessments may be collected up to Cycle 1/Day 1 prior to the PLD dose.

h - See Section 3.1.16 regarding assessments scheduled for both the last on treatment visit and the first post-last treatment visit.

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

4 Study Objectives & Endpoints

Phase	Primary Objectives [Endpoints]	Secondary Objectives [Endpoints]
1	*Safety and tolerability* [DLT/MTD by CTCAE v4.03]	*Clinical Efficacy* [PFS Rate at 6 and 12 months by RECIST v1.1 and irRECIST] [Median PFS by RECIST v1.1 and irRECIST] [ORR by RECIST v1.1 and irRECIST] [Median Overall Survival (OS)] *Biological Activity* [Immunological Response]
2	*Clinical Efficacy* [PFS Rate at 6 months by RECIST v1.1]	*Clinical Efficacy* [PFS rate at 6 months by irRECIST] [PFS Rate at 12 months by RECIST v1.1 and irRECIST] [Median PFS by RECIST v1.1 and irRECIST] [ORR by RECIST v1.1 and irRECIST] [Median Overall Survival (OS)] *Safety and tolerability* [Toxicity by CTCAE v4.03] *Biological Activity* [Immunological Response]

4.1 Clinical Efficacy

The assessment of Clinical Efficacy is the Primary Objective of Phase 2 and the Secondary Objective of Phase 1 of the study and will be performed by RECIST 1.1 and irRECIST.

4.1.1 Endpoints & Assessment Methods

Clinical Efficacy is determined by measuring the Progression-free Survival (PFS), Overall Response Rate (ORR), and Overall Survival (OS). Every attempt should be made to use whichever imaging technique(s) and test(s) are used initially for repeat evaluations throughout the study, whereby the last tumor assessment will be at least 4 weeks from the prior assessment.

4.1.1.1 Progression-free Survival Rate

The proportion of subjects who survive and do not progress - Progression Free Survival (PFS) rate- within the first 6 months of treatment based on RECIST v1.1 evaluated for the per-protocol analysis population constitutes the primary endpoint in Phase 2 of the study. PFS rate at 6 months will be based on disease assessments at the scheduled visit at the start of Cycle 7.

4.1.1.2 Progression-free Survival Time

Progression-free survival time will be defined as the number of days from the date of first dose to the date of earliest disease progression based on RECIST v1.1 and irRECIST, or to the date of death, if disease progression does not occur.

4.1.1.3 Overall Response Rate

Overall Response Rate is defined as the percentage of subjects meeting criteria of CR or PR over a period of at least 4 weeks.

4.1.1.4 Overall Disease Control Rate

Disease Control is defined as SD, PR or CR over a period of at least 4 weeks.

4.1.1.5 Overall Survival Time

Overall survival (OS) time will be measured for each subject with time origin at the date of study Day 1 until recorded date of death or last follow-up. Subjects lost to follow-up will be censored on the date when they were last known to be alive. Every effort will be made to follow subjects for overall survival after they complete or discontinue the study.

4.1.2 Subject Evaluation & Statistics

The *Per-Protocol (PP) Population* for clinical efficacy is defined as all subjects who received at least 75% of the scheduled doses of MEDI4736, motolimod (pre Amendment 2), and PLD over the first 2 cycles, as well as respective disease assessments, without major protocol violations. The *Intent-To-Treat (ITT) Population* for clinical efficacy is defined as all subjects who receive at least one dose of PLD, motolimod (pre Amendment 2) or MEDI4736.

The analysis of clinical efficacy will be based on both the intent-to-treat (ITT) and the per-protocol (PP) populations.

The PFS Rate at 6 months based on RECIST v1.1 evaluated for the per-protocol analysis population constitutes the primary endpoint in Phase 2 of the study. This PFS rate along with its one sided 95% Confidence Interval (CI) based on binomial distribution will be estimated and reported. The one-sided null hypothesis of 6-month PFS ≤0.25 will be rejected at 0.05 level of significance if the 95% one-sided CI does not contain 0.25. The 12-months PFS rate along with its 95% one-sided CI will be calculated and reported as a secondary endpoint.

Tumor Response will be summarized and analyzed descriptively for each cohort and analysis population. A 95% Confidence Interval based on binomial distribution will be constructed for the estimated ORR.

Median OS will be calculated using the Kaplan-Meier method. The analysis of PFS and OS will be updated based on data collected during the Post Study Follow-up (see Section 3.1.16).

4.2 Safety and Tolerability

The assessment of safety and tolerability is the Primary Objective of Phase 1 and Secondary Objective of Phase 2 of the study. It 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. In Phase 1, formal safety reviews will be performed and documented for the purpose of dose escalation / de-escalation in the context of the 3+3 study design.

4.2.1 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. The investigator will evaluate any laboratory abnormalities for clinical significance, and clinically significant abnormalities will be recorded as adverse events. All clinically significant abnormalities and deteriorations from time of signing of informed consent to the end of study visit 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.

4.2.2 Subject Evaluation & Statistics

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

- All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9)
- All subjects with no DLT who receive at least 75% of the scheduled doses of MEDI4736, motolimod (pre Amendment 2), and PLD as well as respective safety assessments, without major protocol violations, over the entire DLT Evaluation Period (as defined in Section 3.1.9).

Refer to Section 3.1.11 for subject replacements.

The *Intent-To-Treat (ITT) Population for safety and tolerability* is defined as all subjects who receive at least one dose of PLD, motolimod (pre Amendment 2) or MEDI4736.

In *Phase 1*, for the primary endpoint of determining DLTs and the MTD, the analysis of safety and tolerability will be based on the PP Population for DLT Assessment.

In both *Phases 1 and 2*, the overall analysis of safety and tolerability will be based on the ITT Population for safety and tolerability.

Appropriate summaries of AEs, laboratory data and vital sign data will be presented. Adverse events will be coded using the MedDRA dictionary. Incidences of treatment-emergent adverse events (TEAE, those events that started after dosing or worsened in severity after dosing) will be presented overall and by maximum severity (according to CTCAE version 4.03) and relationship to study medication.

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

4.3 Biological Activity

Samples for exploratory assessment of correlative immunologic research will be collected according to the Study Flowchart in Section 3.2. Assessments include, but are not limited to: Phenotypic analysis of PBMCs, Characterization of MDSCs, Quantification of tumor-specific T-cell responses, Immune Landscape: Tumor Infiltrating Lymphocytes and Tumor Microenvironment, TCR sequencing, Immune Biomarkers, Pharmacogenomics, and BRCA status of tumors.

A comprehensive list of variables to be analyzed for the exploratory assessment of correlative immunologic research is located in Section 8.7.

4.3.1 Endpoints & Assessment Methods

Subjects who received at least one dose of PLD, motolimod (pre Amendment 2) or MEDI4736, and provide baseline and at least one post-treatment sample, will be evaluated. The assessment methods are described in the respective appendices for each assay.

4.3.2 Subject Evaluation & Statistics

The association of clinical activity with tumor markers will be assessed based on PD-L1 expression level and changes in tumor-infiltrating lymphocytes (TIL) from mandatory pre- and post-treatment biopsies in the Phase 2 cohort. Subjects will be classified as responders or non-responders based on RECIST v1.1 and irRECIST criteria. Within each response group, subject tumors will be assessed as positive or negative for PD-L1 expression. Fisher's Exact test will be used to test whether there is a significant association between responder-status and PD-L1 expression. Assuming evaluable tumor biopsies are available for at least 36 subjects and approximately equal numbers of responders and non-responders, if there are 80% and 30% of subjects with positive PD-L1 expression in the two groups, respectively, there will be at least 80% power to detect a significant difference. A 95% confidence interval for the odds ratio for positive PD-L1 expression will be presented. The association between response and TIL changes (increase, decrease, or no change) will be evaluated similarly.

Results from the remaining correlative studies will be summarized descriptively and evaluated in relation to outcome. All data will be provided in subject data listings.

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:*

<table>
<tr><td>1.</td><td>Subjects must have recurrent or persistent platinum-resistant epithelial ovarian, fallopian tube, or primary peritoneal carcinoma with measureable disease (as defined by RECIST 1.1.) after first or second line platinum-based chemotherapy, for which treatment with PLD is indicated.
Platinum-based therapy is defined as treatment with carboplatin, cisplatin or another organoplatinum compound.
Platinum-resistant is defined as having a platinum-free interval (PFI) of < 12 months after first- or second-line platinum-based chemotherapy, or having disease progression while receiving second-line platinum-based chemotherapy.
Subjects are allowed to have received, but are not required to have received:
one additional cytotoxic regimen and/or PARP inhibitor for management of recurrent or persistent disease.
biologic therapy (e.g., bevacizumab) as part of their primary treatment regimen or as part of their treatment for management of recurrent or persistent disease.</td></tr>
<tr><td>2.</td><td>Histologic documentation of the original primary tumor.</td></tr>
<tr><td>3.</td><td>Documented radiographic disease progression < 12 months after the last dose of first- or second-line platinum-based chemotherapy.</td></tr>
<tr><td>4.</td><td>Subjects in Phase 2 must have disease amenable to biopsy and must be willing to undergo pre- and post-treatment tumor biopsies (see Section 3.2 for biopsy time points). Optional for Phase 1.
NOTE: Archival tissue will be requested for all subjects, preferably from primary tumor site prior to cancer treatment; however, archival tissue is not a requirement for study entry.</td></tr>
<tr><td>5.</td><td>ECOG performance status of 0 or 1.</td></tr>
<tr><td>6.</td><td>Laboratory parameters for vital functions should be in the normal range. Laboratory abnormalities that are not clinically significant are generally permitted, except for the following laboratory parameters, which must be within the ranges specified, regardless of clinical significance:
<table>
<tr><td>Hemoglobin</td><td>≥ 9 g/dL</td></tr>
<tr><td>Neutrophil count</td><td>≥ 1.5 x 10^9/L</td></tr>
<tr><td>Platelet count</td><td>≥ 100,000/mm3</td></tr>
<tr><td>Serum creatinine, or
Creatinine Clearance</td><td>≦ 1.5x Institutional Upper Limit of Normal (ULN), or
≥ 50 mL/min (by Cockcroft-Gault formula)</td></tr>
<tr><td>Serum bilirubin</td><td>≦ 1.2 mg/dL</td></tr>
<tr><td>AST/ALT</td><td>≦ 2.5 x ULN</td></tr>
<tr><td>Alkaline phosphatase</td><td>≤ 2.5 x ULN</td></tr>
</table></td></tr>
<tr><td>7.</td><td>Age ≥18 years.</td></tr>
</table>

8.	Able and willing to give valid written informed consent.
9.	Body weight > 30 kg

5.2 Exclusion Criteria

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

1.	Prior exposure to doxorubicin, PLD or any other anthracycline, motolimod and other TLR agonists (pre Amendment 2), MEDI4736 or checkpoint inhibitors, such as anti-CTLA4 and anti-PD1/anti-PD-L1 antibodies.
2.	Subjects with platinum-refractory disease, defined as disease progression while receiving first line platinum-based therapy.
3.	Clinically significant persistent immune-related adverse events following prior therapy.
4.	Subjects with history or evidence upon physical examination of CNS disease, including primary brain tumor, seizures not controlled with standard medical therapy, any brain metastases, or, within six months prior to Day 1 of this study, history of cerebrovascular accident (CVA, stroke), transient ischemic attack (TIA) or subarachnoid hemorrhage.
5.	Subjects with clinically significant cardiovascular disease. This includes: a. Resistant hypertension. b. Myocardial infarction or unstable angina within 6 months prior to Day 1 of the study. c. History of serious ventricular arrhythmia (i.e., ventricular tachycardia or ventricular fibrillation) or cardiac arrhythmias requiring anti-arrhythmic medications, except for atrial fibrillation that is well controlled with anti-arrhythmic medication. d. Baseline ejection fraction ≤ 50% as assessed by echocardiogram or MUGA. e. New York Heart Association (NYHA) Class II or higher congestive heart failure. f. Grade 2 or higher peripheral ischemia, except for brief (< 24 hrs) episodes of ischemia managed non-surgically and without permanent deficit.
6.	History of pneumonitis or interstitial lung disease.
7.	Active, suspected or prior documented autoimmune disease (including inflammatory bowel disease, celiac disease, Wegner's granulomatosis, active Hashimoto's thyroiditis, rheumatoid arthritis, lupus, scleroderma and its variants, multiple sclerosis, myasthenia gravis). Vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted.
8.	Other malignancy within 2 years prior to Day 1 of the study, except for those treated with surgical intervention only.
9.	Subjects with clinical symptoms or signs of gastrointestinal obstruction and/or who require drainage gastrostomy tube and/or parenteral hydration or nutrition.
10.	Known immunodeficiency or HIV, Hepatitis B or Hepatitis C positivity.
11.	History of severe allergic reactions to any unknown allergens or components of the study drugs.

12.	Other serious illnesses (e.g., serious infections requiring antibiotics, bleeding disorders).
13.	Prior treatment in any other interventional clinical trial within 4 weeks prior to Day 1 of the study.
14.	Mental impairment that may compromise compliance with the requirements of the study.
15.	Lack of availability for immunological and clinical follow-up assessment.
16.	Women of child bearing potential who are found to be pregnant as evidenced by positive serum pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) or nursing. NOTE: Pregnancy tests are not required for subjects who are not of child-bearing potential as defined in #17.
17.	Female subjects of childbearing potential who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception (see table below) from screening, and must agree to continue using such precautions for 90 days after the final dose of investigational product (MEDI4736). Male partners of a female subject must use male condom plus spermicide throughout this period (from screening and for 90 days after subject's receipt of the final dose of investigational product). 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 refrain from breastfeeding throughout the period described above. NOTE: For the standard of care, pegylated liposomal doxorubicin (PLD, Doxil®, Caelyx®), the package insert advises females of reproductive potential to use effective contraception during and for 6 months after last treatment with the drug. Therefore, all subjects of childbearing potential on this study should continue contraception use for 6 months after the last PLD administration. 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.

<table>
<tr><td></td><td>
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:
<table>
<tr><th colspan="2">Highly Effective[a] Methods of Contraception</th></tr>
<tr><th>Barrier/Intrauterine Methods</th><th>Hormonal Methods</th></tr>
<tr><td>• Copper T intrauterine device
• Levonorgesterel-releasing intrauterine system (e.g., Mirena®)[b]</td><td>• Implants: Etonogestrel implants: e.g. Implanon or Norplan
• Intravaginal device: ethinylestradiol and etonogestrel- releasing intravaginal devices: e.g. NuvaRing®
• Injection: Medroxyprogesterone injection: e.g. Depo-Provera
• Combined Pill: Normal and low dose combined oral contraceptive pill
• Patch: Norelgestromin/ethinylestradiol-releasing transdermal system e.g. Ortho Evra®
• “Minipill[c]”: Progesterone based oral contraceptive pill using desogestrel e.g., Cerazette®</td></tr>
<tr><td colspan="2">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</td></tr>
</table>
</td></tr>
<tr><td>18.</td><td>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.</td></tr>
<tr><td>19.</td><td>Subjects must not donate blood while on study and for at least 90 days following the last MEDI4736 treatment.</td></tr>
<tr><td>20.</td><td>History of allogeneic organ transplant</td></tr>
</table>

5.3 Restrictions on Concomitant Therapies

5.3.1 Non-Permitted Concomitant Therapies

*Subject **<u>may not</u>** receive the following concomitant therapies during the study:*

1.	Systemic treatment with glucocorticosteroids 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 (e.g., drug, 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.
The wash-out period prior to Day 1 of the study for all non-permitted drugs should be at least 1 week, unless stated otherwise above.	

5.3.2 Permitted Concomitant Therapies

*Subject **<u>may</u>** receive the following concomitant therapies during the study:*

1.	Intranasal or inhaled steroids for treating mild to moderate asthma or allergies, physiological steroid replacement, intra-articular steroids, or topical steroids for localized dermatitis (<5% of BSA).
2.	NSAIDs, acetylsalicylic acid and specific COX-2 inhibitors.
3.	Antihistamines and other non-steroidal anti-allergy medication.
4.	Hormone replacement therapy.
5.	Palliative radiation of non-target and/or non-index lesions, or for symptom management.
6.	At the discretion of the Investigator, any drug or non-drug therapy necessary to treat any condition arising during the study, including high dose corticosteroids or anti-TNF agents (e.g. infliximab) to treat immune-mediated adverse reactions. Subjects should receive full supportive care, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheal, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines. Use of anticoagulants such as warfarin is permitted however, caution should be exercised and additional International Normalized Ratio (INR) monitoring is recommended. **[*Note:* <u>Motolimod should not be dosed within 24 hours of systemic corticosteroid use. Doses of motolimod should be delayed or skipped as appropriate. See Sections 8.2, 8.3, and 8.4 regarding dose delays.]</u>** **PER Amendment 2, motolimod dosing will be discontinued for all subjects.**
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 Drug Preparation and Administration

6.1 Pegylated Liposomal Doxorubicin (PLD)

Pegylated liposomal doxorubicin (PLD) is commercially available and will be ordered by the pharmacy at the investigative site.

Please refer to the package insert for PLD for the most current formulation, preparation and administration. The dose to be administered is 40 mg/m^2, which is consistent with current clinical practice.

Maximum body surface area for PLD dose calculations will be 2.0 m^2. Dose recalculation for each cycle will be needed if there is a weight change > 10%. NOTE: The maximum body surface area and recalculations are recommendations; standard procedures for maximum body surface and recalculations at each site may be used.

6.2 Motolimod

PER Amendment 2, motolimod dosing will be discontinued for all subjects.

Motolimod is supplied by the Sponsor. Prior to administration, motolimod must be reconstituted using sterile water for injection. Please see to section 6.2.2 for preparation and administrative instructions.

6.2.1 Motolimod Study Drug Information

Manufacturer	VentiRx		
Expiration/Retest Date	*Expiration/retest dates are documented on the Certificate of Analysis and/or stability certification.*		
Container Description	*Type:* Single use vial	*Material:* clear-glass	*Size:* 3-mL
Formulation	Motolimod is supplied as an off-white, lyophilized cake and is comprised of an active pharmaceutical ingredient (VTX-378) formulated with a solubilizing agent at neutral pH.		
Active Ingredient Content	*Mass/Weight:* 8.4mg	*Volume:* n/a	*Concentration:* 10mg/mL when reconstituted with 0.7mL sterile water
Storage Conditions	2°C–8°C (26°F–46°F)		
Stability after reconstitution	24 hours at 2-8°C or 8 hours at ambient		
Labeling	Product name, lot number, route of administration, and storage conditions		

6.2.2 Motolimod Preparation

Prior to administration, motolimod must be reconstituted using sterile water for injection, USP. Reconstituted stock solutions are stable for 8 hours at room temperature and for 24 hours when

refrigerated at 2–8°C. Motolimod should be prepared and transferred using aseptic technique in a biological safety cabinet. Vials of motolimod are intended for single use only.

1. Determine the appropriate dose based on the subject's BSA.
    a. Calculate the total dose to be administered:
    BSA (__.__ __m^2) x dose level (__. __ mg/m^2) = total dose (__.__) mg) of motolimod.
    b. Calculate the dose volume:
    Total dose (__. __) mg.) ÷ 10 mg/mL = dose volume (__. __ __ mL) of motolimod.
2. Reconstitute 1 vial of motolimod with 0.7 mL Sterile Water for Injection
3. Sterile Water for Injection, as described below, to yield 0.84 mL of solution with a concentration of 10 mg/mL.
    a. Add the sterile water for injection while directing the stream at the lyophilized cake.
    b. Swirl the vial to disperse the water throughout the cake
    c. Invert the vial repeatedly for approximately 2–3 minutes until the contents are fully dissolved. The reconstituted solution should be clear, and will range in color from colorless to yellow.
4. Using a syringe appropriate for subcutaneous dosing to draw up __. __ __ mL (dose volume; step 1b) from the vial of 10 mg/mL motolimod.

6.2.3 Motolimod Administration

On days with concurrent motolimod and MEDI4736 dosing, motolimod administration will occur 30-60 minutes after the end of the MEDI4736 infusion. Motolimod is administered as a subcutaneous injection. Within 30 minutes prior to each dose of motolimod, subjects will be administered 650–1000 mg acetaminophen by mouth to help mitigate potential adverse events commonly associated with the administration of motolimod (e.g., fever, myalgia). Subjects will be given or instructed to take an additional dose of 650–1000 mg acetaminophen by mouth approximately 4–6 hours after administration of motolimod, and as needed thereafter for symptoms of fever and/or body aches. Acetaminophen is the preferred over-the-counter analgesic and antipyretic; due to their potentially immunosuppressive effects, administration of NSAIDS within 24 hours of dosing should be avoided if clinically feasible.

To potentially reduce the effects of injection site reaction that may be associated with the administration of motolimod, an ice pack may be applied to the injection site for approximately 30 minutes prior to injection, immediately following injection, and throughout the day of injection. Additionally, at the discretion of the Investigator, single doses of motolimod may be divided and administered at two different anatomical locations.

The dose of motolimod should be administered with a syringe suitable for subcutaneous injection. To administer the injection, 1–2 inches of fatty tissue should be pinched up to avoid injection into the muscle layer. The needle can be inserted at either 45 or 90 degrees; a 45 degree angle is recommended when less than 2 inches of tissue can be pinched. Appropriate anatomic areas for subcutaneous injection include the fatty tissue over the abdomen, triceps, thighs, or lower back. The injection site should be rotated among anatomically appropriate locations to help avoid injection site reaction.

Standard medications to treat possible hypersensitivity reactions and/or symptoms of cytokine release syndrome (CRS) should be readily available at the time of treatment, including

epinephrine, H1 antihistamines (e.g., diphenhydramine), H2 antihistamines (e.g., ranitidine), narcotics, IV fluids for volume expansion and supplemental oxygen.

Due to their immunosuppressive effect, administration of systemic corticosteroids (e.g., dexamethasone) should be avoided in this setting if other means of treatment are available and appropriate. If systemic corticosteroid use is clinically necessary, motolimod should not be administered within 24 hours. Doses of motolimod should be delayed or skipped as appropriate.

6.3 MEDI4736

MEDI4736 is supplied by the Sponsor. Commercially available 0.9% (w/v) saline or 5% (w/v) dextrose will be supplied by each site. Please see Section 7.2.8, for additional details.

6.3.1 MEDI4736 Study Drug Information

Manufacturer	MedImmune		
Expiration/Retest Date	*Expiration/retest dates are documented in the QA Disposition of Investigational Medicinal Product (IMP) Report.*		
Container Description	*Type:* Single use vial	*Material:* glass	*Size:* 10 mL
Formulation	Liquid solution containing 500 mg MEDI4736 per vial. 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:* 500 mg	*Volume:* 10 mL	*Concentration:* 50 mg/mL
Storage Conditions	2°C to 8°C (36°F to 46°F) Do not freeze		
Labeling	Product name, lot number, route of administration, and storage conditions		

6.3.2 MEDI4736 Investigational Product Inspection

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

6.3.3 MEDI4736 Preparation

Preparation of MEDI4736 and preparation of the intravenous bag are to be performed aseptically by the IP manager or designated personnel. No incompatibilities between MEDI4736 and polyvinylchloride or polyolefin copolymers have been observed.

6.3.3.1 MEDI4736 Preparation for Cohort at Dose Level 0a

Dose Calculation:
The volume of MEDI4736 (in mL) 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)

The corresponding volume of MEDI4736 should be rounded to the nearest tenth mL (0.1 mL). Dose adjustments for each cycle are only needed for a greater than 10% change in weight.

Dose Preparation:
MEDI4736 will be administered using a 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose. 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 x 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.

Per Amendment 3, fixed dosing will be used for the optional study treatment extension as described in Section 3.1.12 and Section 8.9. See Section 6.3.3.2.

6.3.3.2 MEDI4736 Preparation for all Subjects except Cohort at Dose Level 0a and for Treatment Extension

Per Amendment 3, fixed dosing will be used for all subjects who proceed with the optional study treatment extension as described in Section 3.1.12 and Section 8.9.

Dose Calculation:
Subjects will receive a fixed dose of MEDI4736: 1500 mg Q4W 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 equivalent to 20 mg/kg Q4W for MEDI4736 as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of MEDI4736 1500 mg.

The volume of MEDI4736 (in mL) to add to the IV bag is calculated as follows:

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

Dose Preparation:
MEDI4736 will be administered using a 250 mL IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose. 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 1500 mg dose (for subjects > 30 kg in weight), 30 mL of MEDI4736 is to be diluted in a 250 mL IV bag. First, 30 mL of diluent is removed from the IV bag, and then 30 mL of MEDI4736 is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag.

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

6.3.4 MEDI4736 Administration

Following preparation of the dose, MEDI4736 will be administered according to the following guidelines:

- The entire contents of the IV bag should be administered as an IV infusion over approximately 60 (± 5) minutes, using a 0.2- or 0.22-µm in-line filter. **An infusion of less than 55 minutes is considered a deviation.**
- After the contents of the IV bag are fully administered, the IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used. Alternatively, 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.
- MEDI4736 must be administered at room temperature by controlled infusion 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.
- MEDI4736 solution should not be infused with other solutions or medications.
- A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational products. Fully functional resuscitation facilities should be available.
- MEDI4736 must not be administered via IV push or bolus but as an IV infusion.
- 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 6.3.5.
- See Section 8.4.2.2 for management guidelines for infusion-related reactions.
- The total time between needle puncture of the MEDI4736 vial to start of administration should not exceed 4 hours at room temperature, or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion, the total allowed infusion time should not exceed 8 hours. In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials.

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

6.3.5 Monitoring of MEDI4736 Dose Administration

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

Vital Signs Assessment on study drug administration days	Pre dose	During Infusion	End of Infusion (± 5 minutes)	Post infusion + 30 (± 5) minutes	Post Infusion + 60 (± 5) minutes)
MEDI4736 Vital Signs	X	every 15 (± 5) minutes	X	X	x

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)	Pre dose	During Infusion	End of Infusion (± 5 minutes)	Post infusion + 15 (± 5) minutes
MEDI4736 Vital Signs	X	every 30 (± 5) minutes	X	X

6.4 Estimated Study Drug Requirements for Motolimod and MEDI4736

Drug	***Calculation***	***Required Quantity***
Motolimod	53 subjects X 12 cycles 53 subjects Cycles 1 - 3: 3 vials per cycle = 477 vials 6 subjects (Dose Level 0a): 2 vials per Cycles 4-12: 108 vials 47 subjects (all others): 1 vial per Cycles 4-12: 423 vials Total = 1,008 vials Total + 20% overage: 1,210 vials **PER Amendment 2, motolimod dosing will be discontinued for all subjects.**	1,210 Vials
MEDI4736	53 subjects X 12 cycles: 6 subjects (Dose Level 0a): 4 vials per cycle: 288 vials 6 subjects (Dose Level -1): 1 vial per cycle: 72 vials 41 subjects (all others): 3 vials per cycle: 1476 vials Total = 1836 vials Total + 20% overage: 2,203	2,203 Vials
MEDI4736	Additional MEDI4736 for optional study treatment extension per Section 3.1.12 Assumptions: 15% of subjects will continue for 12 cycles beyond Core Study	343 vials

6.5 Drug Overdose Management

Any overdose with PLD should be managed according to the package insert/ prescribing information.

Any overdoses with motolimod and MEDI4736 should be managed symptomatically. There are no known antidotes available for these drugs. An overdose is defined as a subject receiving any dose in excess of that specified in this protocol by >10%. All such overdoses must be reported, with or without associated AEs/SAEs, according to Section 7.1.2.2.

7 Administrative, Legal & Ethical Requirements

7.1 Documentation and Reporting of Adverse Events

7.1.1 General AE/SAE Definitions per ICH Guidelines

An **Adverse Event (AE)** is any untoward medical occurrence in a subject 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 subject is on study, i.e., during the actual treatment period, as well as during drug-free, pre- and post-treatment periods.

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

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

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

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

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

7.1.2 Additional Expedited Reporting Requirements for this Study

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

1. Pregnancy
2. Overdose (as defined in Section 6.5)
3. Hepatic function abnormality (as defined in Section 7.1.8).

7.1.2.1 Pregnancy

7.1.2.1.1 Maternal Exposure

Female subjects should avoid becoming pregnant and breastfeeding during the study and for 90 days after the last dose of study drug (see Section 5.2, #17).

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

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

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

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

The same timelines apply when outcome information is available.

7.1.2.2 Overdose

Any overdose (as defined in Section 6.5) of a study subject, with or without associated AEs/SAEs, is required to be reported **within 24 hours of knowledge of the event** to the Sponsor (see Section 7.1.6 for Sponsor contact information). If the overdose results in an AE, the AE must also be recorded as an AE according to Section 7.1.5. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE according to Section 7.1.6. There is currently no specific treatment in the event of an overdose of MEDI4736 or motolimod. The Investigator will use clinical judgment to treat any overdose. See Section 6.5 for additional details.

7.1.2.3 Hepatic Function Abnormality

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

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

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

7.1.3 Severity of an Adverse Event

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

7.1.4 Relationship of Adverse Events to Study Drug

The relationship of all serious and non-serious 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 Section 1 of this protocol may support these evaluations.

7.1.5 General Reporting Requirements

All serious and non-serious adverse events must be documented in the source records and on the respective section of the CRF, regardless of severity or the assumption of a causal relationship. The documentation includes: dates of onset and resolution, severity, seriousness, study drug intervention, treatment and outcome, as well as the causal relationship between the event and

the study drug in accordance with Section 7.1.4. This documentation is required for all AEs that occur:

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

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

7.1.6 Expedited Serious Adverse Event (SAE) Reporting Requirements

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

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

If the "Initial Serious Adverse Event Report Form" is being used, the expedited reports should be directed by fax or e-mail to the Drug Safety Contact (primarily) or, alternatively, the Primary Sponsor Contact. Studies utilizing Medidata RAVE (and the "Safety Gateway"), built into the eCRF, and respective SAE reporting procedures, do not require reporting by fax or email. Questions related to Medidata RAVE and "Safety Gateway" procedures should be directed to the Drug Safety Contact or Primary Sponsor Contact (see table below for contact information).

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

Drug Safety Contact:	*Primary Sponsor Contact:*
[redacted] Senior Manager, Drug Safety Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave, 28th Floor New York, New York 10017 [redacted]	[redacted] Director, Clinical Project Management Clinical Trials Management Ludwig Institute for Cancer Research 666 3rd Ave, 28th Floor New York, New York 10017 [redacted]

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(s) 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 or, if Medidata RAVE data capture is utilized, using the respective Adverse Event and Safety Case Summary eCRFs.

7.1.8 Adverse Events of Special Interest (AESIs)

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

AESIs for MEDI4736 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 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 version of the MEDI4736 Investigator Brochure. Guidelines for the management of subjects experiencing toxicities for MEDI4736 can be found in Section 8.4 and in the following Medimmune guideline: ***"Medimmune's Dosing Modification and Toxicity Management Guidelines for Immune- mediated, Infusion Related, and Non Immune-mediated Reactions (MEDI4736 (durvalumab) Monotherapy or Combination therapy with Tremelimumab or Tremelimumab monotherapy)."***

- **Colitis/Gastrointestinal Disorders**
  Diarrhea and colitis are the most commonly observed treatment-emergent AEs following dosing with MEDI4736. In rare cases colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome, if not properly managed.

- **Pneumonitis/Interstitial lung disease (ILD)**
  Pneumonitis has been reported with use of anti-PD-1 mAbs.(51) Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Typically, pulmonary consultation is highly recommended.

- **Hepatic Function Abnormality (Hepatotoxicty, Hepatitis)**
  Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies.(52) Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin. Hepatic function abnormality is defined as any increase in ALT or AST to > 3 × ULN and concurrent increase in total bilirubin to > 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a concurrent or pre-existing disease (e.g., 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.

- **Neurotoxicity (Neuropathy/Neuromuscular toxicity)**
  Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)

- **Endocrine Disorders**
  Immune-mediated endocrinopathies include hypophysitis/hypopituitarism, adrenal insufficiency, and hyper- and hypothyroidism, diabetes insipidus, and Type 1 diabetes mellitus.
  Type 1 diabetes mellitus: For subjects with suspected diabetes mellitus, Investigators should obtain an endocrinology consult and institute appropriate management which may include the administration of insulin.

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

- **Nephritis and increases in serum creatinine**
  Consult with Nephrologist should be done as well as monitoring for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc.). Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, etc.). Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event.

- **Pancreatic Disorders**
  Immune-mediated pancreatitis includes autoimmune pancreatitis (or labs suggestive of pancreatitis: increased serum lipase, increased serum amylase)

- **Hypersensitivity and Infusion Reactions**
  Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy.(52) As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of monoclonal antibodies (MAbs) can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

- **Other inflammatory responses** that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis.

7.1.8.1 Additional AESIs for this Study

Guidelines for the management of subjects experiencing toxicities for PLD and motolimod can be found in Sections 8.2 and 8.3, respectively.

PER Amendment 2, motolimod dosing will be discontinued for all subjects.

7.1.8.1.1 Cytokine Release Syndrome (CRS) ≥Grade 3

CRS is a symptom complex and is characterized by systemic symptoms which may include fever, nausea, chills, tachycardia, hypotension, dyspnea, asthenia, headache, and rash. Motolimod directly targets TLR8, which is expressed on immune cells. CRS may result from the release of cytokines from the activated immune cells, or from 'downstream' events that can be associated with cytokine production. Symptoms of CRS may be acute or delayed by several hours after dosing with motolimod.

7.1.8.1.2 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. In addition, preclinical toxicology studies of motolimod, but not clinical studies, identified inflammatory uveitis as a drug-related toxicity; however, these observations occurred at dose levels higher than those currently administered in any clinical trial of motolimod and no specific requirement for ophthalmologic surveillance is required in this study. Physicians should initiate ophthalmologic evaluation should symptoms develop.

7.2 Administrative Sponsor Requirements

7.2.1 Study Master Files

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

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

7.2.2 Case Report Form Data Collection

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

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

The Investigators electronic signature indicates a thorough inspection of the data in the CRF and will certify its content.

7.2.3 Language

The protocol is written in English. All correspondence between the study site and the Sponsor should be maintained in English. Case Report Forms must be completed in English. All written

material to be used by subjects and para-clinical staff must use vocabulary that is clearly understood, and be in the language appropriate for the trial site.

7.2.4 Monitoring

The Sponsor will oversee the conduct of the study and perform clinical monitoring visits for site 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, regulatory inspection and sponsor 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 subject charts, laboratory reports and other subject records needed to verify the entries on the case report forms ("source data verification").

7.2.5 Protocol Amendments

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

7.2.6 Premature Subject Withdrawal

A subject may withdraw 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 the study. Specific subject withdrawal reasons 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, and an attempt should be made to perform a follow-up evaluation.

7.2.7 Early Trial Termination

"End of study" is defined as the last visit of the last subject. 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.

7.2.8 Study Drug Shipments & 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 the accounting of all used and unused trial supplies. 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 & 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-specific 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 subject letter code, date of birth and subject number on the case report forms or other documents submitted to the Sponsor. The subject letter code does not necessarily have to correlate to the subject's name.

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.

8 Appendices

8.1 Protocol Version History

Version 000 (Original Issue)
Issue Date: 30-MAR-2015
Summary of Changes: n/a

Amendment 001
Issue Date: 09-DEC-2015
Summary of Changes:

1. Administrative changes:
   - Updated footer and synopsis page with new protocol format and logo. Formatted headings to be aligned with current protocol templates
   - Changed "patient" to "subject" where appropriate
   - Changed format of Section 8.1 to allow for more space to record protocol changes
   - General spelling, capitalization, and formatting changes, as needed.
   - US Study Chair, Bradley J. Monk MD, was added
2. Synopsis and Section 3.1.7:
   - The starting dose level cohort was renamed as dose level 0a, and dose level 0b was added to Phase 1 (dosing is detailed in the table below). Depending on the timing of Amendment 1, dose level 0b cohort could be running concurrently with the cohort at dose level 0a, -1, or +1. The dosing for the cohort in dose level 0a will continue per the protocol prior to Amendment 1 (i.e., MEDI4736 at 3 mg/kg Q2W); however, escalation or de-escalation dosing will be conducted according to Amendment 1.
   - A fixed dosing schedule for MEDI4736 was added for all subjects except those in the cohort that had already been started prior to Amendment 1 (i.e., dose level 0a). See table below for details.
   - Treatment schedule for cohort at dose level 0a will continue as it was prior to Amendment 1
   - Treatment schedule for all subjects except those at dose level 0a will be as follows:

Day	Cycles 1 – 3	Cycles 4 – 12
1	PLD (IV)	PLD (IV)
3	MEDI4736 (IV) + Motolimod (SC)	MEDI4736 (IV) + Motolimod (SC)
10	Motolimod (SC)	n/a
17	Motolimod (SC)	n/a

     - table was updated to indicate MEDI4736 will be administered only on Day 3 of each cycle (Q4W instead of Q2W)
     - for Cycles 4-12, motolimod will be administered on Day 3 only instead of Days 3 and 17

- Dose level table was updated as follows:

Dose Level	PLD [mg/m² IV]	MEDI4736 [IV]	Motolimod [mg/m² SC]
-1	40	450 mg Q4W	2.0
0a (Starting Level)	***40***	***3 mg/kg Q2W (equivalent to 450 mg Q4W)***	***2.5***
0b	40	1500 mg **Q4W**	2.0
+1	40	1500 mg Q4W	2.5
Q2W = every 2 weeks; Q4W = every 4 weeks			

  - Dose level -2 was deleted
  - Dose level -1 and +1 were changed to fixed dosing for MEDI4736 Q4W
  - Dose level 0b was added

3. Sections 1.3 and 1.4.1 were updated with current information.
4. Section 2.1: Rationale for implementing the changes in Synopsis and Section 3.1.7 was provided.
5. Section 3.1.2:
   - The first sentence in paragraph 2 was modified (changes in bold): "For each cohort in Phase 1, the start of the **Cycle 1 Day 3** study drug administration **(MEDI4736 + motolimod)…**."
   - The following paragraph was added: "Per Amendment 1, the cohort at dose level 0b will be added to Phase 1. Depending on the timing of Amendment 1, dose level 0b cohort could be running concurrently with the cohort at dose level 0a, -1, or +1. Thus, subject enrollment will occur as follows:
     a) when only 1 cohort is open: sequential enrollment;
     b) when 2 parallel cohorts are open: preferential sequential enrollment into the cohort with the higher motolimod dose level or into the cohort with the higher MEDI4736 dose level if both cohorts have the same motolimod dose level.

     Subject enrollment will be centrally administered."
6. Section 3.1.9:
   - DLT Observation period was changed from 2 cycles to one cycle, i.e., "DLTs will be observed over a period of the first cycle including the pre-dose assessment for Cycle 2, defined as the DLT Evaluation Period."
   - Neurological event and uveitis were added to #1, #2, and bullet for #2
   - For #3, bullet 3: "Grade 3 asymptomatic endocrinopathy" was changed to "Grade 3 endocrinopathy that becomes asymptomatic …"
7. Section 3.1.10:
   - Section was clarified to indicate reasons for withdrawal from treatment vs. withdrawal from study. Additional detail was added to conform to current standard protocol language.
8. Section 3.1.15: duration of Post Study Follow-up was added.
9. Section 3.1.16:
   - Clarification was provided for On Study Follow-up versus Post Study Follow-up.
   - Clarification was provided to indicate that If the determination is made to remove a subject from treatment at a visit that coincides with the first visit of the On Study Follow-up Period (which is 14 days after the last dose of study treatment), any assessments required in the 14 day 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 14 day post-last treatment visit should not be repeated.
- Post Study Follow-up was clarified to indicate that frequency will be "Every 3 months for 3 years from initiation of treatment." This was also clarified in Section 3.1.7.

10. Section 3.2, Study Flowchart:
    - Changed Day 0 to Day -1 to agree with standard conventions and eCRF
    - Moved visit windows from "Cumulative Visit Day" line to "Visit Day per Cycle." "Cumulative Visit Day" to remain, but without windows. This will allow for better data management control if cycles are delayed to manage toxicity.
    - Cycle 2 cumulative visit days were corrected; there was computation error in the original issue.
    - On Study Follow-up: Last Study Drug Administration +12, +45, and +90 days was changed to +14, +42, and +91 days, respectively, to be consistent with standard protocol format.
    - Free T3, Free T4, and TSH were separated from the rest of the chemistry panel, and assessment on Day 3 of each cycle was removed. Due to multiple visits during Week 1 of each cycle, assessment on Day 1 was considered to be sufficient.
    - Footnote was added regarding the monitoring of vital signs during MEDI4736 administration.
    - Serum collection was removed from PBMC sampling; plasma will be collected.
    - Footnote was added to indicate that "Screening/Baseline specimens for correlative assessments may be collected up to Cycle 1/Day1 prior to the PLD dose."
    - "US sites only" was removed from Serametrix in the analysis of MDSC
    - For MEDI4736 PK, Cycle 1 Day 1 and Cycle 7 Day 1 post-infusion sample collection was added to Cycle 1 Day 3 and Cycle 7 Day 3 respectively in order to align with end of MEDI4736 IV dosing. Cycle 1 Day 1 and Cycle 7 Day 1 remained for the collection of pre-dose samples. Footnote for post-infusion sample was updated
    - For tumor biopsy, ImmunoSeq was changed to TCR Sequencing.
    - The following note was added to the footnote for tumor biopsy: "Archival tissue will be requested for all subjects, preferably from primary tumor site prior to cancer treatment; however, archival tissue is not a requirement for study entry."
    - Footnote was added to indicate that pregnancy tests are not required for subjects who are not of child-bearing potential as defined in Section 5.2, # 17.
    - Footnote regarding cumulative dose >550 mg / m^2 – increasing Echo / MUGA frequency was removed because the maximum PLD exposure is 480 mg / m^2 per protocol.
    - Clarification was provided to indicate that the second list of specimens in the flowchart are those for "Correlative Assessments."
    - Footnote regarding pre-dose collections was clarified and/or added where applicable
    - Post Study Follow-up was clarified to indicate that frequency will be "Every 3 months for 3 years from initiation of treatment."
    - Blood volume requirements were removed from the flowchart. These are included in the Informed Consent Form.
    - Administrative changes were made as needed for uniformity of layout and appearance
    - Two separate flowcharts were created to align with dosing schedule changes for all subjects except those in dose level 0a. The 2 flowcharts are labeled as follows:

1. Flowchart for subjects in dose level 0a cohort only – dosing schedule remained the same as prior to Amendment 1.
2. Flowchart for all subjects except dose level 0a cohort:
    - Deleted Day 17 dose of MEDI4736 for each cycle; dosing was changed from Q2W to Q4W
    - Deleted Day 17 dose of motolimod from Cycles 4-12
    - Deleted Day 17 study visit from Cycles 4-12
    - Moved echocardiogram or MUGA assessment from Day 157 to 143; Day 241 to 227; and Day 325 to 311. This was done to align with new dosing and visit schedules.

11. Section 5.1:
    - #1, bullet 2: The following sentence was modified (changes in bold): "biologic therapy (e.g., bevacizumab) as part of their primary treatment regimen or **as part of their treatment** for management of recurrent or persistent disease."
    - #4: The following note was added: Archival tissue will be requested for all subjects, preferably from primary tumor site prior to cancer treatment; however, archival tissue is not a requirement for study entry.
    - #6: inclusion criteria for AST/ALT was changed from ≤ 3.0 x ULN to ≤ 2.5 x ULN
12. Section 5.2:
    - #5: Changed "Uncontrolled Hypertension, defined as systolic >150 mm Hg or diastolic >90 mm Hg" to "Resistant hypertension." This was based on input from Investigators.
    - #7: deleted irritable bowel syndrome, as this is not an autoimmune disease.
    - #7: added "active" to Hashimoto's thyroiditis.
    - #13: Changed "Participation" to "Prior treatment" in any other interventional clinical trial within 4 weeks prior to Day 1 of the study."
    - #16: Note was added to indicate that Pregnancy tests are not required for subjects who are not of child-bearing potential as defined in Section 5.2, # 17
    - #17: Language for highly effective methods of contraception was updated based on current standards from MedImmune/AstraZeneca. Definition of post-menopausal was updated.
13. Section 5.3.1:
    - #2: added "or 5 half-lives (whichever is shorter)" to the wash-out period of 4 weeks.
    - Added #3, Live attenuated vaccines 1 month prior to Day 1 and for at least 6 months after the last dose of treatment. This statement was omitted in the original issue.
14. Section 6.1: The following note was added: "NOTE: The maximum body surface area and recalculations are recommendations; standard procedures for maximum body surface and recalculations at each site may be used. Rationale: Sites have their own PLD dosing procedures, which would be difficult to modify for study purposes.
15. Section 6.3.3:
    - Section 6.3.3.1 was identified as MEDI4736 dose preparation for dose level 0a.
    - Section 6.3.3.2 was added for MEDI4736 fixed dose preparation.
16. Section 6.3.4:
    - Reference to Section 6.3.5 was added for monitoring MEDI4736 administration
    - Timing for the IV infusion was changed from 60 (± 10) to 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**. (additions in bold; based on recommendations from MedImmune/AstraZeneca)

17. Section 6.3.5: Monitoring of MEDI4736 Dose Administration was added to align vital sign safety measurements with other protocols using MEDI4736.
18. Section 6.4: study drug requirements were updated based on study changes.
19. Section 7.1.2: was updated according to current recommendations from MedImmune/AstraZeneca:
    - Defined additional expedited reporting requirements for study, specifically pregnancy, overdose, and hepatic function abnormality
20. Section 7.1.5: Clarification was provided for recording of AEs during the On Study Follow-up based on clarifications provided in Sections 3.1.10 and 3.1.16.
21. Section 7.1.6:
    - Additional detail and clarification were added regarding reporting of SAEs to the Sponsor within 24 hours**.**
    - Sponsor Contact information for reporting SAEs was added.
22. 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.
    - Updated language in the entire section according to current recommendations from MedImmune/AstraZeneca.
23. Section 7.3.4: The Subject's "initials" was changed to "subject letter code." The following was added: "The subject letter code does not necessarily have to correlate to the subject's name." This change was required because a subject's initials and date of birth are not allowed to appear together per Swiss Ethics Committee.
24. Section 8.2.4: For PLD dose modifications for subjects with impaired hepatic function, the phrase "give 25% normal dose." Was replaced with "give 25% normal dose, or proceed according to institutional standards."
25. Section 8.4.2: MEDI4736 Dose Modifications due to toxicity were updated according to current recommendations from MedImmune/AstraZeneca (Dated 02-OCT-2015).
26. Section 8.4.3: MEDI4736 Dose Modifications not due to toxicities were added.
27. Section 8.6.4: Two occurrences of irRC were corrected to irRECIST.
28. Section 8.7.1: In the sentence: "T cell subsets will be assessed for activation/exhaustion by expression of PD-1…," the first occurrence of PD-1 was changed to PD-L1.
29. Section 8.7.6: Specific references to ImmunoSeq and Adaptive Biotechnologies were removed.
30. Section 8.7.7: The following paragraph was removed: "Additionally, select pre- and post-treatment plasma samples of interest will also be tested by a seromics approach for the autoantibodies directed against a panel of >9000 purified human proteins coated onto microarray slides (Invitrogen ProtoArrays)." Assay is no longer planned.
31. Section 8.7.14 (mRNA and miRNA profiling) was added to coincide with the PaxRNA testing in the flowchart.
32. Section 8.8 "ECOG PS Criteria" table was added.
33. Section 8.9 "Abbreviations" table was added.

Amendment 2
Issue Date: 05-OCT-2016
Summary of Changes:

1. All sections, as appropriate (i.e., Synopsis, Sections 1.3, 2.1, 3.1.2, 3.1.6, 3.1.7, 3.1.8, 3.1.9, 3.1.14, 4.1.2, 4.2.2, 4.3.1, 5.2, 5.3.2, 6.2, 6.4, 7.1.8.1, and 8.3): Notations or changes were made to indicate that motolimod dosing was discontinued PER Amendment 2.
2. Section 2.1: the following paragraph was added to rationale for fixed dosing of MEDI4736: "This dosing of MEDI4736 is recommended only for subjects with > 30 kg body weight due to endotoxin exposure. Subjects with a body weight ≤ 30 kg are not eligible for enrollment in the current study. If a subject's body weight drops to ≤ 30 kg while on the study, the subject will be dosed at 600 mg Q4W as long as the body weight remains ≤ 30 kg." The Note was also added to Sections 3.1.7 and 6.3.3.2).
3. Synopsis and Section 3.1.7: PLD was changed to pegylated liposomal doxorubicin. This was based on request from DFCI to ensure clarity.
4. Synopsis page: Added signature line for Local sponsor in Switzerland
5. Section 3.1.8: the following statement was added: "If a toxicity occurs that requires toxicity management in accordance with the toxicity management guidelines referenced above, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed." The statement was also added to Sections 8.2, 8.3, and 8.4.
6. Section 3.1.10: for the list of reasons for a subject to be **withdrawn from the study,** reason #2 was changed as follows (changes in bold): "Initiation of alternative anti-cancer therapy including **marketed or** another investigational agent."
7. Added Section 3.1.0.1: Treatment beyond Progression
8. Section 3.1.11: The following was changed **FROM**: "**Phase 1:** Subjects are fully evaluable for DLT if 1) they experienced a DLT as per Section 3.1.9, or 2) in the absence of a DLT, they fulfill the criteria for the Per-Protocol Population as per Section 4.2.2." **TO: "Phase 1:** Subjects are fully evaluable for DLT if they fulfill the criteria for the Per-Protocol Population for DLT Assessment as defined in Section 4.2.2."
9. Section 3.1.13: Changed **FROM**: "No formal interim analyses will be performed, except for the cohort safety assessments for DLTs in Phase 1 (see Section 3.1.7)" **TO:** "Interim safety reviews will be performed to assess DLTs in Phase 1 (see Section 3.1.7). Interim analyses may be performed to analyze the endpoints of progression free survival at 6 and 12 months and/or as specified in the statistical analysis plan.
10. Section 3.1.15: Duration of On Study Follow-up was added.
11. Section 3.1.16:
    - Paragraph 3 was changed **FROM: "**If the determination is made to remove a subject from treatment at a visit that coincides with the first visit of the On Study Follow-up Period (which is 14 days after the last dose of study treatment), any assessments required in the 14 day 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 14 day post-last treatment visit should not be repeated." **TO:** "If the determination is made to remove a subject from treatment at a visit that coincides with

the first visit of the On Study Follow-up Period, any assessments required in the first On Study Follow-up 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 last on-treatment visit and the first On Study Follow-up visit should not be repeated."

- The following statement 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 3.1.16.1, End of Study Visit, was added.

12. Section 3.2, Flowchart:
    - Motolimod dosing was removed
    - Study visits that were specific only to motolimod were removed: (1) for Cohort 0a, Day 10 for Cycles 1 to 3 were deleted; (2) for all other cohorts, Days 10 and 17 for Cycles 1 to 3 were deleted. PBMC collection on Cycle 1/Day 10 was also deleted.
    - HumanMAP® and TruCulture™ specimen collections were deleted, as these were specific for motolimod.
    - ECOG Perf Status was deleted as a single assessment at baseline and added to Physical Exam assessments
    - Deleted "and Pre-existing symptoms" from the Medical history line.
    - Added amylase and lipase assessments, as these are required for monitoring pancreatitis.
    - Deleted the following assessments: MEDI4736 PK, MEDI4736 ADA, sPD-L1, circulating soluble factors. Medimmune has determined that they have adequate data and samples are no longer needed.
    - Footnote a: added "Note: It is strongly recommended that hematology, chemistry and pregnancy test (when applicable) results are reviewed before dosing."
    - Footnote b: added "before" to assessment of vital signs
    - Added Footnote h: "See Section 3.1.16 regarding assessments scheduled for both the last on treatment visit and the first post-last treatment visit."
    - Echo/MUGA assessment: deleted assessment at Cycle 12/Day17 for Cohort 0A and Cycle 12/Day3 for all other subjects. Rationale: Only one echo/MUGA is needed after the last dose of PLD at cycle 12. This will be covered at the on study follow-up visit.
    - Moved echo/MUGA assessment from Day 73 to Day 87 for all subjects except those in Cohort 0a. This was done to align with visit schedule after removal of motolimod.
    - Added Footnote i: "Standard of Care procedures may be used for eligibility assessments provided they meet the criteria specified in either the inclusion criteria or flowchart."
    - Added Footnote J: "See section 7.1.5 for details regarding collection of AEs for 90 days after last study drug administration."
    - Footnote c was added to Pharmacogenomics and changed to: "An aliquot of the PBMC and or Tumor Biopsy/Archival Tissue will be used for pharmacogenomics – a separate sampling is not needed."
    - Footnote d (which was related to motolimod) was deleted and Footnote J was re-numbered as Footnote d
    - Changed Post Study Follow-up **FROM**: "Every 3 months for 3 years from initiation of treatment. Telephone contact or medical record review: Vital status, tumor status;

directed AE assessment for new onset or worsening of pre-existing autoimmune disease." **TO:** "Every 3 months for 3 years from initiation of treatment. Clinical outcomes data (dates of progression/relapse and survival) will be recorded (See Section 3.1.16). The new language is in agreement with Section 3.1.16 and other ongoing studies.

- In the Study Flowchart for non-Cohort 0a Subjects, On Study Follow-up Intervals were changed from +14 to +28 days and from +42 to +56 days to align with the Q4W dosing intervals of the study.
- MDSC: it was clarified that MDSC will be collected at US sites only (logistical reasons).
- Disease assessment during On Study Follow-up was changed from a specific study visit to "'+84 ± 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.

13. Section 4.1.1.1: the following sentence was added: "PFS rate at 6 months will be based on disease assessments at the scheduled visit at the start of Cycle 7."
14. Section 4.2.2: The following was changed **FROM**: "The *Per-Protocol (PP) Population* for safety and tolerability is defined as all subjects who received at least 75% of the scheduled doses of MEDI4736, motolimod, and PLD over the first **2 cycles**, as well as respective safety assessments, without major protocol violations over the entire DLT Evaluation Period (as defined in Section 3.1.9). The *Intent-To-Treat (ITT) Population* for safety and tolerability is defined as all subjects who receive at least one dose of PLD, motolimod or MEDI4736. In *Phase 1*, for the primary endpoint of determining DLTs and the MTD, the analysis of safety and tolerability will be based on the PP Population. In both *Phases 1 and 2*, the overall analysis of safety and tolerability will be based on the ITT Population." **TO**: "The *Per-Protocol (PP) Population for DLT Assessment* includes:
    - All subjects who experience a DLT at any time during the DLT Evaluation Period (as defined in Section 3.1.9)
    - All subjects with no DLT who receive at least 75% of the scheduled doses of MEDI4736, motolimod, and PLD as well as respective safety assessments, without major protocol violations, over the entire DLT Evaluation Period (as defined in Section 3.1.9).

    Refer to Section 3.1.11 for subject replacements. The *Intent-To-Treat (ITT) Population for safety and tolerability* is defined as all subjects who receive at least one dose of PLD, motolimod or MEDI4736. In *Phase 1*, for the primary endpoint of determining DLTs and the MTD, the analysis of safety and tolerability will be based on the PP Population for DLT Assessment. In both *Phases 1 and 2*, the overall analysis of safety and tolerability will be based on the ITT Population for safety and tolerability.
15. Section 4.3: "Baseline Immune Responsiveness to TLR8 activation" was removed from the list of analyses.
16. Section 5: the following statement 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."
17. Section 5.1:
    - Inclusion criterion 1, bullet 1 was changed as follows (changes in bold): "one additional cytotoxic regimen **and/**or PARP inhibitor for management of recurrent or persistent disease.
    - Inclusion criterion #4: added "see Section 3.2 for biopsy time points"

- Added “Body weight > 30 kg”

18. Section 5.2:
    - #17: the definition of post-menopausal was expanded; updated language for highly effective methods of contraception
    - Added “History of allogenic organ transplant”
    - Added blood donor restriction
19. Section 5.3.2: For the last sentence, the following change was made (change in bold): All non-drug therapies must be recorded in the respective sections of the case report form ~~**or as Adverse Events**~~.
20. Section 6.2.2: Added stability for motolimod (changes in bold): “Prior to administration, motolimod must be reconstituted using sterile water for injection, **USP. Reconstituted stock solutions are stable for 8 hours at room temperature and for 24 hours when refrigerated at 2–8°C.”**
21. Section 6.3: the option of using dextrose instead of saline as diluent for MEDI4736 was added.
22. Section 6.3.3.2: for fixed dose of MEDI4736, the following statement replaced “regardless of weight”: “Subjects will receive a fixed dose of MEDI4736: 1500 mg Q4W 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.”
23. Section 7.1.2: Paragraph 1 was changed **FROM**: “For the purpose of this study, the following events are considered medically important conditions and must be reported in an expedited manner (See Section 7.1.6 for Sponsor contact information):” **TO**: “For the purpose of this study, the following events must be reported by phone or email to the Sponsor within 24 hours of knowledge of the event (See Section 7.1.6 for Sponsor contact information) and may result in submission of an SAE based on certain criteria outlined below:”
24. Section 7.1.2.1.1: the following statement was added: “Female subjects should avoid becoming pregnant and breastfeeding during the study and for 90 days after the last dose of study drug (see Section 5.2, #17).”
25. Section 7.1.5: Text 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 <u>between the date of signing the informed consent and the off-study date (see Section 3.1.16 for definition of On Study Follow-up)</u> 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. During the On Study Follow-up period, all AEs must be documented for 90 days after the last dose of study drug for subjects who complete the study as well as those subjects who discontinue study treatment prematurely (see Section 3.1.10 for subjects who begin other anti-cancer treatment).” **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)."

26. Section 7.1.6: added the following statement: "Serious adverse event reporting to AstraZeneca/Medimmune is described in separate agreement."
27. Section 7.2.2: The following statement was added: "All subjects who sign an informed consent form, regardless of study procedures performed, will be assigned a screening number and have their data entered into the eCRF."
28. Section 8.4.1:
    - The statement, which referenced guidelines for ipilimumab, nivolumab, and pembrolizumab was deleted.
    - The title of the Medimmune Guideline for Toxicity Management for MEDI4736 was inserted.
29. Section 8.4.2: MEDI4736 dose modifications were updated according to the 19Aug2016 version of the AZ/Medimmune guidelines. Section 8.4.2.3 was changed as follows:
    - Grade 3 was separated from Grade 2 modifications
    - Grade 3 modifications were added: "Hold MEDI4736. If AEs downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume MEDI4736 administration at next scheduled dose. Otherwise, discontinue MEDI4736 permanently."
30. Section 8.4.3:
    - 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."
31. Section 8.7: the following Note was added to the following assessments:
    - Section 8.7.4: "NOTE: PER Amendment 2, samples will no longer be collected for analysis of TruCulture™, as the analyses were related to motolimod dosing. The collection time points for these assays have been removed from the flowchart in Section 3.2."
    - Section 8.7.7: "NOTE: PER Amendment 2, samples will no longer be collected for analysis of HumanMap®. The collection time points for these assays have been removed from the flowchart in Section 3.2."
    - Section 8.7.10: "NOTE: PER Amendment 2, samples will no longer be collected for analysis of MEDI4736 PK and immunogenicity for 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 8.7.11: "NOTE: PER Amendment 2, 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 8.7.12: "NOTE: PER Amendment 2, 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."
32. Sections 8.7.1, 8.7.3, 8.7.4, and 8.7.7: clarification was provided to indicate that collection of samples will be done according to the flowchart in Section 3.2.

33. Section 8.7.6: the following clarification was added: "PBMCs will be assayed from 3 time points, which will be matched as closely as possible to the tumor biopsies (baseline, Cycle 2 Day 1 and the PBMC collection closest to disease progression)."
34. Section 8.7.8: The following statement was added: "An aliquot of the PBMC collection and/or tumor biopsy/archival tissue will be used for pharmacogenomics." The sentence "DNA will be isolated from whole blood" was deleted.
35. Sections 8.7.4, 8.7.5, 8.7.7, and 8.7.8: "shipped to" was changed to "analyzed by"
36. Administrative:
    - Spelling, grammar and typographical errors were corrected.
    - Formatting/administrative changes were implemented, as applicable.
    - Monitor and Study Monitor were standardized as "Clinical Monitor"
    - Study Physician was changed to Medical Monitor in Section 7.1.8

Amendment 3
Issue Date: 05-DEC -2016
Summary of Changes:

1. Synopsis**:** The following statement was added: "**Per Amendment 3**, optional MEDI4736 treatment extension beyond the initial 12-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 for up to 12 additional cycles upon agreement with subject, Sponsor and Investigator. See Section 8.9 for details."
2. Section 3.1.12, Optional Study Treatment Extension: This section was changed **FROM:** "Treatment extension beyond 12 cycles is not planned" **TO**: "Optional MEDI4736 treatment extension beyond the initial 12-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 for up to 12 additional cycles upon agreement with subject, Sponsor and Investigator. See Section 8.9 for details."
3. Section 3.1.15, Duration of Study: For Duration of Treatment, the following statement was added: "See Section 3.1.12 for optional treatment extension."
4. Section 3.1.16, On Study and Post Study Follow-up: The following statement was added: "See Section 3.1.12 for optional study treatment extension."
5. Section 3.1.16.1, End of Study Visit: The last sentence of paragraph 1 was clarified (changes in bold): "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**."
6. Section 3.2, Flowchart:
    a. For last On Study Follow-up visit, changed from 91 to 90 days to allow consistency with protocol text.
    b. Added Physical exam to On Study Follow-up visits
    c. Added Concomitant meds collection to On Study Follow-up visits 2 and 3.
    d. Added pregnancy test to last On Study Follow-up visit
7. Section 6.3.3, MEDI4736 Prep: The following sentence was updated based on feedback from Medimmune (changes in bold): "No incompatibilities between MEDI4736 and ~~**polyethylene, polypropylen**~~e, polyvinylchloride, or polyolefin copolymers have been observed.

8. Section 6.3.3.1, MEDI4736 Prep for Cohort 0a: the following statement was added: "**Per Amendment 3, fixed dosing will be used for the optional study treatment extension as described in Section 3.1.12 and Section 8.9. See Section 6.3.3.2."**
9. Section 6.3.3.2**,** MEDI4736 Prep for all other cohorts: The following statement was added: "**Per Amendment 3, fixed dosing will be used for all subjects who proceed with the optional study treatment extension as described in Section 3.1.12 and Section 8.9.**
10. Section 6.3.4, MEDI4736 administration: The following changes were made based on feedback from Medimmune (changes in bold):
    a. "Investigational product(s) must be administered at room temperature by controlled infusion ~~**via an infusion pump**~~ into a peripheral vein or central line."
    b. "~~**Since the compatibility of MEDI4736 with other IV medications and solutions, other than normal saline (0.9% [w/v] Sodium Chloride for Injection) or dextrose, is not known, the**~~ MEDI4736 solution should not be infused **with** ~~**through an IV line in which**~~ other solutions or medications. ~~**are being administered.**~~"
    c. "The total time between needle puncture of the MEDI4736 vial to start of administration should not exceed 4 hours at room temperature, or 24 hours at 2°C to 8°C (36°F to 46°F). **Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion (total infusion time not to exceed 4 hours), the total allowed time 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.** ~~**If MEDI4736 administration has to be delayed, temporally interrupted or the infusion rate decreased, or if administration time exceeds these limits, a new dose must be prepared from new vials.**~~"
    d. Added "See Section 8.4.2.2 for management guidelines for infusion-related reactions."
11. Section 6.4, Drug Requirements: Additional MEDI4736 requirements for optional study treatment extension were added.
12. Section 7.1.8, AESIs: additional details were added for AESIs to correspond with current Medimmune/AZ guidelines.
13. Section 8.4.2.2, Infusion-related reactions: The following clarification was added to Grades 1 and 2: "total infusion time not to exceed 4 hours"
14. Section 8.4.3, MEDI4736 Dose Modifications not due to Toxicities: The rules were clarified by changing **FROM**: 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**:
    1. The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two doses shall be no less than 21 days (for subjects on Q2W dosing, the interval shall be no less than 10 days). All resulting protocol deviations should be documented.

2. If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued.
3. If the dosing interruption is ≤ 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.

15. Section 8.9 was added to provide additional details and flowchart for subjects who receive optional MEDI4736 treatment extension according to Section 3.1.12.
16. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.

Amendment 4
Issue Date: 08-SEP-2017
Summary of Changes:

1. The duration of the treatment extension beyond the Core Study for MEDI4736 was changed from 12 cycles to "until confirmed disease progression."
   a. This change was implemented in the Synopsis and in Sections 3.1.12 and 8.9. Language was changed as follows (changes in bold): "Optional MEDI4736 treatment extension beyond the initial 12-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 ~~**for up to 12 additional cycles**~~ upon agreement with subject, Sponsor and Investigator, **and it may continue until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met**. See Section 8.9 for details **regarding treatment extension and collection/reporting of adverse events during this period**"
   b. The header and footnote 2 for the flowchart in Section 8.9.1 were also modified to reflect this change.
   c. The following procedure point was added to Section 8.9: "AE/SAE collection and reporting will be performed according to the protocol requirements (Section 7.1) and until disease progression is documented. For AEs/SAEs that may be ongoing at the time of disease progression, follow-up will be performed until resolution or stabilization of the events or up to 90 days after the last dose of MEDI4736."
2. Per current Medimmune recommendations, the language was updated for MEDI4736 dosing of subjects whose body weight drops to ≤ 30 kg while on the study; in these cases, MEDI4736 dose will be weight based. Previously a fixed dose of 600 mg was recommended for ≤ 30 kg. This change was made in the Synopsis and in Sections 2.1, 3.1.7, 6.3.3.2, and 8.9. The following clarification was added in Sections 6.3.3.2 and 8.9: "If a subject's body weight drops to ≤ 30 kg while on the study, the subject will receive weight-based dosing equivalent to 20 mg/kg of MEDI4736 as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of MEDI4736 1500 mg."
3. Section 5.2: the following change was made to exclusion criterion #17 (changes in bold): " Female subjects of childbearing potential who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception (see table below)

from screening, and must agree to continue using such precautions for 90 days after the final dose of investigational product **(MEDI4736)**."

The following note was added: "**NOTE: For the standard of care, pegylated liposomal doxorubicin (PLD, Doxil®, Caelyx®), the package insert advises females of reproductive potential to use effective contraception during and for 6 months after last treatment with the drug. Therefore, all subjects of childbearing potential on this study should continue contraception use for 6 months after the last PLD administration."**

4. Sections 6.3 (MEDI4736)- subsections for MEDI4736 information, preparation and administration were clarified and/or reorganized per current Medimmune recommendations and to maintain consistency with current protocols. The following statement was updated (changes in bold):
   "The total time between needle puncture of the MEDI4736 vial to start of administration should not exceed 4 hours at room temperature, or 24 hours at 2°C to 8°C (36°F to 46°F). Standard infusion time is 60 ± 5 minutes. However, if there are interruptions during infusion ~~**(total infusion time not to exceed 4 hours)**~~, the total allowed **infusion** time 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."
5. Section 7.1.8 (AESIs): section was updated per current Medimmune recommendations. Diabetes insipidus and Type 1 diabetes mellitus were added to endocrine disorders. The following bullet was added:
   - **Other inflammatory responses** that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis.
6. Section 8.4.2 (MEDI4736 Dose Modifications due to toxicities)
   a. Added myocarditis to Pneumonitis/ILD bullet In Grades 1, 2, and 3 per current recommendations.
   b. For Infusion-related reactions Grades 1 and 2, the phrase "total infusion time not to exceed 4 hours." was deleted per current Medimmune guidelines.
7. Administrative: Spelling, grammar and typographical errors were corrected; formatting changes were implemented, as applicable.
8. US Study Chair's affiliation was changed from University of Arizona College of Medicine at St Joseph's Hospital to Arizona Oncology.

8.2 Pegylated Liposomal Doxorubicin (PLD) Dose Delays and Adjustments

If a toxicity occurs that requires toxicity management in accordance with Sections 8.2, 8.3, or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed.

Please refer to the package insert/product information for pegylated liposomal doxorubicin (PLD) for current instructions on dose delays and adjustments.

Subjects should be carefully monitored for toxicity. Adverse reactions, such as HFS, hematologic toxicities, and stomatitis may be managed by dose delays and adjustments. Following the first appearance of a Grade 2 or higher adverse reactions, the dosing should be adjusted or delayed as described in the following tables. Once the dose has been reduced, it should not be increased at a later time.

In the event of a delay in PLD dosing due to drug-related toxicity, doses of MEDI4736 and motolimod should also be delayed, as per Section 3.1.8.

As the standard of care agent, PLD is administered every 28 days. Every effort should be made to adhere to this schedule. Delays due to motolimod and/or MEDI4736 should not delay or shift the timing of PLD dosing.

8.2.1 Hematological Toxicity

Grade	ANC	Platelets	Modification
1	1,500 – 1,900	75,000 – 150,000	Resume treatment with no dose reduction.
2	1,000 – <1,500	50,000 – <75,000	Wait until ANC ≥1,500 and platelets ≥75,000; redose with no dose reduction.
3	500 – 999	25,000 – <50,000	Wait until ANC ≥1,500 and platelets ≥75,000; redose with no dose reduction.
4	<500	<25,000	Wait until ANC ≥1,500 and platelets ≥75,000; redose at 25% dose reduction or continue full dose with cytokine support.

8.2.2 Hand Foot Syndrome (HFS)

HFS Toxicity Grade	Dose Adjustment
1 (mild erythema, swelling, or desquamation not interfering with daily activities)	**Redose unless subject has experienced previous Grade 3 or 4 HFS.** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2 (erythema, desquamation, or swelling interfering with, but not precluding normal physical activities; small blisters or	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, PLD should be discontinued. If resolved to Grade 0-1 within 2 weeks, and there are no prior Grade 3-4 HFS, continue treatment at previous dose and return to original dose interval.

ulcerations less than 2 cm in diameter)	If subject experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.
3 (blistering, ulceration, or swelling interfering with walking or normal daily activities; cannot wear regular clothing)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, PLD should be discontinued.
4 (diffuse or local process causing infectious complications, or a bedridden state or hospitalization)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, PLD should be discontinued.

8.2.3 Stomatitis

Stomatitis Toxicity Grade	Dose Adjustment
1 (painless ulcers, erythema, or mild soreness)	**Redose unless subject experienced previous Grade 3 or 4 toxicity.** If so, delay up to 2 weeks and decrease dose by 25%. Return to original dose interval.
2 (painful erythema, edema, or ulcers, but can eat)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** If after 2 weeks there is no resolution, PLD should be discontinued. If resolved to Grade 0-1 within 2 weeks and there was no prior Grade 3-4 stomatitis, continue treatment at previous dose and return to original dose interval. If subject experienced previous Grade 3-4 toxicity, continue treatment with a 25% dose reduction and return to original dose interval.
3 (painful erythema, edema, or ulcers, and cannot eat)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to original dose interval. If after 2 weeks there is no resolution, PLD should be discontinued.
4 (requires parenteral or enteral support)	**Delay dosing up to 2 weeks or until resolved to Grade 0-1.** Decrease dose by 25% and return to PLD original dose interval. If after 2 weeks there is no resolution, PLD should be discontinued.

8.2.4 Subjects with Impaired Hepatic Function

Limited clinical experience exists in treating subjects with hepatic impairment with PLD. Based on experience with doxorubicin HCl, it is recommended that the PLD dosage be reduced if the bilirubin is elevated as follows: serum bilirubin 1.2 to 3.0 mg/dL - give 50% normal dose; serum bilirubin >3 mg/dL - give 25% normal dose, or proceed according to institutional standards.

8.3 Motolimod Toxicity Management and Dose Adjustments

PER Amendment 2, motolimod dosing will be discontinued for all subjects.

If a toxicity occurs that requires toxicity management in accordance with Sections 8.2, 8.3, or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed.

8.3.1 Management of Injection Site Reactions

Acute symptoms of injection site reactions typically resolve within 48 hours of injection, but more persistent reactions are not unexpected. Grade 2 and 3 reactions may include a painful, raised, fluid-filled blister that mimics a sterile abscess. Injection site reactions do not typically warrant antibiotic intervention as they have been found to be sterile. A culture of the fluid can be obtained—using sterile technique—if infection is strongly suspected (i.e., associated with fever persisting more than 24 hours after injection).

Ice and acetaminophen should be administered prophylactically. Symptomatic treatment with ice, acetaminophen and narcotics is acceptable. Due to their potentially suppressive effects, the use of NSAIDs within 24 hours of dosing with motolimod should be avoided, if clinically feasible.

8.3.2 Management of Systemic Toxicities

The most common systemic drug-related adverse events—Grade 1 or 2 chills, flu-like symptoms and fever—typically resolve in < 48 hours and do not require dose reductions or a delay in the dosing regimen. Less commonly, dosing with motolimod may result in cytokine release syndrome (CRS), which is most likely to be grade 1 or 2, but more severe reactions have been reported.

CRS is a symptom complex and is characterized by systemic symptoms which may include fever, nausea, chills, tachycardia, hypotension, dyspnea, asthenia, headache, and rash. Motolimod directly targets TLR8, which is expressed on immune cells. CRS may result from the release of cytokines from the activated immune cells, or from 'downstream' events that can be associated with cytokine production. Symptoms of CRS may be acute or delayed by several hours after dosing with motolimod.

Treatment of systemic drug-related events should be consistent with the severity of the reaction as well as institutional standards and may include: acetaminophen, H1- and H2-receptor antagonists, narcotics, IV fluids for volume expansion, and supplemental oxygen. Due to their potentially immunosuppressive effect, administration of NSAIDs and systemic steroids (e.g., dexamethasone) should be avoided if other means of treatment are available and medically appropriate.

In most cases the CRS will be Grade 1 or 2. However, a severe, life-threatening reaction resulting from a substantial release of cytokines is possible. Severe CRS is a medical emergency and urgent intervention must be taken to prevent life-threatening complications. This may include administration of sympathomimetic amines for pressor support and/or hospitalization for acute monitoring and intervention.

8.3.3 Motolimod Dose Modifications due to Toxicities

Motolimod will be dosed as defined in Section 3.1.7. Any dose reductions that become necessary due to the toxicities outlined below, should be done in steps of 1 level of 0.5 mg/m^2, down to a minimum dose of 1.5 mg/m^2. If 1.5 mg/m^2 is not tolerated, motolimod should be discontinued. Delays in motolimod dosing should not delay or shift the timing of other treatment agents. In the event of Grade 3 or 4 toxicities attributed to motolimod, subsequent doses should be delayed until recovery to ≤ Grade 1.

8.3.3.1 Cytokine Release Syndrome

Grade 1	**Dose reduction not required;** consider prophylactic precautions—including volume expansion and treatment with oral or IV antihistamines—with next dose.
Grade 2	**Reduce dose by 1 level at investigator's discretion;** consider prophylactic precautions—including volume expansion and treatment with oral or IV antihistamines—with next dose.
Grade 3-4	**Reduce dose by 1 level;** use prophylactic precautions with next dose.

8.3.3.2 Injection Site Reaction

Grade 1	**Dose reduction not required;** consider administering subsequent injections at distal anatomic site(s).
Grade 2	**Delay dosing for up to 2 weeks if needed;** administer subsequent injections at distal anatomic site(s) until resolved to ≤ grade 1.
	Reduce dose by 1 level if > 2 weeks delay or > 2 delays are required with consecutive injections.
Grade 3-4	**Reduce dose by 1 level;** delay dosing until resolved to ≤ grade 1.

8.3.3.3 Non-Hematologic Drug-Related AEs

Grade 1–2	**Dose reduction not required**; manage per institutional standards.
Grade 3-4	**Reduce dose by 1 level.**

8.3.3.4 Hematologic Drug-Related AEs

Grade 1–3	**Dose reduction not required**; manage per institutional standards.
Grade 4	**Reduce dose by 1 level.**

8.4 MEDI4736 Toxicity Management and Dose Adjustments

If a toxicity occurs that requires toxicity management in accordance with Sections 8.2, 8.3, or 8.4, and the toxicity causing drug can be clearly identified, then the respective guideline should be followed. If the toxicity causing drug cannot be identified, then the more conservative guideline should be followed.

8.4.1 Management of MEDI4736-related Toxicities

Based on the mechanism of action of MEDI4736 leading to T-cell activation and proliferation, Immune-related Adverse Events (irAE) may be observed during the conduct of this study. IrAEs are defined as AEs of immune nature (i.e., inflammatory) in the absence of a clear alternative etiology. Subjects should be monitored for signs and symptoms of irAEs.

Potential irAEs with MEDI4736 are expected to be similar to those seen with other immune checkpoint inhibitors, and may include immune-mediated enterocolitis, pneumonitis, dermatitis, hepatotoxicity or hepatitis, endocrinopathy, neurotoxicity and uveitis.

It is recommended that management of irAEs follow the Medimmune Guideline for Toxicity Management for MEDI4736 [**"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)"**] and the current MEDI4736 Investigator's Brochure.

In general, the following is recommended:

1. Subjects should be evaluated to identify any alternative etiology.
2. In the absence of clear alternative etiology, all events of an inflammatory nature should be considered to be immune-related.
3. Symptomatic and topical therapy should be considered for low-grade events.
4. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event.
5. More potent immunosuppressive therapies should be considered for events not responding to systemic steroids (e.g., infliximab, mycophenolate, etc.).

8.4.2 MEDI4736 Dose Modifications due to Toxicities

MEDI4736 may have to be modified or discontinued due to toxicities. Dose modifications will not be required for AEs that are clearly not attributed to MEDI4736 (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Delays in MEDI4736 dosing should not delay or shift the timing of other study drugs.

Note: If MEDI4736 dosing is held temporarily until resolution of the event as per instructions below, treatment should resume at the next scheduled treatment date (and not at the date of resolution).

8.4.2.1 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 MEDI4736 depicted below, **permanently discontinue MEDI4736** 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 and myocarditis*, consider holding MEDI4736 dosing as clinically appropriate and during diagnostic work-up for other etiologies.
Grade 2	• In general, hold MEDI4736 until resolution to ≤ Grade 1 and after the end of any steroid taper, and discontinue MEDI4736 permanently if such resolution does not occur within 60 days (30 days for neurotoxicities). Criteria for temporary hold or permanent discontinuation of MEDI4736 may differ by event as detailed below. • For *pneumonitis/interstitial lung disease and myocarditis*, the decision to reinitiate MEDI4736 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 MEDI4736 permanently if there are signs of respiratory insufficiency or autonomic instability. • For *endocrinopathies*, *other than isolated hypothyroidism*, follow general instructions above, but subjects may be retreated if the endocrinopathy is controlled and the subject is clinically stable while requiring steroid doses of ≤ 10 mg/day prednisone equivalent. • For *isolated hypothyroidism* managed with hormone replacement therapy, and for *sensory neuropathy/neuropathic pain*, holding MEDI4736 is at the discretion of the Investigator. • For *elevated creatinine* or *rash*, MEDI4736 should be held until resolution to ≤ Grade 1 or baseline. • For *vitiligo*, no dose modification required.

Grade 3	• In general, hold MEDI4736 until resolution to ≤ Grade 1, and after the end of any steroid taper, and discontinue MEDI4736 permanently if such resolution does not occur within 60 days (30 days for neurotoxicities and rash). Criteria for permanent discontinuation of MEDI4736 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, myocarditis and elevated serum creatinine (e.g., nephritis or renal dysfunction)*, always discontinue MEDI4736 permanently. • For *asymptomatic increases of amylase or lipase* levels, hold MEDI4736, and if complete work up shows no evidence of pancreatitis, MEDI4736 may be continued. • For *hepatitis*, discontinue MEDI4736 permanently for (1) transaminases or bilirubin not resolving to ≤ Grade 1 or baseline within 14 days, (2) transaminases > 8 × 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*, MEDI4736 should be held until resolution to ≤ Grade 1 or baseline.
Grade 4	• In general, discontinue MEDI4736 permanently. • For *endocrinopathies,* follow Grade 2 instructions above. • For *asymptomatic increases of amylase or lipase* levels, hold MEDI4736, and if complete work up shows no evidence of pancreatitis, MEDI4736 may be continued.

8.4.2.2 Infusion-related Reactions

Grade 1	• The infusion rate of MEDI4736 may be decreased 50% or temporarily interrupted until resolution of the event. • 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.
Grade 3-4	• **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).

8.4.2.3 All other Adverse Events

Grade 1	• No dose modification required.
Grade 2	• Hold MEDI4736 until resolution to ≤ Grade 1 or baseline, and discontinue MEDI4736 permanently if such resolution does not occur within 60 days.
Grade 3	• Hold MEDI4736. If AEs downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume MEDI4736 administration at next scheduled dose. Otherwise, discontinue MEDI4736permanently.
Grade 4	• In general, discontinue MEDI4736 permanently. • For isolated lab results, decision to discontinue should be based on accompanying clinical signs/symptoms and per Investigator's clinical judgment and in consultation with the Sponsor.

8.4.3 MEDI4736 Dose Modifications Not Due to Toxicities

MEDI4736 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 (after consultation with the Medical Monitor, if necessary):

1. The originally planned visit/treatment schedule should be maintained in general, i.e., dosing interruptions should not reset the original treatment schedule. Exceptions may be made only for individual dosing days, whereby the interval between any two doses shall be no less than 21 days (for subjects on Q2W dosing, the interval shall be no less than 10 days). All resulting protocol deviations should be documented.
2. If the dosing interruption causes 2 consecutive planned doses to be missed, the treatment should be discontinued.
3. If the dosing interruption is ≤ 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.

8.5 RECIST 1.1 Guidelines

This section outlines the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) as published (53) and as summarized by NCI for CTEP-involved clinical trials. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

8.5.1 Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same subject, these are preferred for selection as target lesions.

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

8.5.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm or less. If CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT: At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published.(54-56) In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.(57)

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (e.g., residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a) Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b) No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.
c) FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication.

However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

8.5.3 Response Criteria

8.5.3.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm.

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progressions).

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

8.5.3.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm short axis)

Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

8.5.3.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The subject's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Subjects with Measurable Disease (i.e., Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks. Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks. Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	documented at least once ≥4 wks. from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Subjects with Non-Measurable Disease (i.e., Non-Target Disease)

Non-Target Lesions	New Lesions	Overall Response
CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an end-point for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

8.5.3.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

8.6 irRECIST Guidelines

Determination of response via irRECIST should take into consideration all target and non-target lesions.

A key distinction between standard RECIST 1.1 criteria and immune-related response criteria is that irRECIST requires early evidence of progressive disease (i.e., a determination of irPD ≤ 12 weeks after starting study treatment) be confirmed by repeat, consecutive imaging ≥ 4 weeks after the initial documentation in the absence of rapid clinical deterioration. During this interim ≥ 4 week period, subjects should continue to be followed per protocol, including continued dosing of the study drug(s).

8.6.1 Response in Measurable Lesions

At baseline, the sum of the longest diameters (SumD) of all target lesions (up to 2 lesions per organ, up to total 5 lesions) is measured. At each subsequent tumor assessment (TA), the SumD of the target lesions and of new, measurable lesions (≥ 10 mm [lymph nodes ≥ 15 mm in shortest diameter]; up to 2 new lesions per organ, total 5 new lesions) are added together to provide the total measurable tumor burden (TMTB):

TMTB = SumD target lesions + SumD new, measurable lesions.

Percentage changes in TMTB per assessment time-point describe the size and growth kinetics of both old and new, measurable lesions as they appear. At each TA, the response in target and new, measurable lesions is defined based on the change in TMTB (after ruling out irPD) as follows:

Complete Response (irCR)	Complete disappearance of all target and new, measurable lesions, with the exceptions of lymph nodes which must decrease to < 10 mm in short axis.
Partial Response (irPR)	Decrease in TMTB ≥ 30% relative to baseline.
Stable Disease (irSD)	Not meeting criteria for irCR or irPR, in absence of irPD.
Progressive Disease (irPD)	Increase in TMTB ≥ 20% relative to nadir.

8.6.2 Response in Non-measurable Lesions

At each TA, the presence of any new, non-measurable lesions is assessed. The presence of such lesions will rule out an overall response of irCR. An increase in the size or number of new, non-measurable lesions does not necessarily imply an overall response of irPD; if these lesions

become measurable (≥ 10 mm) at a subsequent TA, their measurement will at that point start to contribute to the TMTB. In addition, the response in non-target lesions is defined as follows:

Complete Response (irCR)	Complete disappearance of all non-target lesions.
Stable Disease (irSD)	Non-target lesions are stable.
Progressive Disease (irPD)	Unequivocal increases in number or size of non-target lesions. To achieve unequivocal progression of non-target lesions, there must be an overall level of substantial worsening of non-target disease that is of a magnitude that the treating physician would feel it is important to change therapy.*

*NOTE: Equivocal findings of progression of non-target lesions (e.g., small and uncertain new lesions; cystic changes or necrosis in existing lesions) should be considered irSD, and treatment may continue until the next scheduled assessment.

8.6.3 Evaluation of Biomarkers

Serum CA-125 must be within normal limits for a subject to be considered in complete clinical response.

8.6.4 Overall Response

The OR according to the irRECIST is derived from the responses in measurable lesions (based on TMTB) as well as the presence of any non-measurable lesions as follows:

Complete Response (irCR)	Complete disappearance of *all lesions* (whether measurable or not); lymph nodes must decrease to < 10 mm in shortest dimension. Serum CA-125 within normal limits.
Partial Response (irPR)	Decrease in TMTB ≥ 30% relative to baseline.
Stable Disease (irSD)	Not meeting criteria for irCR or irPR, in absence of irPD.
Progressive Disease (irPD)	Increase in TMTB ≥ 20% relative to nadir.

Target Lesions Baseline (Index) and New Measurable Lesions	**Non-Target Lesions***		**irRECIST Overall Response**
Total Measurable Tumor Burden (TMTB)	**Baseline Lesions**	**Unequivocal New Lesions**	
irCR	irCR	No	irCR
irCR	irSD	No	irPR
irPR	irCR or irSD	No	irPR
irSD	irCR or irSD	No	irSD
irPD	Any	Yes or No	irPD
Any	Unequivocal Progression	Yes or No	irPD
Any	Any	Yes	irPD

*Any increase in the size or number of non-measurable lesions does not necessarily imply an overall response of irPD. If new, non-measurable lesions become measurable (≥ 10 mm) at a subsequent TA, their measurement will at that point start to contribute to the TMTB. To achieve unequivocal progression of non-target lesions, there must be an overall level of substantial worsening in non-target disease that is of a magnitude that the treating physician would feel it is important to change therapy. Equivocal findings of progression of non-target lesions (e.g., small and uncertain

new lesions; cystic changes or necrosis in existing lesions) should be considered irSD, and treatment may continue until the next scheduled assessment.

8.6.5 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for irCR or irPR (whichever is first recorded) until the first date that progressive disease (irPD) is objectively documented (taking as reference for progressive disease the smallest measurements recorded [nadir] since the treatment started).

The duration of overall irCR is measured from the time measurement criteria are first met for irCR until the first date that irPD is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for irPD are met.

8.7 Exploratory Assessment of Correlative Immunologic Research

Please refer to the lab manual for additional instructions and information on lab specimen handling and logistics.

8.7.1 Phenotypic Analysis of PBMCs

Samples for peripheral blood T-cells will be collected at the time points designated in the flowchart (Section 3.2). Peripheral blood cell subsets will be quantitated through multiparametric flow cytometry for the following T-cell subsets: CD3, CD4, CD8, FoxP3. T-cell subsets will be assessed for activation/exhaustion by expression of PD-L1, Ki-67, ICOS, PD-1, LAG-3, TIM-3, CTLA-4. PBMC may additionally be evaluated in a T-regulatory cell panel for the following: CD3, CD4, CD8, FoxP3, CD25, CD127, CD45A, CCR7, GITR, OX40, Ki-67, PD-1, CD56.

8.7.2 Myeloid Derived Suppressor Cells (MDSC)

MDSCs constitute a heterogeneous population of immature myeloid cells with various immune suppressive functions including suppression of T-cell proliferation, inducement of T-cell apoptosis and disruption of T-cell signaling pathways. Levels of circulating MDSCs are increasingly recognized as important in determining clinical responses to novel drugs for cancer and autoimmune disease. Samples will be collected for analyses at time points designated in the study flowchart (Section 3.2).

MDSCs are defined as events that are:

$Lineage^{neg}$, $CD14^{pos}$, $HLA\text{--}DR^{low/neg}$

Each sample is analyzed using well-established flow cytometry techniques for the presence of MDSCs. For each sample a single data point will be delivered, being the mean of values for the percentage of $Lineage^{neg}$, $CD14^{pos}$ events that are $HLA\text{--}DR^{low/neg}$ to study the effects of treatment on levels of MDSCs.

8.7.3 Quantification of Tumor-specific T-cell Responses

PBMCs will be collected at the time points designated in the flowchart (Section 3.2). Peripheral blood T-cell responses against known tumor-associated antigens (TAAs) expressed in most ovarian cancers, including Her-2, p53, MUC-1, hTERT, survivin, mesothelin, folate binding protein, MAGE-A3, NY-ESO-1, SP-17, and WT1 will be assessed. Overlapping peptides (15-mers overlapping by 11 amino acids) that allow assaying T-cells independently of the haplotypes will be used. Functional assays will be performed both *ex vivo* and after *in vitro* T-cell expansion and readouts will include the analysis of biomarkers in the culture supernatant (e.g. using MSD to screen for up to 40 analytes as IFN-γ and granzyme-B, for instance), IFN-γ ELISpot and polychromatic intracellular cytokines staining. As controls, T-cell response to control non-tumor related peptides (e.g. the standard CEF peptide pool including immunodominant peptides from Cytomegalovirus, Epstein Barr Virus and Influenza or tetanus toxoid) will be tested.

Whether therapy elicits T-cells specific against private mutated tumor antigens will be tested. Candidate antigens will be identified through exome sequencing of tumor tissue combined with gene expression profiling, and will be screened for candidate peptides for the subject's haplotypes using appropriate bioinformatics algorithms, tested and validated in the Lausanne

Ludwig center. *In silico*-predicted candidate peptides will be tested for fitness and binding affinity to cognate class I HLAs using recombinant HLA in an *in vitro* screening algorithm developed by Immanuel Luescher at Ludwig Lausanne and provided by TC Metrics. Finally, best-in-class peptides will be validated using PBMCs as above.

8.7.4 Baseline Immune Responsiveness to TLR8 activation

TruCulture™ samples will be collected at the time points designated in the flowchart (Section 3.2). Processed TruCulture™ tubes will be analyzed by Myriad/Rules Based Medicine (Austin, TX) to assess baseline immune responsiveness motolimod and MEDI4736.

Considerable variability in immune reactivity can exist between individuals. Despite the fact that motolimod activates a specific receptor (TLR8) on a restricted class of dendritic cells and monocytes, marked differences in responsiveness to treatment with this agent may relate to pre-existing difference in immune activation at baseline. It is hypothesized that measureable differences in response to motolimod at baseline (prior to dosing) may predict the pharmacodynamic response, and potentially clinical responses, to this agent.

A validated assay (TruCulture™) will be used to measure the baseline response to motolimod. In preliminary studies using healthy volunteers and cancer patients and the TruCulture system, VentiRx has demonstrated variability between individuals following immune activation with lipopolysaccharide or motolimod, particularly with regards to IFN-γ and interleukin-12 production. Data from TruCulture at baseline will be correlated with TLR8 SNP data, immune responses after treatment, and clinical responses.

NOTE: PER Amendment 2, samples will no longer be collected for analysis of TruCulture™, as the analyses were related to motolimod dosing. The collection time points for these assays have been removed from the flowchart in Section 3.2.

8.7.5 Immune Landscape: TILs and Tumor Microenvironment

Immunohistochemisty (IHC): Unstained sections of tumor will be analyzed by The Center of Experimental Therapeutics in Lausanne, Switzerland, where an immune signature will be assessed using a multiplexed immunohistochemical approach followed by multispectral imaging and unmixing. Multispectral imaging and linear unmixing offers the ability to analyze in a comprehensive, spatially oriented and quantitative fashion tumor slides, each stained with multiple antibodies, in either a brightfield (up to 3-4 antibodies + counterstain) or fluorescence (up to 6-8 antibodies + counterstain + autofluorescence removal) mode. More specifically, lineage specific markers i.e. CD3, CD4, CD8 for T lymphocytes (and FoxP3 for Tregs), combined with markers of activation, or functional exhaustion, for example CD45RO, CD38, HLA-DR, TIA-1, granzyme-B, Ki67, PD-1, ICOS, LAG-3, Tim-3 and/or CTLA-4 will be used. Furthermore, the spatial distribution of immune cell subsets with the level of expression on tumor cells of major components of the antigen presenting machinery i.e. HLA class I and II molecules, β2 microglobulin, tapasin, and TAP1 and 2 will be evaluated. Tumor cells and the whole microenvironment can also be interrogated for immunosuppressive factors such expression of PD-L1 and PD-L2, TGF-b, IL-10, COX1 and 2, IDO-1 etc. Tumor cells can be interrogated for proliferation (Ki67), apoptosis (cleaved caspase-3), necrosis (HMGB1) or autophagy (beclin, LC3). Finally, innate cells can be characterized, for example by CD68 and CD163 for M1 and M2

macrophages, CD33 for MDSCs and NKp46 for NK cells. Finally, the vasculature will be interrogated using several markers of activated and tumor endothelium and pericytes.

As a complementary approach to the IHC, Nanostring platform will be used to assess the mRNA expression level of genes reflecting tumor microenvironment signatures, including genes of innate and adaptive immunity, inflammation, wound healing and angiogenesis.

8.7.6 TCR sequencing

In order to better understand the role of TCR in the control of tumor, next generation sequencing will be used to perform a large and comprehensive analysis of the repertoire in various tumors for whose clinical outcome is known. DNA will be extracted from tumors and PBMCs to sequence the TCR beta chain of the infiltrating lymphocytes. The data will reveal the nucleotide sequences of the TCR present and thus allow analysis of the diversity and the clonality of the repertoire. PBMCs will be assayed from 3 time points, which will be matched as closely as possible to the tumor biopsies (baseline, Cycle 2 Day 1 and the PBMC collection closest to disease progression).

8.7.7 Immune biomarkers

Cytokines and chemokines in peripheral blood will be assessed using the Rules Based Medicine platform (HumanMAP®). HumanMAP® samples will be collected at the time points designated in the flowchart (Section 3.2). Samples will be analyzed by Myriad/Rules Based Medicine (Austin, TX), and plasma will be used to assess specific analytes including chemokines, cytokines, and other inflammatory mediators by protein array technology.

Plasma obtained from subjects pre- and post-treatment will be screened by ELISA for the presence of antibodies against a panel of cancer testis antigens and other tumor-associated antigens.

NOTE: PER Amendment 2, samples will no longer be collected for analysis of HumanMap®. The collection time points for these assays have been removed from the flowchart in Section 3.2.

8.7.8 Pharmacogenomics

DNA will be analyzed by the University of Washington, Tumor Vaccine Group (Seattle, WA) and used to examine single nucleotide polymorphisms (SNPs) in the TLR8 gene by conventional methods. An aliquot of the PBMC collection and/or tumor biopsy/archival tissue will be used for pharmacogenomics.

Genes encoding TLRs, particularly those encoding the intracellular TLR (TLR3, TLR7, TLR8 and TLR9) are evolutionarily conserved. Still, various single nucleotide polymorphisms (SNPs) in the TLR8 gene have been identified from large scale sequencing efforts in multiple ethnic populations. Recently, a common TLR8 SNP [denoted TLR8 A1G (rs3764880)] has been found to be associated with various infectious diseases, notably progression of HIV and TB. This allele is present in all populations tested, and is found at a frequency of approximately 30% in most ethnic groups. While one report suggests that the TLR8 A1G encodes a variant of TLR8 which decreases activity relative to the wild type allele, there are scant data, at present, to support this conclusion.

Given the relatively high allele frequency of this common TLR8 genetic variant, the potential functional differences in this allele, and the human genetic association between this variant and several infectious diseases, it is reasonable to genotype individuals from clinical trials investigating motolimod. Reliable methods to analyze DNA from blood or saliva to detect the TLR A1G SNP have been developed. Genotyping of all subjects in the proposed trial for the A1G SNP will be conducted to assess the potential relevance of this allele to clinical responses (related to efficacy and safety) following treatment with motolimod.

8.7.9 BRCA status of tumors

The BRCA status of tumors by testing for mutations in the full *BRCA1* and *BRCA2* exons as well as additional genes involved in the homologous recombination repair pathway will be assessed. Expression of BRCA1 and BRCA2 proteins in tumors by immunohistochemistry will be tested; absence will indicate loss of expression, presumably through epigenetic regulation.

8.7.10 MEDI4736 PK and Immunogenicity for Anti-drug Antibodies (ADA)

A validated electrochemiluminescence assay (ECLA) using a Meso Scale Discovery (MSD) platform will be used for the quantitative determination of MEDI4736 concentrations in serum. Anti-MEDI4736 antibodies in human serum will be detected using a validated MSD electrochemi-luminescence assay.

NOTE: PER Amendment 2, samples will no longer be collected for analysis of MEDI4736 PK and immunogenicity for 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.

8.7.11 sPD-L1

The association of sPD-L1with response to treatment and clinical outcome will be evaluated.

NOTE: PER Amendment 2, 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.

8.7.12 Circulating soluble factors

Analyses of circulating levels of soluble factors such as cytokines and chemokines may include but are not limited to VEGF, FGF, TGF, IL-1 IL-2, IL-4, IL-6, IL-8, IL-10, IFN, G-CSF, TNF. Their association with treatment and clinical outcome will be explored.

NOTE: PER Amendment 2, 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.

8.7.13 Additional translational and exploratory studies

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

8.7.14 mRNA/miRNA Profiling

Whole blood samples (pre- and during MEDI4736 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 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.

8.8 ECOG Performance Status

ECOG Performance Status: Developed by the Eastern Cooperative Oncology Group, Robert L. Comis, MD, Group Chair. *

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

*Oken M, Creech R, Tormey D, et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. *Am J Clin Oncol.* 1982;5:649-655

8.9 Details for Subjects Who Continue Optional MEDI4736 Treatment beyond the Core Study

According to Section 3.1.12, optional MEDI4736 treatment extension 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 the subject, Sponsor and Investigator, and it may continue until confirmed disease progression, unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met.

Subjects who receive optional study treatment extension will receive the currently recommended fixed dose of 1500 mg MEDI4736 Q4W for subjects > 30 kg. If a subject's body weight drops to ≤ 30 kg, the subject will receive weight-based dosing equivalent to 20 mg/kg Q4W for MEDI4736 as long as the body weight remains ≤ 30 kg (e.g., a 30 kg subject would receive a 600 mg dose; a 25 kg subject would receive a 500 mg dose; etc.). When the weight improves to >30 kg, the subject may return to fixed dosing of MEDI4736 1500 mg.

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 6.3.3.2.
2. Administration of MEDI4736 will proceed according to Section 6.3.4.
3. Subjects will be monitored by assessment of vital signs before, during and after each MEDI4736 dose administration according to Section 6.3.5.
4. The 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 the first dose, MEDI4736 dosing will continue Q4W.
6. The flowchart for optional treatment extension, which is provided in Section 8.9.1, will be followed.
7. AE/SAE collection and reporting will be performed according to the protocol requirements (Section 7.1) and until disease progression is documented. For AEs/SAEs that may be ongoing at the time of disease progression, follow-up will be performed until resolution or stabilization of the events or up to 90 days after the last dose of MEDI4736.

8.9.1 Study Flowchart for Subjects Who Continue Optional MEDI4736 Treatment beyond the Core Study

Study Flowchart for Subjects who Continue Optional MEDI4736 Treatment after Core Study	Optional Study Treatment[1,2] (Q4W following first optional study treatment dose)	On Study Follow-up			Post Study Follow-Up
		Last Study Drug Administration +28 ±3 days	Last Study Drug Administration +56 ±7 days	Last Study Drug Administration +90 ±7 days End of Study	Every 3 months for 3 years from initiation of treatment. Clinical outcomes data (dates of progression/relapse and survival) will be recorded (See Section 3.1.16).
Study Drug					
MEDI4736 (IV)	**1500 mg**				
Tumor & Disease Assessments					
Disease Assessment by RECIST and irRECIST (including appropriate imaging)	**SOC**	**+84 ± 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**	
12-Lead ECG[3]	**At first optional treatment visit, then Q12W**	**X**			
Echocardiogram or MUGA	**At first optional treatment visit, then Q12W**	**X**			
Concomitant Medication / Procedure (name, indication, dose, route, start & end dates)	**X**	**X**	**X**	**X**	
Adverse Events (starting or worsening after IC)[5]	**X**	**X**	**X**	**X**	
Specimens for Laboratory Procedures					
Blood Hematology (complete blood count, differential, platelets)[3]	**At first optional treatment visit, then Q12W**	**X**		**X**	
Chemistry (gluc., BUN, crea., Na, K, Ca, Cl, CO_2, PO_4, Mg, prot., alb., Tbili., AST, ALT, ALP,LDH)[3]	**At first optional treatment visit, then Q12W**	**X**		**X**	
Chemistry cont. (Amylase and lipase)[3]	**At first optional treatment visit, then Q12W**	**X**		**X**	
Chemistry cont. (Free T_3, Free T_4, TSH)[3]	**At first optional treatment visit, then Q12W**	**X**		**X**	
Serum pregnancy test[3]	**At first optional treatment visit, then Q12W**	**X**		**X**	
CA-125[3]	**SOC**	**+84 ± 7 days from last disease assessment**			
Specimens for Correlative Assessments					
PBMC/Plasma Collection & Banking[3]	**At first optional treatment visit only**	**X**		**X**	
MDSC (Serametrix)[3] (US sites only)	**At first optional treatment visit only**	**X**			
Tumor Biopsy (Tumor microenvironment, PD-L1 expression, TCR sequencing)		optional at disease progression			
Pharmacogenomics (including BRCA1 and BRCA2 tumor status)[6]					
PAX RNA[3]		optional at disease progression			

Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; Q12W = every 12 weeks; SOC = Standard of Care

1 - First MEDI4736 dose during optional treatment extension will be administered according to the following schedule:

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 according to Section 8.9; assessments will continue Q4W unless otherwise noted.

3 - Collected pre-dose. Note: It is strongly recommended that results for hematology, chemistry and pregnancy test (when applicable) are reviewed before dosing. Pregnancy tests are not required for subjects who are not of child-bearing potential as defined in Section 5.2, #17

4 - See Section 6.3.5 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.

6 -An aliquot of the PBMC and/or Tumor Biopsy tissue will be used for pharmacogenomics – a separate sampling is not needed

8.10 Abbreviations

ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALT	alanine aminotransferase
AST	aspartate aminotransferase
CD	Cluster of differentiation
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	Cytotoxic T lymphocyte-associated antigen 4
DC	Dendritic cell
DLT	dose-limiting toxicity
ECLA	Electrochemiluminescence assay
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HLA	Human Leukocyte Antigen
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IGSF	Immunoglobulin superfamily
IHC	Immunohistochemistry
IL	interleukin
IND	Investigational new drug
IP	Investigational Product
irAE	Immune-related adverse event
irRC	immune-related response criteria
irRECIST	Immune-related Response Evaluation Criteria In Solid Tumors
IV	intravenous
IRB	Institutional Review Board
LICR	Ludwig Institute for Cancer Research
mAb	Monoclonal antibody
mDC	Myeloid dendritic cell
MDSC	myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
MSD	Meso Scale Discovery
MTD	maximum tolerated dose

NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	Natural killer
ORR	Objective Response Rate
OS	Overall survival
PBMC	Peripheral blood mononuclear cell
PD-1	Programmed death-1
PD-L1	Programmed death ligand 1
PEG	polyethylene-glycol
PFS	Progression free survival
PK	Pharmacokinetics
PLD	Pegylated Liposomal Doxorubicin
Q2W	Every 2 weeks
Q4W	Every 4 weeks
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SCCHN	squamous cell carcinoma of the head and neck
SD	Standard Deviation
SOC	Standard of care
TME	Tumor microenvironment
TIL	tumor-infiltrating lymphocyte
ULN	Upper limit of normal

9 References

1. Gabizon AA. Pegylated liposomal doxorubicin: metamorphosis of an old drug into a new form of chemotherapy. Cancer Invest. 2001;19(4):424-36.
2. Rose PG, Maxson JH, Fusco N, Mossbruger K, Rodriguez M. Liposomal Doxorubicin in Ovarian, Peritoneal, and Tubal Carcinoma: A Retrospective Comparative Study of Single-Agent Dosages. Gynecol Oncol. 2001;82(2):323-8.
3. Northfelt DW, Ramanathan RK, Cohen PA, Von Hoff DD, Weiss GJ, Dietsch GN, et al. A phase I dose-finding study of the novel Toll-like receptor 8 agonist VTX-2337 in adult subjects with advanced solid tumors or lymphoma. Clin Cancer Res. 2014;20(14):3683-91.
4. Monk BJ, Brady WE, Lankes HA, Facciabene A, Manjarrez KL, et al. VTX-2337, a TLR8 agonist, plus chemotherapy in recurrent ovarian cancer: Preclinical and phase I data by the Gynecologic Oncology Group. J Clin Oncol 2013;31(s):Abstr 3077.
5. Chow LQ. Phase 1 Clinical Trial of VTX-2337, a Small Molecule Toll-Like Receptor 8 (TLR8) Agonist in Combination with Cetuximab in Patients with Recurrent or Metastatic Squamous Cell Carcinomas of the Head and Neck (SCCHN). Multidisciplinary Head and Neck Symposium. 2014.
6. Ishida Y, Agata Y, Shibahara K, Honjo T. Induced expression of PD-1, a novel member of the immunoglobulin gene superfamily, upon programmed cell death. EMBO J. 1992;11(11):3887-95.
7. Finger LR, Pu J, Wasserman R, Vibhakar R, Louie E, Hardy RR, et al. The human PD-1 gene: complete cDNA, genomic organization, and developmentally regulated expression in B cell progenitors. Gene. 1997;197(1-2):177-87.
8. Shinohara T, Taniwaki M, Ishida Y, Kawaichi M, Honjo T. Structure and chromosomal localization of the human PD-1 gene (PDCD1). Genomics. 1994;23(3):704-6.
9. Zhang X, Schwartz JC, Guo X, Bhatia S, Cao E, Lorenz M, et al. Structural and functional analysis of the costimulatory receptor programmed death-1. Immunity. 2004;20(3):337-47.
10. Dong H, Strome SE, Salomao DR, Tamura H, Hirano F, Flies DB, et al. Tumor-associated B7-H1 promotes T-cell apoptosis: a potential mechanism of immune evasion. NatMed. 2002;8(8):793-800.
11. Dong H, Zhu G, Tamada K, Chen L. B7-H1, a third member of the B7 family, co-stimulates T-cell proliferation and interleukin-10 secretion. NatMed. 1999;5(12):1365-9.
12. Freeman GJ, Long AJ, Iwai Y, Bourque K, Chernova T, Nishimura H, et al. Engagement of the PD-1 immunoinhibitory receptor by a novel B7 family member leads to negative regulation of lymphocyte activation. JExpMed. 2000;192(7):1027-34.
13. Yamazaki T, Akiba H, Iwai H, Matsuda H, Aoki M, Tanno Y, et al. Expression of programmed death 1 ligands by murine T cells and APC. JImmunol. 2002;169(10):5538-45.
14. Thompson RH, Gillett MD, Cheville JC, Lohse CM, Dong H, Webster WS, et al. Costimulatory B7-H1 in renal cell carcinoma patients: Indicator of tumor aggressiveness and potential therapeutic target. ProcNatlAcadSciUSA. 2004;101(49):17174-9.
15. Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. ProcNatlAcadSciUSA. 2007;104(9):3360-5.
16. Inman BA, Sebo TJ, Frigola X, Dong H, Bergstralh EJ, Frank I, et al. PD-L1 (B7-H1) expression by urothelial carcinoma of the bladder and BCG-induced granulomata: associations with localized stage progression. Cancer. 2007;109(8):1499-505.

17. Ishida M, Iwai Y, Tanaka Y, Okazaki T, Freeman GJ, Minato N, et al. Differential expression of PD-L1 and PD-L2, ligands for an inhibitory receptor PD-1, in the cells of lymphohematopoietic tissues. ImmunolLett. 2002;84(1):57-62.
18. Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. AnnuRevImmunol. 2008;26:677-704.
19. Liu J, Hamrouni A, Wolowiec D, Coiteux V, Kuliczkowski K, Hetuin D, et al. Plasma cells from multiple myeloma patients express B7-H1 (PD-L1) and increase expression after stimulation with IFN-{gamma} and TLR ligands via a MyD88-, TRAF6-, and MEK-dependent pathway. Blood. 2007;110(1):296-304.
20. Nakanishi J, Wada Y, Matsumoto K, Azuma M, Kikuchi K, Ueda S. Overexpression of B7-H1 (PD-L1) significantly associates with tumor grade and postoperative prognosis in human urothelial cancers. Cancer ImmunolImmunother. 2007;56(8):1173-82.
21. Ohigashi Y, Sho M, Yamada Y, Tsurui Y, Hamada K, Ikeda N, et al. Clinical significance of programmed death-1 ligand-1 and programmed death-1 ligand-2 expression in human esophageal cancer. ClinCancer Res. 2005;11(8):2947-53.
22. Parsa AT, Waldron JS, Panner A, Crane CA, Parney IF, Barry JJ, et al. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. NatMed. 2007;13(1):84-8.
23. Schreiner B, Mitsdoerffer M, Kieseier BC, Chen L, Hartung HP, Weller M, et al. Interferon-beta enhances monocyte and dendritic cell expression of B7-H1 (PD-L1), a strong inhibitor of autologous T-cell activation: relevance for the immune modulatory effect in multiple sclerosis. JNeuroimmunol. 2004;155(1-2):172-82.
24. Wu C, Zhu Y, Jiang J, Zhao J, Zhang XG, Xu N. Immunohistochemical localization of programmed death-1 ligand-1 (PD-L1) in gastric carcinoma and its clinical significance. Acta Histochem. 2006;108(1):19-24.
25. Salih HR, Wintterle S, Krusch M, Kroner A, Huang YH, Chen L, et al. The role of leukemia-derived B7-H1 (PD-L1) in tumor-T-cell interactions in humans. Exp Hematol. 2006;34(7):888-94.
26. Latchman Y, Wood CR, Chernova T, Chaudhary D, Borde M, Chernova I, et al. PD-L2 is a second ligand for PD-1 and inhibits T cell activation. NatImmunol. 2001;2(3):261-8.
27. Tseng SY, Otsuji M, Gorski K, Huang X, Slansky JE, Pai SI, et al. B7-DC, a new dendritic cell molecule with potent costimulatory properties for T cells. JExpMed. 2001;193(7):839-46.
28. Zhong X, Tumang JR, Gao W, Bai C, Rothstein TL. PD-L2 expression extends beyond dendritic cells/macrophages to B1 cells enriched for V(H)11/V(H)12 and phosphatidylcholine binding. Eur J Immunol. 2007;37(9):2405-10.
29. Bennett F, Luxenberg D, Ling V, Wang IM, Marquette K, Lowe D, et al. Program death-1 engagement upon TCR activation has distinct effects on costimulation and cytokine-driven proliferation: attenuation of ICOS, IL-4, and IL-21, but not CD28, IL-7, and IL-15 responses. JImmunol. 2003;170(2):711-8.
30. Carter L, Fouser LA, Jussif J, Fitz L, Deng B, Wood CR, et al. PD-1:PD-L inhibitory pathway affects both CD4(+) and CD8(+) T cells and is overcome by IL-2. EurJImmunol. 2002;32(3):634-43.
31. Fife BT, Bluestone JA. Control of peripheral T-cell tolerance and autoimmunity via the CTLA-4 and PD-1 pathways. ImmunolRev. 2008;224:166-82.
32. Nurieva R, Thomas S, Nguyen T, Martin-Orozco N, Wang Y, Kaja MK, et al. T-cell tolerance or function is determined by combinatorial costimulatory signals. EMBO J. 2006;25(11):2623-33.
33. Saunders PA, Hendrycks VR, Lidinsky WA, Woods ML. PD-L2:PD-1 involvement in T cell proliferation, cytokine production, and integrin-mediated adhesion. EurJImmunol. 2005;35(12):3561-9.

34. Chemnitz JM, Parry RV, Nichols KE, June CH, Riley JL. SHP-1 and SHP-2 associate with immunoreceptor tyrosine-based switch motif of programmed death 1 upon primary human T cell stimulation, but only receptor ligation prevents T cell activation. JImmunol. 2004;173(2):945-54.
35. Okazaki T, Maeda A, Nishimura H, Kurosaki T, Honjo T. PD-1 immunoreceptor inhibits B cell receptor-mediated signaling by recruiting src homology 2-domain-containing tyrosine phosphatase 2 to phosphotyrosine. ProcNatlAcadSciUSA. 2001;98(24):13866-71.
36. Abiko K, Mandai M, Hamanishi J, Yoshioka Y, Matsumura N, Baba T, et al. PD-L1 on tumor cells is induced in ascites and promotes peritoneal dissemination of ovarian cancer through CTL dysfunction. Clinical cancer research : an official journal of the American Association for Cancer Research. 2013;19(6):1363-74.
37. Matsuzaki J, Gnjatic S, Mhawech-Fauceglia P, Beck A, Miller A, Tsuji T, et al. Tumor-infiltrating NY-ESO-1-specific CD8+ T cells are negatively regulated by LAG-3 and PD-1 in human ovarian cancer. ProcNatlAcadSciUSA. 2010;107(17):7875-80.
38. Duraiswamy J, Kaluza KM, Freeman GJ, Coukos G. Dual blockade of PD-1 and CTLA-4 combined with tumor vaccine effectively restores T-cell rejection function in tumors. Cancer research. 2013;73(12):3591-603.
39. Oganesyan V, Gao C, Shirinian L, Wu H, Dall'Acqua WF. Structural characterization of a human Fc fragment engineered for lack of effector functions. Acta crystallographica Section D, Biological crystallography. 2008;64(Pt 6):700-4.
40. Sato E, Olson SH, Ahn J, Bundy B, Nishikawa H, Qian F, et al. Intraepithelial CD8+ tumor-infiltrating lymphocytes and a high CD8+/regulatory T cell ratio are associated with favorable prognosis in ovarian cancer. Proceedings of the National Academy of Sciences of the United States of America. 2005;102(51):18538-43.
41. Curiel TJ, Coukos G, Zou L, Alvarez X, Cheng P, Mottram P, et al. Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival. Nat Med. 2004;10(9):942-9.
42. Pinheiro SP, Hankinson SE, Tworoger SS, Rosner BA, McKolanis JR, Finn OJ, et al. Anti-MUC1 antibodies and ovarian cancer risk: prospective data from the Nurses' Health Studies. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology. 2010;19(6):1595-601.
43. Chen DS, Mellman I. Oncology meets immunology: the cancer-immunity cycle. Immunity. 2013;39(1):1-10.
44. Motz GT, Coukos G. Deciphering and reversing tumor immune suppression. Immunity. 2013;39(1):61-73.
45. Gajewski TF, Woo SR, Zha Y, Spaapen R, Zheng Y, Corrales L, et al. Cancer immunotherapy strategies based on overcoming barriers within the tumor microenvironment. Current opinion in immunology. 2013;25(2):268-76.
46. Lee M, Park CS, Lee YR, Im SA, Song S, Lee CK. Resiquimod, a TLR7/8 agonist, promotes differentiation of myeloid-derived suppressor cells into macrophages and dendritic cells. Archives of pharmacal research. 2014;37(9):1234-40.
47. Colombo N, Kutarska E, Dimopoulos M, Bae DS, Rzepka-Gorska I, Bidzinski M, et al. Randomized, open-label, phase III study comparing patupilone (EPO906) with pegylated liposomal doxorubicin in platinum-refractory or -resistant patients with recurrent epithelial ovarian, primary fallopian tube, or primary peritoneal cancer. J Clin Oncol. 2012;30(31):3841-7.
48. Ferrandina G, Ludovisi M, Lorusso D, Pignata S, Breda E, Savarese A, et al. Phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in progressive or recurrent ovarian cancer. J Clin Oncol. 2008;26(6):890-6.

49. Mutch DG, Orlando M, Goss T, Teneriello MG, Gordon AN, McMeekin SD, et al. Randomized phase III trial of gemcitabine compared with pegylated liposomal doxorubicin in patients with platinum-resistant ovarian cancer. J Clin Oncol. 2007;25(19):2811-8.
50. Gordon AN, Fleagle JT, Guthrie D, Parkin DE, Gore ME, Lacave AJ. Recurrent epithelial ovarian carcinoma: a randomized phase III study of pegylated liposomal doxorubicin versus topotecan. J Clin Oncol. 2001;19(14):3312-22.
51. Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. The New England journal of medicine. 2012;366(26):2443-54.
52. Brahmer JR, Tykodi SS, Chow LQ, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. The New England journal of medicine. 2012;366(26):2455-65.
53. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). European journal of cancer. 2009;45(2):228-47.
54. Rustin GJ, Quinn M, Thigpen T, du Bois A, Pujade-Lauraine E, Jakobsen A, et al. Re: New guidelines to evaluate the response to treatment in solid tumors (ovarian cancer). Journal of the National Cancer Institute. 2004;96(6):487-8.
55. Bubley GJ, Carducci M, Dahut W, Dawson N, Daliani D, Eisenberger M, et al. Eligibility and response guidelines for phase II clinical trials in androgen-independent prostate cancer: recommendations from the Prostate-Specific Antigen Working Group. J Clin Oncol. 1999;17(11):3461-7.
56. Scher HI, Halabi S, Tannock I, Morris M, Sternberg CN, Carducci MA, et al. Design and end points of clinical trials for patients with progressive prostate cancer and castrate levels of testosterone: recommendations of the Prostate Cancer Clinical Trials Working Group. J Clin Oncol. 2008;26(7):1148-59.
57. Vergote I, Rustin GJ, Eisenhauer EA, Kristensen GB, Pujade-Lauraine E, Parmar MK, et al. Re: new guidelines to evaluate the response to treatment in solid tumors [ovarian cancer]. Gynecologic Cancer Intergroup. Journal of the National Cancer Institute. 2000;92(18):1534-5.