A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects With Advanced Solid Tumors

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List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
APC	antigen presenting cells
AST	aspartate aminotransferase
BICR	blinded independent central review
BoR	best overall response
CD	cluster of differentiation
CI	confidence interval
C_{max}	maximum observed concentration
CNS	central nervous system
CR	complete response
CRC	colorectal cancer
CRF	case report form
CT	computed tomography
CTC	circulating tumor cells
CTCAE	Common Terminology Criteria for Adverse Events
CTLA-4	cytotoxic T-lymphocyte antigen 4
cynoPD-L1	cynomolgus monkey programmed death ligand 1
DC	disease control
DCR	disease control rate
DCR-24w	disease control rate at 24 weeks
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	epidermal growth factor receptor
EORTC QLQ-C30	European Organisation for Research and Treatment of Cancer quality-of-life questionnaire
EU	European Union
FACT-BL	Functional Assessment of Chronic Illness Therapy-bladder
FACT-G	Functional Assessment of Chronic Illness Therapy-general
FAS	full analysis set
Fc	fragment crystallizable

Abbreviation or Specialized Term	Definition
FFPE	formalin fixed paraffin embedded
FLAIR	fluid attenuated inversion recovery
FTIH	first-time-in-human
GBM	glioblastoma multiforme
GCP	Good Clinical Practice
GGT	gamma glutamyl transferase
GLP	Good Laboratory Practice
HCC	hepatocellular carcinoma
HCV	hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	human immunodeficiency virus
hPD-L1	human programmed death ligand 1
HPV	human papilloma virus
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IFN	interferon
IgG1	immunoglobulin G1
IgG1κ	immunoglobulin G1 kappa
IHC	immunohistochemistry
IL	interleukin
IM	immunogenicity
irAE	immune-related adverse event
IRB	Institutional Review Board
irRC	immune-related response criteria
[redacted]	[redacted]
IV	intravenous(ly)
IVRS	interactive voice response system
IWRS	interactive web response system
MAb	monoclonal antibody
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MRSD	maximum recommended starting dose
MSI	microsatellite instability
MTD	maximum tolerated dose
NCI	National Cancer Institute
NK	natural killer
NOAEL	no-observed adverse-effect-level

Abbreviation or Specialized Term	Definition
NSCLC	non-small cell lung cancer
OBD	optimal biological dose
OR	objective response
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cell
PD	progressive disease
PD-1	programmed death 1
PD-L1	programmed death ligand 1
PFS	progression-free survival
PK	pharmacokinetic
PR	partial response
PRO	patient-reported outcome
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RANO	Response Assessment in Neuro-oncology
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SCLC	small-cell lung cancer
SD	stable disease
SID	subject identification
sPD-L1	soluble programmed death ligand 1
SRT	Safety Review Team
SUSAR	suspected unexpected serious adverse reaction
TIL	tumor-infiltrating lymphocyte
TKI	tyrosine kinase inhibitor
TNBC	triple negative breast cancer
TNF-α	tumor necrosis factor alpha
UBC	urothelial bladder cancer
ULN	upper limit of normal
USA	United States of America
US FDA	United States Food and Drug Administration
WFI	water for injection
w/v	weight/volume

Study Abstract

TITLE

A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects With Advanced Solid Tumors

OBJECTIVES

Primary Objectives

Dose-escalation phase

The primary objective of the dose-escalation phase is to determine the maximum tolerated dose (MTD) or optimal biological dose (OBD), and the safety profile of MEDI4736 in subjects with advanced melanoma, renal cell carcinoma (RCC), non-small cell lung cancer (NSCLC), and colorectal cancer (CRC) refractory to standard therapy or for which no standard therapy exists.

Dose-exploration cohort

The primary objective of the dose-exploration cohort is to determine the safety profile of MEDI4736 using an every 4 weeks (Q4W) dosing schedule in subjects with advanced cutaneous melanoma, uveal melanoma, hepatocellular carcinoma (HCC), squamous cell carcinoma of the head and neck (SCCHN), NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, triple negative breast cancer (TNBC) and pancreatic adenocarcinoma.

Dose-expansion phase

The primary objectives of the dose-expansion phase are:

1. To determine the safety profile of MEDI4736 in subjects with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, pancreatic adenocarcinoma, urothelial bladder cancer (UBC), glioblastoma multiforme (GBM), ovarian cancer, soft tissue sarcoma, small-cell lung cancer (SCLC), microsatellite instability (MSI)-high cancers, human papilloma virus (HPV)-positive cancers, and nasopharyngeal carcinoma.
2. To evaluate the antitumor activity of MEDI4736 in subjects with non-squamous NSCLC who have received 2 or more prior lines of therapy and subjects with squamous NSCLC who have received 1 prior lines of therapy and 2 or more prior lines of therapy as assessed by Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 guidelines.
3. To evaluate the antitumor activity of MEDI4736 in subjects with programmed death ligand 1 (PD-L1)-positive UBC as assessed by RECIST v1.1.

Secondary Objectives

1. To describe the pharmacokinetics (PK) of MEDI4736.
2. To determine the immunogenicity (IM) of MEDI4736.
3. To evaluate the antitumor activity of MEDI4736 (except for subgroups of UBC and NSCLC subjects where this is considered a primary objective) as assessed by RECIST v1.1.
4. To evaluate the antitumor activity of MEDI4736 in subjects with UBC, regardless of PD-L1 status as assessed by RECIST v1.1.
5. To evaluate the antitumor activity of MEDI4736 in subjects with PD-L1-negative UBC as assessed by RECIST v1.1.
6. To evaluate the antitumor activity of MEDI4736 as assessed by RECIST v1.1 in subjects with PD-L1-positive UBC as compared to PD-L1-negative UBC.

Exploratory Objectives

[redacted]

STUDY DESIGN

This is a multicenter, open-label, first-time-in-human (FTIH) dose-escalation, dose-exploration, and dose-expansion study of MEDI4736 to evaluate the safety, tolerability, PK, IM, and antitumor activity of MEDI4637 in adult subjects with solid tumors. The dose-escalation phase will be conducted in subjects with advanced melanoma, RCC, NSCLC, or CRC followed by a dose -expansion phase in subjects with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, pancreatic adenocarcinoma, UBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, HPV -positive cancers, or nasopharyngeal carcinoma. In addition, a dose -exploration cohort will examine MEDI4736 at an alternative dosing schedule in subjects with advanced cutaneous melanoma, uveal melanoma, NSCLC, HCC, SCCHN, gastroesophageal cancer, TNBC, or pancreatic adenocarcinoma.

Dose Escalation

In the dose-escalation phase of the study, MEDI4736 will be administered every 2 weeks (Q2W), in sequential cohorts of 3-6 subjects each receiving one of 5 doses of MEDI4736 (0.1, 0.3, 1.0, 3.0, or 10 mg/kg) via intravenous (IV) infusion. Dose escalation will be considered completed once an MTD or OBD is identified or the top dose of 10 mg/kg is reached. Provided the MTD is not exceeded at the 10 mg/kg dose level, additional cohorts of 3-6 subjects using doses above 10 mg/kg of MEDI4736 Q2W may be explored based on emerging PK or pharmacodynamic data suggesting maximal suppression of soluble programmed death ligand 1 (sPD-L1) is not being maintained throughout the dosing interval or T-cell activation has not plateaued, respectively. Intermediate doses may be evaluated at the discretion of the sponsor based on available data. A total of 20 subjects were enrolled in the Q2W dose-escalation phase including 4 subjects in each of the 0.1 and 0.3 mg/kg cohorts, 3 subjects in each of the 1.0 and 3.0 mg/kg cohorts and 6 subjects in the 10 mg/kg cohort. The planned Q2W dose-escalation phase of the study is complete.

Upon completion of dose escalation for the MEDI4736 Q2W dose-escalation arm, a separate dose-escalation arm of MEDI4736 administered every 3 weeks (Q3W) will be initiated. This arm will be conducted in parallel with the dose-expansion phase. The first cohort of 3-6 subjects will receive MEDI4736 Q3W at the highest dose level that has not exceeded the MTD or the OBD in the Q2W dose-escalation arm. MEDI4736 Q3W dose escalation may proceed with sequential cohorts of 3-6 subjects dependent upon acceptable safety, PK/pharmacodynamic, and clinical data. A total of 7 subjects have been enrolled in the 15 mg/kg Q3W dose-escalation arm and the planned Q3W dose-escalation phase of the study is complete.

Dose Exploration

Approximately 20 subjects with advanced cutaneous melanoma, uveal melanoma, NSCLC, HCC, SCCHN, gastroesophageal cancer, TNBC or pancreatic adenocarcinoma are being enrolled into the dose-exploration cohort at select sites in the United States. MEDI4736 will be administered Q4W, at a dose of 20 mg/kg MEDI4736 via IV infusion.

Dose Expansion

The dose-expansion phase of the study will be conducted following completion of dose escalation for the MEDI4736 Q2W dose-escalation arm and in parallel with the MEDI4736 Q3W dose-escalation arm. The 10 mg/kg dose administered Q2W was chosen to take into expansion. A minimum of 20 subjects each with advanced cutaneous melanoma, uveal melanoma, HCC, gastroesophageal cancer, TNBC, UBC, SCCHN, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, and HPV-positive cancers will be enrolled (Table 1). In addition, a minimum of 10 subjects with pancreatic adenocarcinoma or nasopharyngeal carcinoma will be enrolled. Additional subjects, up to a total of 60 subjects in any of these dose-expansion cohorts may be enrolled if promising clinical activity is observed in that cohort. Approximately 110-140 subjects with non-squamous histology NSCLC will be enrolled including approximately 10-30 subjects who are treatment naive, approximately 20-30 subjects who have received 1 prior line of therapy, and approximately 80 subjects who have received at least 2 prior lines of therapy. Approximately 170-190 subjects with squamous histology NSCLC will be enrolled including approximately 10-30 subjects who are treatment-naive, approximately 80 subjects who have received 1 prior line of therapy, and approximately 80 subjects who have received at least 2 prior lines of therapy.

Table 1. Number of Subjects Enrolled by Tumor Type in Dose-expansion Cohorts

Tumor Type	Total Planned Enrollment	Subjects Enrolled as of 20Nov2015	Planned Enrollment Under Amendment 8 and Beyond
Advanced cutaneous melanoma	20	21	0
Uveal melanoma	20-60	24	Up to 36
HCC	20-60	41	Up to 19
SCCHN	20-60	63	0
Squamous NSCLC (Total) 1L 2L ≥ 3L	170-190 10-30 80 80	151 29 51 70	Up to 39
Non-squamous NSCLC (Total) 1L 2L ≥ 3L	110-140 10-30 20-30 80	143 30 34 79	0
Gastroesophageal	20-60	51	Up to 9
TNBC	20-60	40	Up to 20
Pancreatic adenocarcinoma	10-60	31	Up to 29
UBC (Total) Initial UBC subjects Amendment 8 and beyond PD-L1 positive PD-L1 negative Non-evaluable for PD-L1	20-192 20-60 132 ≥ 70 50 12	60 60 0 0 0 0	Up to 132 0 Up to 132 ≥ 70 50 12
GBM (Total) MGMT negative	20-60 ≥ 10	20	Up to 40
Ovarian cancer (Total) Platinum sensitive	20-60 ≥ 10	46	Up to 14
Soft tissue sarcoma	20-60	20	Up to 40
SCLC	20-60	21	Up to 39
MSI-high cancers	20-60	57	Up to 3
HPV-positive tumors (Total) Cervical cancer	20-60 ≤ 10 [a]	22 10	Up to 38
Nasopharyngeal carcinoma	10-60	10	Up to 50
Total	**692-1,322**	**821**	**Up to 508**

GBM = glioblastoma multiforme; HCC = hepatocellular carcinoma; HPV = human papilloma virus; L = line; MGMT = O6-methylguanine-deoxyribonucleic acid methyltransferase promoter methylation; MSI = microsatellite instability; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; SCCHN = squamous cell carcinoma of the head and neck; SCLC = small-cell lung cancer; TNBC = triple negative breast cancer; UBC = urothelial bladder cancer.

[a] A maximum of 10 cervical cancer subjects will be enrolled out of the initial 20 subjects in the HPV-positive tumors cohort. If the cohort is expanded beyond 20 subjects based on clinical activity, additional cervical cancer subjects may be enrolled.

An evaluation of a possible correlation between clinical activity of MEDI4736 and potential biomarkers (eg, PD-L1 expression on tumor or sPD-L1) will be ongoing throughout the study. Initially, tumoral PD-L1

expression will be assessed on screening samples after enrollment on an ongoing basis. After the first 20-40 subjects in the HCC, gastroesophageal cancer, TNBC, UBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, HPV-positive cancers, pancreatic adenocarcinoma, and nasopharyngeal carcinoma dose-expansion cohorts are enrolled, additional subjects in the applicable cohorts may be required to have tumoral PD-L1 expression as determined by prospective testing prior to enrollment.

Under previous amendments of this protocol, a minimum of 5-10 subjects in the SCCHN dose expansion cohort were required to have tumoral PD-L1 expression. That requirement has been met and enrollment into the SCCHN cohort is complete.

Under Amendment 7, all remaining subjects in the non-squamous NSCLC dose-expansion cohort were required to have tumoral PD-L1 expression as determined by prospective testing prior to enrollment. In the squamous NSCLC dose-expansion cohort, a minimum of 10 subjects in the first-line therapy cohort, and a minimum of 35 subjects in each of the second-line therapy and third-line or greater therapy cohorts will be required to have tumoral PD-L1 expression as determined by prospective testing prior to enrollment.

Under Amendment 8 and beyond of this protocol, the UBC cohort will be expanded to evaluate the antitumor activity of MEDI4736 in subjects with PD-L1-positive UBC and validate the potential of PD-L1 expression (determined by immunohistochemistry [IHC]) to predict response to MEDI4736 treatment. Approximately 132 additional UBC subjects will be enrolled in this cohort in order to include a minimum of 70 PD-L1-positive subjects and 50 PD-L1-negative subjects, and approximately 12 subjects with non-evaluable PD-L1 status. [redacted]

To ensure that all of the additional UBC subjects contribute to the biomarker validation, subjects must have measurable disease at baseline by blinded independent central review (BICR). PD-L1 status will be determined by a central testing laboratory and will be derived from a fresh tumor biopsy taken during screening or an available tumor sample taken from ≤ 6 months prior to study entry. The tumor sample (fresh and/or recent [within 6 months prior to study entry]) used for PD-L1 analysis must be shipped to, and confirmed as received by, the Sponsor or central vendor prior to the first dose of MEDI4736. It is highly recommended that efforts are taken to ensure presence of tumor cells within the tumor sample prior to shipping for PD-L1 analysis. The tumor PD-L1 status will be determined by IHC with PD-L1-positive samples defined as ≥ 25% tumor cell or immune cell staining and PD-L1-negative samples defined as < 25% tumor cell and immune cell staining. In cases where subjects have more than one tumor sample from ≤ 6 months prior to study entry available for testing, PD-L1 status will be derived from the most recent evaluable sample. PD-L1 status determined by IHC testing from tumor samples evaluated for screening into MedImmune Study D4190C00010 may be used if derived from a sample taken ≤ 6 months prior to study entry. Additional archival tumor tissue, from beyond 6 months prior to study entry is also required, if available.

All subjects will be evaluated regularly and their clinical status classified according to RECIST v1.1(Eisenhauer et al, 2009) with modification except for subjects with GBM who will have their clinical status classified according to the Response Assessment in Neuro-oncology (RANO) guidelines (Wen et al, 2010). Modification of RECIST as described may discourage the early discontinuation of MEDI4736 and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted primarily based on RECIST v1.1. All subjects will be followed indefinitely for survival until the sponsor closes the study.

SUBJECT POPULATION

The subjects in this study will be adults 18 years of age or older. Subjects in the dose-escalation phase will have advanced melanoma, RCC, NSCLC, or CRC refractory to standard therapy or for which no standard therapy exists. Subjects in the dose-expansion phase will have advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, pancreatic adenocarcinoma, UBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, HPV-positive cancer, or nasopharyngeal carcinoma. Subjects in the dose-exploration cohort will have advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC or pancreatic adenocarcinoma. If approved first-line standard therapy is available, subjects must have failed, be intolerant to, be ineligible for, or have refused treatment.

TREATMENT REGIMEN

Subjects will be treated in either a dose-escalation or a dose-expansion phase of the study or a dose-exploration cohort.

Dose Escalation

Subjects enrolled in the Q2W dose-escalation arm will receive one of 5 doses of MEDI4736 (0.1, 0.3, 1.0, 3.0, or 10 mg/kg) via IV infusion Q2W ± 3 days. Provided the MTD is not exceeded at the 10 mg/kg dose level, additional cohorts of 3-6 subjects using doses above 10 mg/kg of MEDI4736 Q2W may be initiated based on PK or pharmacodynamic data suggesting maximal suppression of sPD-L1 is not being maintained throughout the dosing interval or T-cell activation has not plateaued, respectively. Intermediate doses may be evaluated at the discretion of the sponsor based on available data.

Upon the completion of dose escalation for the Q2W dose-escalation arm, a separate dose-escalation arm of MEDI4736 administered Q3W will be initiated. This Q3W dose-escalation arm will be carried out in parallel to the dose-expansion phase. The first cohort of subjects will receive MEDI4736 Q3W ± 3 days at the highest dose level that does not exceed the MTD or the OBD in the Q2W dose-escalation arm. Higher doses of MEDI4736 may be explored based upon acceptable safety, PK/pharmacodynamic, and clinical data.

Treatment in the Q2W or Q3W dose-escalation arm will continue for 12 months or until confirmed progressive disease (PD), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur. In the event of confirmed PD, subjects may continue to receive MEDI4736 in the absence of clinical deterioration and if investigators consider that subjects continue to receive benefit from treatment. Subjects who have achieved and maintained disease control (DC; ie, complete response [CR], partial response [PR], or stable disease [SD]) or clinical benefit through to the end of the 12-month treatment period will enter follow-up. Upon evidence of PD during follow-up, subjects will be re-administered MEDI4736 at the dose previously received or at 10 mg/kg, the dose chosen for the expansion phase via IV infusion Q2W or Q3W as appropriate. Subjects may continue MEDI4736 retreatment for up to 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Only one round of retreatment with MEDI4736 will be allowed. Subjects who have confirmed PD during the 12-month initial treatment or retreatment period and cannot continue to receive MEDI4736 will enter follow-up for 90-day safety assessments and survival follow-up.

Dose Exploration

MEDI4736 will be administered Q4W, at a dose of 20 mg/kg MEDI4736 via IV infusion. Treatment in the dose exploration cohort will continue on a Q4W schedule for 12 months or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent or other reasons to discontinue treatment occur. In the event of confirmed PD, subjects may continue to receive MEDI4736 in the absence of clinical deterioration and if investigators consider that subjects continue to receive benefit from treatment. Subjects who have achieved and maintained DC (ie, CR, PR, or SD) or clinical benefit through to the end of the 12-month treatment period will enter follow-up. Upon evidence of PD during follow-up, subjects will be re-administered MEDI4736 at 20 mg/kg via IV infusion Q4W. Subjects may continue MEDI4736 retreatment for up to 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Only one round of retreatment with MEDI4736 will be allowed. Subjects who have confirmed PD during the 12-month Q4W initial treatment or retreatment period and cannot continue to receive MEDI4736 will enter follow-up for 90-day safety assessments and survival follow-up.

Dose Expansion

The dose-expansion phase of the study will be conducted following completion of dose escalation for the MEDI4736 Q2W dose-escalation arm and in parallel with the MEDI4736 Q3W dose-escalation arm. Subjects will receive MEDI4736 Q2W via IV infusion at the MTD/OBD or the highest dose evaluated during Q2W dose escalation if no MTD or OBD is determined.

Treatment in the dose-expansion phase will continue on a Q2W schedule for 12 months or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent or other reasons to discontinue treatment occur. In the event of confirmed PD, subjects may continue to receive MEDI4736 in the absence of clinical deterioration and if investigators consider that subjects continue to receive benefit from treatment. Subjects who have achieved and maintained DC (ie, CR, PR, or SD) or clinical benefit through to the end of the 12-month treatment period will enter follow-up. Upon evidence of PD during follow-up, subjects will be re-administered MEDI4736 at the dose previously received via IV infusion Q2W. Subjects may continue MEDI4736 retreatment for up to 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Only one round of retreatment with MEDI4736 will be allowed. Subjects who have confirmed PD during the 12-month initial treatment or retreatment period and cannot continue to receive MEDI4736 will enter follow-up for 90-day safety assessments and survival follow-up.

ASSESSMENT OF ENDPOINTS

MTD or OBD: Endpoints related to the primary objective of determining MTD or OBD include evaluation of dose-limiting toxicities (DLTs), overall safety, and parameters related to the OBD. The MTD evaluation will be based on data from subjects who completed the DLT evaluation period. The OBD will be determined based upon analysis of all available subject data, including safety, PK, pharmacodynamic, biomarker, and response data.

Safety: Endpoints include assessments of adverse events (AEs), serious adverse events (SAEs), laboratory evaluations, vital signs, electrocardiograms (ECGs; digital and central read at selected sites), and physical examinations.

Pharmacokinetics: Individual MEDI4736 concentrations will be tabulated by dose cohort

Immunogenicity: The immunogenic potential of MEDI4736 will be assessed by summarizing the number and percentage of subjects who develop detectable anti-drug antibodies (ADAs).

Antitumor activity: Assessments of antitumor activity will be based on the objective response rate (ORR), disease control rate (DCR), duration of response (DR), progression-free survival (PFS), and overall survival (OS). Response Evaluation Criteria in Solid Tumors v1.1 guidelines will be used to determine tumor response and to guide treatment decisions. The primary endpoint of antitumor activity in the NSCLC and UBC cohorts is objective response (OR), which is defined as a best overall response (BoR) of CR or PR according to RECIST v1.1 as determined by BICR. BoR is defined as the best response (in the order of CR, PR, SD, PD, and not evaluable) among all overall responses recorded from the start of treatment until objective documentation of PD (per RECIST v1.1 as assessed by BICR), or the last evaluable disease assessment in the absence of PD prior to initiation of subsequent anticancer therapy or discontinuation from the study, whichever occurs first. The best overall response of CR or PR must be confirmed. The ORR is defined as the proportion of subjects with OR. The 95% confidence interval (CI) of ORR will be estimated using the exact probability method.

The ORR (based on RECIST v1.1 by BICR) along with its 95% CI will be provided for all NSCLC subjects in each line by histology and for the subpopulation in the ≥ second-line squamous NSCLC subjects who have tumoral PD-L1 expression as determined by prospective testing prior to enrollment.

For UBC, the primary analysis of ORR based on RECIST v1.1 by BICR will be performed for all UBC subjects (second- or greater line of therapy) in the PD-L1-positive full analysis set (FAS) enrolled in the entire study. The FAS include all subjects who have been treated, have measurable disease at baseline per BICR, and have opportunity to be followed for at least 24 weeks. The primary endpoint for UBC cohort in PD-L1-positive subgroup is considered to be met if the lower-limit of the exact 2-sided 95% CI for ORR excludes a historical response rate of 10% or less (Bellmunt et al, 2009). An analysis of ORR for all UBC subjects in the PD-L1-positive FAS enrolled under Amendment 8 and beyond will be conducted as a supportive analysis.

If the primary endpoint for the PD-L1-positive subgroup of the UBC cohort is met, the ORR based on RECIST v1.1 by BICR along with its 95% CI will be also provided for all UBC subjects (second or greater line of therapy) in the FAS (regardless of PD-L1 status) enrolled in the entire study. The primary endpoint

for UBC cohort in all-comers is considered to be met if the lower-limit of the exact 2-sided 95% CI for ORR excludes a historical response rate of 10% or less (Bellmunt et al, 2009). In addition, the ORR based on RECIST v1.1 by BICR along with its 95% CI will be provided for all UBC subjects (second- or greater line of therapy) in the PD-L1-negative FAS enrolled in the entire study and in the PD-L1-negative FAS enrolled under Amendment 8 and beyond. The primary analysis for UBC cohort will occur at least 24 weeks after the last PD-L1-positive UBC subject's first dose of study treatment. The analyses of ORR per BICR described above for the UBC cohort will be repeated for the UBC subjects (second- or greater line of therapy) in the PD-L1-positive FAS, the PD-L1-negative FAS, and the FAS (regardless of PD-L1 status) enrolled in the entire study.

INTERIM ANALYSIS

For the UBC cohort, the first interim analysis will be conducted after approximately 30 PD-L1-positive UBC subjects are enrolled and followed for at least 12 weeks. The efficacy analysis will be based on investigator RECIST data.

The second interim analysis for the UBC cohort will be conducted after a minimum of 60 PD-L1-positive second- or greater line UBC subjects are enrolled in the entire study and followed for at least 16 weeks. The primary efficacy analysis population for this analysis will be based on the treated PD-L1-positive UBC subjects (second- or greater line) with measurable disease at baseline per BICR who have had an opportunity of being followed up for at least 16 weeks by the interim analysis. The analysis will be primarily based on RECIST v1.1 by BICR, and additional analysis based on investigator RECIST data will be conducted as supportive. [redacted] The enrollment will not be interrupted or terminated for efficacy based on the interim analysis.

SAMPLE SIZE AND POWER CALCULATIONS

[redacted]

Dose-escalation phase: The number of subjects required will depend upon the toxicities observed as the study progresses. Up to approximately 50 evaluable subjects could be required if the separate Q3W dose escalation is implemented upon completion of dose escalation for the MEDI4736 Q2W dose-escalation arm. More subjects may be enrolled to investigate intermediate doses for MTD evaluation if DLTs are observed in either the 3.0 or 10 mg/kg dose cohort. In addition, more subjects may be enrolled if doses higher than 10 mg/kg Q2W are evaluated during dose escalation. Table 2 provides the probability of dose escalation to the next higher level for each underlying true DLT rate. For example, for a common toxicity that occurs in 10% of subjects, there is a greater than 90% probability of escalating to the next higher dose level. Conversely, for a toxicity that occurs at a rate of 60%, the probability of escalating to the next higher dose level is less than 10%.

Table 2. Probability of Escalating for Different True Underlying Dose-limiting Toxicity Rate at a Given Dose Level

True underlying dose-limiting toxicity rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of escalating dose	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.009	0.001

Dose-exploration cohort: Approximately 20 subjects will be enrolled in the dose-exploration cohort of the study to determine the safety of 20 mg/kg Q4W dose schedule. [redacted]

Dose-expansion phase: A minimum of approximately 692 subjects will be enrolled in the dose-expansion phase as described below. Additional subjects, described in each cohort below, may be enrolled if promising clinical activity is observed in any of these cohorts.

- Advanced cutaneous melanoma, uveal melanoma, HCC, gastroesophageal cancer, TNBC, SCCHN, UBC (initial cohort enrolled prior to Amendment 8), GBM, ovarian cancer, soft tissue sarcoma, SCLC,

MSI-high cancers, and HPV-positive cancers cohorts: A minimum of 20 subjects will be enrolled in each of these 13 disease cohorts. The sample size is chosen to obtain a preliminary assessment of antitumor activity in terms of DCR for each disease cohort. The DCR will be estimated by the proportion of subjects with CR, PR, or SD ≥ 12 weeks in each disease cohort and its 80% CI will be estimated by the exact probability method [redacted]

Table 3. [redacted]

[redacted]									
[redacted]									
[redacted]									
[redacted]									

- Pancreatic adenocarcinoma and nasopharyngeal carcinoma cohorts: A minimum of 10 subjects will be enrolled in each of these cohorts. The DCR will be estimated by the proportion of subjects with CR, PR, or SD ≥ 12 weeks in each cohort and its 80% CI will be estimated by the exact probability method [redacted]. Additional subjects, up to a total of 60 subjects in either of these 2 cohorts may be enrolled if promising clinical activity is observed in that cohort.

Table 4. [redacted]

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- NSCLC: Preliminary data from the dose-escalation phase of this study as well as data from other antibodies targeting the PD1/PD-L1 pathway suggest that subjects with NSCLC may benefit from treatment with an agent such as MEDI4736. As a result, a minimum of approximately 110 subjects in the non-squamous histology NSCLC cohort and 170 subjects in the squamous histology NSCLC cohort will be enrolled from among specific subpopulations of NSCLC as outlined below.
  - For the non-squamous NSCLC cohort, the enrollment will include approximately 10 subjects who are treatment-naïve, approximately 20 subjects who have received 1 prior line of therapy, and approximately 80 subjects who have received at least 2 prior lines of therapy. Additional subjects, up to 30 each for first-line and second-line therapy groups, may be enrolled.
  - For the squamous NSCLC cohort, the enrollment will include approximately 10 subjects who are treatment-naïve, approximately 80 subjects who have received 1 prior line of therapy, and approximately 80 subjects who have received at least 2 prior lines of therapy. Additional subjects, up to 30 for first-line therapy group, may be enrolled.
  - The minimum sample sizes of 10 and 20 subjects were chosen to provide a preliminary assessment of the ORR for MEDI4736 as first-line therapy for both squamous and non-squamous NSCLC and second-line therapy for non-squamous NSCLC, respectively, similar to the aforementioned cohorts in other tumor types.
  - The sample size of 80 subjects for MEDI4736 in ≥ third-line therapy in non-squamous NSCLC and as second-line therapy as well as ≥ third-line therapy for squamous NSCLC, respectively, was chosen to provide a formal statistical testing of the following hypothesis

$$H_0: ORR \leq 10\% \text{ vs } H_1: ORR > 10\%$$

[redacted]

- UBC: Under Amendment 7, approximately 60 UBC subjects were enrolled. Under Amendment 8 and beyond, approximately 132 additional UBC subjects with inoperable or metastatic disease (second- or greater line) will be enrolled, which includes a minimum total of 70 PD-L1-positive and 50 PD-L1-negative subjects, and approximately 12 subjects with tumor samples non-evaluable for PD-L1, assuming a PD-L1-positive prevalence of 60% and approximately 10% of subjects with tumor samples not evaluable for PD-L1 (based on preliminary data from the initial UBC cohort of this study).

Of 192 UBC subjects enrolled in the study, it is expected that there will be approximately 100 PD-L1-positive subjects in the second- or greater line of treatment (approximately 30 enrolled under Amendment 7 and approximately 70 enrolled under Amendment 8 and beyond). As shown in Table 5, when the ORR is expected to be in the 17% to 33% range (Plimack et al, 2015; Rosenberg et al, 2015), a total of 100 subjects would provide a width of < 9% between the observed ORR and its lower limit of the exact 95% C [redacted]

Table 5. [redacted]

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The prevalence of PD-L1 status for UBC subjects will be monitored through the study. After a total of approximately 132 subjects are enrolled under Amendment 8 and beyond, the enrollment of only PD-L1-positive subjects may continue to ensure a minimum total of 70 PD-L1-positive subjects are enrolled.

With 70 PD-L1-positive and 50 PD-L1-negative UBC subjects enrolled under Amendment 8 and beyond to validate the potential of PD-L1 expression to predict response to MEDI4736 treatment, [redacted] The response rate for the PD-L1-negative group is assumed to be similar to that observed with chemotherapy in a second-line UBC population (Bellmunt et al, 2009).

1 INTRODUCTION

1.1 Disease Background

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

Recent advances in the treatment of advanced melanoma using ipilimumab (YERVOY™) have led to improvements in overall survival (OS) in both the first- and second-line setting (Robert et al, 2011; Hodi et al, 2010). Despite these improvements, there remains a need for new therapies as only a small proportion of melanoma patients attain durable responses and a survival benefit. In addition, treatment with anti-cytotoxic T-lymphocyte antigen 4 (CTLA-4) antibodies has been shown to result in significant immune-related toxicity that could lead to serious complications if not properly managed. The development of novel approaches to treatment may lead to improved outcomes in these populations.

The immune system is capable of identifying tumor-associated antigens and eliminating the cancerous cells expressing them. This process of tumor immune surveillance plays an important role in preventing and combating the growth of tumors. The process of immune surveillance is believed to result in a co-evolution of the tumor and immune response termed immunoediting, which is thought to follow 3 stages (Swann and Smyth, 2007). During the initial phase of elimination, the innate and adaptive immune systems detect and eliminate tumor cells. Elimination can result in complete clearance of tumor cells as is seen in rare cases of spontaneous regression of melanoma (Kalialis et al, 2009). However, if elimination is incomplete, the immune system and tumor may enter a state of equilibrium. During this second phase of immunoediting, the immune response selectively eliminates susceptible tumor cells and may prevent tumor progression. As the equilibrium phase persists, the tumor may evolve mechanisms to avoid or attenuate the immune response. The emergence of tumor cells with reduced immunogenicity (IM) or enhanced immunosuppressive mechanisms leads to the escape phase of immunoediting. During escape, many factors may contribute to the failure of the immune system to control tumor growth including expression of T-cell

inhibitory molecules, downregulation of tumor antigens, and presence of immunosuppressive regulatory T cells or immunosuppressive cytokines within the tumor microenvironment.

Enhancing the immune response may provide a means to regain control of tumors that have progressed to the escape phase during immunoediting. A number of mechanisms to stimulate the antitumor immune response have been successfully employed. Interleukin (IL)-2 and interferon (IFN) alpha have shown objective response rates (ORRs) of 12% to 23% in renal cell carcinoma (RCC), with durable complete responses (CRs) and partial responses (PRs) in some patients (Motzer et al, 2009; McDermott et al, 2005). High-dose IL-2 has also led to survival benefit, but only in subjects with durable CRs (6%) in melanoma (Atkins et al, 1999). Recently sipuleucel-T, an immunotherapy consisting of activated autologous antigen-presenting cells, was granted United States Food and Drug Administration (US FDA) approval for treatment of metastatic hormone refractory prostate cancer (Madan and Gulley, 2011). Blockade of negative regulatory signals to T cells such as CTLA-4 and programmed death ligand 1 (PD-L1) has also shown promising clinical activity. Ipilimumab, which binds to CTLA-4 and prevents the interaction of CTLA-4 with cluster of differentiation 80 (CD80) and CD86, results in enhanced T-cell activation and proliferation (Lipson and Drake, 2011). Ipilimumab was granted US FDA approval in 2011 for the treatment of metastatic melanoma and is currently under investigation for several other malignancies.

PD-L1 (B7-H1, CD274) is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. In normal tissue, PD-L1 is expressed on T cells, B cells, dendritic cells, macrophages, mesenchymal stem cells, bone marrow-derived mast cells, as well as various nonhematopoietic cells (Keir et al, 2008). Its normal function is to regulate the balance between T-cell activation and tolerance through interaction with its 2 receptors, programmed death 1 (PD-1, CD279) and CD80 (B7-1). PD-L1 is also expressed by tumors and acts at multiple sites to help tumors evade detection and elimination by the host immune system. In the lymph nodes, PD-L1 on antigen presenting cells (APC) binding to PD-1 (CD279) or CD80 (B7-1) on activated T cells delivers an inhibitory signal to the T cell (Keir et al, 2008; Park J et al, 2010). Likewise, binding of CD80 on APCs to PD-L1 on T cells leads to inhibitory signaling in the T cell. These and bidirectional interactions between CD80 and PD-L1, expressed on both APCs and T cells, lead to further inhibition of T-cell activation. These interactions result in reduced T-cell activation and fewer activated T cells in the circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target tumor cells, and protecting the tumor from immune elimination (Zou and Chen, 2008).

PD-L1 is expressed in a broad range of cancers with a high frequency, up to 88% in some types of cancer. In a number of these cancers, including lung (Mu et al, 2011), renal (Thompson et al, 2005; Thompson et al, 2006; Krambeck et al, 2007), pancreatic (Nomi et al, 2007; Loos et al, 2008; Wang et al, 2010), and ovarian (Hamanishi et al, 2007), the expression of PD-L1 is associated with reduced survival and unfavorable prognosis. In ovarian cancer, for example, the 5-year survival rate in patients with low levels of PD-L1 was 80.2%, compared to 52.6% in patients with high levels of PD-L1 (Hamanishi et al, 2007). In lung cancer, only 20% of patients with tumors expressing PD-L1 survived for more than 3 years, compared to 49% of patients with tumors lacking PD-L1 (Mu et al, 2011). Based on these data, and on assessments of expression of PD-L1 on the surface of human tumors using proprietary immunohistochemistry methods for assessment, MEDI4736 has the potential to affect multiple types of solid tumors, including those with a high incidence rate and some less common types with limited treatment options and poor outcomes.

The levels of tumor-infiltrating lymphocytes (TILs), and more specifically cytotoxic T cells, have been correlated to improved prognosis in a number of cancers including colorectal, melanoma, and lung (Pages et al, 2010), suggesting that an antitumor immune response is beneficial to patients. It has been shown in vitro that an antibody that blocks the interaction between PD-L1 and its receptors can relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of antitumor T cells (Blank et al, 2006). Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of several preclinical studies using mouse tumor models support this hypothesis. In these studies, antibodies directed against PD-L1, or its receptor PD-1, showed antitumor activity (Hirano et al, 2005; Iwai et al, 2002; Okudaira et al, 2009; Zhang et al, 2008).

Blocking PD-L1 is a similar approach to that taken by ipilimumab, but has some potential advantages. Firstly, the expression of CTLA-4 and its ligands is restricted to the hematopoietic system; thus the site of action for molecules targeting CTLA-4 is solely the peripheral lymphoid organs. In contrast, PD-L1 is expressed not only on cells of the hematopoietic system but also on a range of tumor types. Targeting of PD-L1 could therefore have additional effects within the tumor microenvironment. Secondly CTLA-4 plays an early and critical role in controlling T-cell activation. This is reflected in the phenotype of CTLA-4 knockout mice, which die at an age of between 3 and 4 weeks due to lymphoproliferative disease and tissue destruction. In contrast PD-L1, via binding to PD-1, acts later in the process of T-cell activation (Fife and Bluestone, 2008) and is considered more dispensable for the control of initial T-cell activation. This is reflected in the phenotype of PD-L1

knockout mice, which are viable and have normal T-cell numbers and activation levels, but which have increased T-cell activation in response to antigen and increased susceptibility in certain autoimmunity models (Dong et al, 2004; Latchman et al, 2004). Similarly, PD-1 knockout mice show strain-specific phenotypes milder than those seen in CTLA-4 knockouts (Nishimura et al, 1998; Nishimura and Honjo, 2001). Based on these data, inhibition of PD-L1 would be expected to have reduced toxicity relative to inhibition of CTLA-4. In support of this, recent Phase 1 clinical studies testing the tolerability of agents targeting PD-1 have shown a more favorable toxicity profile than ipilimumab (Brahmer et al, 2010; Berger et al 2008; Wolchok et al, 2010).

1.2 Description of MEDI4736

MEDI4736 is briefly described below. Refer to the current Investigator's Brochure for details.

1.2.1 Product Derivation

MEDI4736 is a human immunoglobulin G1 kappa (IgG1κ) 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 immunoglobulin G1 (IgG1) heavy chain that reduces binding to the complement component C1q and the Fcγ receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC) (Oganesyan et al, 2008). 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 CD80 receptors.

1.2.2 Summary of Nonclinical Experience

[redacted]

[redacted]

[redacted]

1.2.3 Summary of Clinical Experience

[redacted]

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1.3 Research Hypothesis

The primary objectives of this Phase 1/2, first-time-in-human (FTIH), dose-escalation and dose-expansion study are to determine the maximum tolerated dose (MTD) or optimal biological dose (OBD), and safety profile of MEDI4736 in subjects with advanced solid malignancies and the antitumor activity of subjects with NSCLC and UBC. Secondary objectives include evaluation of the PK, IM, and antitumor activity of MEDI4736. The exploratory objectives are to evaluate biomarkers that may correlate with activity or prospectively identify patients likely to respond to MEDI4736 and to evaluate the effect of MEDI4736 on patient-reported outcomes (PROs).

The research hypothesis is that MEDI4736 will be adequately tolerated following administration in ascending doses to subjects with refractory solid tumors and that such administration may result in clinical benefit.

1.4 Rationale for Study Conduct

Currently available therapies for the advanced solid malignancies included in this study result in poor outcomes and there is a significant unmet medical need for additional treatment options in these patient populations. MEDI4736, an antibody that blocks the interaction between PD-L1 and its receptors, may relieve PD-L1-dependent immunosuppressive effects and enhance the cytotoxic activity of antitumor T cells. Given the preliminary clinical activity observed in all tumor types in the dose-expansion phase of this study, the recently available data from similar agents and the immunomodulatory mechanism of an anti-PD-L1 MAb, MEDI4736 may offer benefit to patients with a broad range of cancers. Rationale for the selection of specific tumor types is provided in Section 3.4.

This study is intended to establish the MTD or OBD and the safety profile of MEDI4736, as well as the preliminary antitumor activity in subgroups of NSCLC and UBC. Other data to be evaluated include the PK, pharmacodynamics, IM, antitumor activity in additional tumor types, and potential biomarkers, which may correlate with response to MEDI4736 treatment. Specifically, the dose-expansion phase of this study will evaluate the antitumor activity of

MEDI4736 in several advanced solid malignancies where historical outcomes are poor and scientific rationale suggests that treatment with an anti-PD-L1 MAb may be beneficial. Potential biomarkers, including PD-L1 expression, will be evaluated on an ongoing basis. The results from this study will form the basis for decisions applied to ongoing and future studies.

1.5 Benefit-risk and Ethical Assessment

Subjects with advanced solid tumors refractory to standard treatment or for which no standard therapy exists represent a patient population with unmet medical needs. MEDI4736, a human MAb directed against hPD-L1, may offer benefit to this patient population. MEDI4736 has a high affinity for hPD-L1 and is able to completely block the interaction of recombinant hPD-L1 with both recombinant hPD-1 and recombinant human CD80 in a biochemical assay. In vitro, MEDI4736 enhances the proliferation and activation of primary human T cells cultured in the presence of recombinant PD-L1.

Nonclinical studies demonstrate that MEDI4736 inhibits tumor growth in mouse xenograft models. This activity is shown to be dependent upon the presence of human T cells, supporting the hypothesis that PD-L1 blockade can enhance antitumor immune response. No MEDI4736-associated risks have been reported in nonclinical safety studies in cynomolgus monkeys.

Promising evidence of clinical activity has been observed for molecules similar to MEDI4736, including other MAbs targeting the PD-1/PD-L1 pathway (Topalian et al, 2012; Hamid et al, 2013; Brahmer et al, 2012; Herbst et al, 2013). In these studies, encouraging response rates and durable responses have been observed across a range of tumor types. The experience to date with anti-PD-1/PD-L1 MAbs suggests that these agents can provide significant clinical activity with a manageable safety profile that is superior to that of the anti-CTLA-4 class.

[redacted]

[redacted]

Clinically significant risks of interest with MEDI4736 and related molecules include immune-mediated reactions and their associated signs and symptoms, risks due to IM and other potential risks. Immune-mediated reactions/immune-related AEs (irAEs), also considered to be AEs of special interest (AESIs), are important risks of immune checkpoint inhibitors, and are being closely monitored in clinical studies with MEDI4736 monotherapy and combination therapy.

Under previous versions of this protocol, inclusion criteria required that subjects have a creatinine clearance of ≥ 50 mL/min. Under Amendment 9, UBC subjects will be permitted to enroll with a creatinine clearance of ≥ 30 mL/min. In the UBC population, impaired renal function is common due to age, urinary tract obstruction, smoking-related vascular disease, or prior treatments including nephrectomy, cystectomy, and prior nephrotoxic chemotherapy (ie, commonly used platinum-based chemotherapy; Galsky et al, 2011). As such, lowering the creatinine clearance requirement for these subjects will allow for evaluation of MEDI4736 in a broader UBC patient population that may be more representative of a real world population. Given that MEDI4736 is an IgG1 MAb, and MAbs are not expected to be cleared through renal mechanisms, it is anticipated that exposure will not be significantly altered in subjects with impaired renal function. This is supported by population PK analysis of patients treated with MEDI4736, which demonstrated that creatinine clearance was not a significant covariate for drug clearance (Song et al, 2015).

[redacted]

[redacted]

In the overall study population, the most frequently reported MEDI4736-related renal AESIs of all grades were acute kidney injury and blood creatinine increased (2 subjects each; 0.2%). In the UBC population, MEDI4736-related renal AESIs were reported in 1 subject (Grade 3 acute kidney injury; 1.6%).

Table 1.5-1 [redacted]

[redacted]

Given the available PK, clinical activity, and safety data observed in UBC subjects treated with MEDI4736 and the limited treatment options after failure of standard platinum-based regimens, allowing subjects with creatinine clearance ≥ 30 mL/min to be treated with MEDI4736 is justified.

In order to mitigate potential risks to patients, this study has incorporated toxicity management guidelines developed for use across the broader MEDI4736 clinical development program. These guidelines are based on evidence and experience from ongoing studies of MEDI4736 and similar immune-modulating agents and are focused on frequent

monitoring for and early identification of potential immune-mediated events. Management principles include interruption of dosing and/or treatment with corticosteroids or more potent immunosuppressive agents as needed. In addition, the study has incorporated eligibility criteria to ensure patients that may be at risk would not be included (ie, by excluding those with prior autoimmune disease, inflammatory bowel disease, unresolved toxicities from prior therapies, or inadequate hematologic or organ function).

2 STUDY OBJECTIVES

2.1 Primary Objective

Dose-escalation Phase

The primary objective of the dose-escalation phase is to determine the MTD or OBD, and the safety profile of MEDI4736 in subjects with advanced melanoma, RCC, NSCLC, and colorectal cancer (CRC) refractory to standard therapy or for which no standard therapy exists.

Dose-exploration Cohort

The primary objective of the dose-exploration cohort is to determine the safety profile of MEDI4736 using an every 4 weeks (Q4W) dosing schedule in subjects with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC or pancreatic adenocarcinoma.

Dose-expansion Phase

The primary objectives of the dose-expansion phase are:

1. To determine the safety profile of MEDI4736 in subjects with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, pancreatic adenocarcinoma, UBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, HPV-positive cancers, or nasopharyngeal carcinoma.
2. To evaluate the antitumor activity of MEDI4736 in subjects with non-squamous NSCLC who have received 2 or more prior lines of therapy and subjects with squamous NSCLC who have received 1 prior lines of therapy and 2 or more prior lines of therapy as assessed by RECIST v1.1.
3. To evaluate the antitumor activity of MEDI4736 in subjects with PD-L1-positive UBC as assessed by RECIST v1.1.

2.2 Secondary Objectives

The secondary objectives of this study are:

1. To describe the PK of MEDI4736.
2. To determine the immunogenicity of MEDI4736.
3. To evaluate the antitumor activity of MEDI4736 (except for subgroups of UBC and NSCLC subjects where this is considered a primary objective) as assessed by RECIST v1.1.
4. To evaluate the antitumor activity of MEDI4736 in subjects with UBC, regardless of PD-L1 status as assessed by RECIST v1.1.
5. To evaluate the antitumor activity of MEDI4736 in subjects with PD-L1-negative UBC as assessed by RECIST v1.1.
6. To evaluate the antitumor activity of MEDI4736 as assessed by RECIST v1.1 in subjects with PD-L1-positive UBC as compared to PD-L1-negative UBC.

2.3 Exploratory Objectives

[redacted]

3 STUDY DESIGN

3.1 Overview of Study Design

This is a multicenter, open-label, FTIH dose-escalation, dose-exploration, and dose-expansion study of MEDI4736 to evaluate the safety, tolerability, PK, IM, and antitumor activity of MEDI4637 in adult subjects with solid tumors. A dose-escalation phase in subjects with advanced melanoma, RCC, NSCLC, or CRC using a Q2W (at doses up to 10 mg/kg) schedule has completed enrollment without identification of an MTD. In addition, a dose-escalation cohort using a Q3W schedule at a dose of 15 mg/kg has fully enrolled without identification of an MTD. A dose-expansion phase using a dose and schedule of 10 mg/kg Q2W is currently enrolling. A dose-exploration cohort using an alternative dose and schedule of 20 mg/kg Q4W is ongoing at select sites in the USA in parallel to the ongoing dose-expansion cohorts.

The dose-escalation phase will include subjects with advanced melanoma, RCC, NSCLC, or CRC followed by a dose-expansion phase in subjects with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, pancreatic adenocarcinoma, UBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, HPV-positive cancers, or nasopharyngeal carcinoma. In addition, a dose-exploration cohort will include subjects with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC or pancreatic adenocarcinoma. Therapeutic response criteria for these tumor types are defined in Section 4.2.1.

Up to approximately 1,392 subjects could be required for the dose-escalation (n = 50), dose-exploration (n = 20), and dose-expansion (n = 692 – 1,322 based on emerging safety and clinical activity data) phases of the study. Subjects will be enrolled at approximately 100 sites globally. A study flow diagram of the study design is shown in Figure 3.1-1.

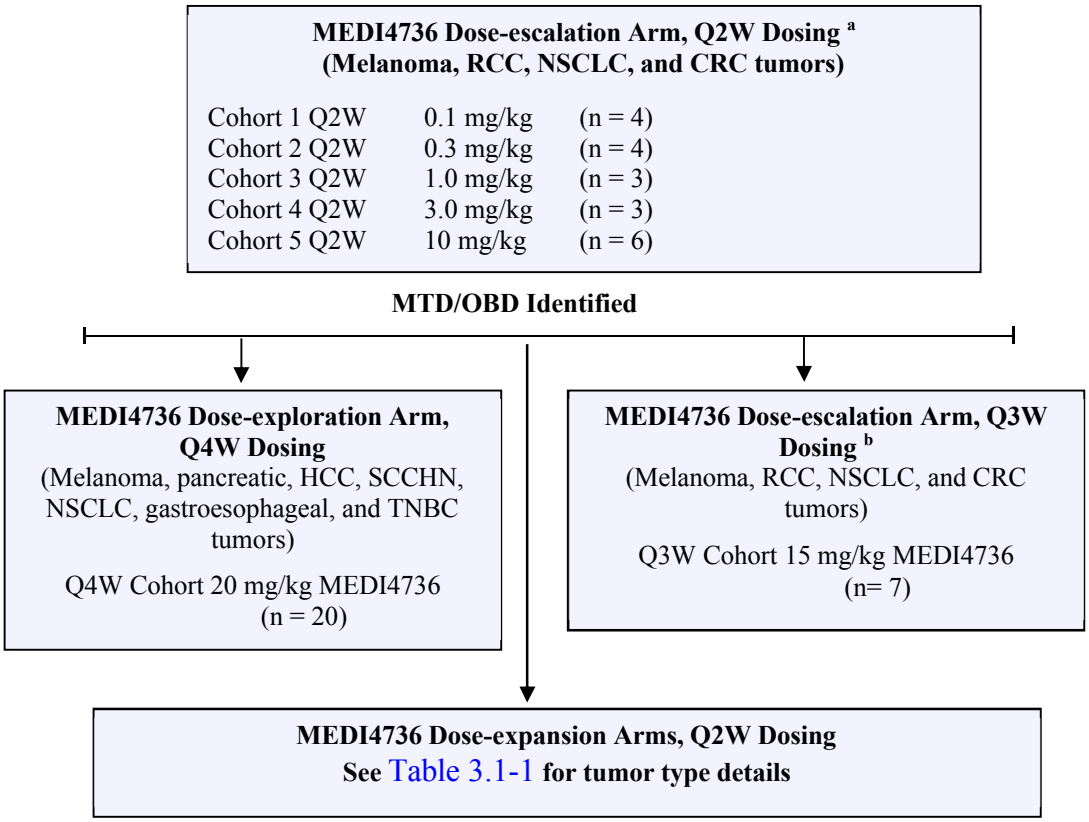

Figure 3.1-1 Study Flow Diagram

CRC = colorectal cancer; HCC = hepatocellular carcinoma; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; OBD = optimal biological dose; PK = pharmacokinetic; Q2W = every 2 weeks; Q3W = every 3 weeks; Q4W = every 4 weeks; RCC = renal cell carcinoma; SCCHN = squamous cell carcinoma of the head and neck; TNBC = triple negative breast cancer.

A minimum of approximately 750 subjects are to be enrolled in this study, including approximately 50 subjects in the dose-escalation phase, 20 subjects in the Q4W dose-exploration cohort, and 692 subjects in the dose-expansion phase, with the possibility of enrolling more subjects in the expansion phase, if necessary, up to a maximum of 1,322 subjects based on the emerging safety and clinical activity profile (total study population = 1,392).

The Q3W MEDI4736 dose-escalation arm, the Q4W dose-exploration cohort, and the MEDI4736 dose-expansion phase will be conducted in parallel.

[a] If 2 or more dose-limiting toxicities are observed in the first cohort, the starting dose may be de-escalated to 0.05 mg/kg given Q3W. Provided the MTD is not exceeded at the 10 mg/kg dose level, higher doses may be further explored based on clinical, safety, and PK/pharmacodynamic data. Intermediate doses may also be explored at the discretion of the sponsor based on available data.

[b] The first cohort of 3-6 subjects will receive MEDI4736 at a dose equivalent to the highest dose level that has not exceeded the MTD or the OBD in the Q2W dose-escalation arm. Dose escalation may proceed with sequential cohorts of 3-6 subjects dependent upon acceptable safety, PK/pharmacodynamic, and clinical data.

Table 3.1-1 Number of Subjects Enrolled by Tumor Type in Dose-expansion Cohorts

Tumor Type	Total Planned Enrollment	Subjects Enrolled as of 20Nov2015	Planned Enrollment Under Amendment 8 and Beyond
Advanced cutaneous melanoma	20	21	0
Uveal melanoma	20-60	24	Up to 36
HCC	20-60	41	Up to 19
SCCHN	20-60	63	0
Squamous NSCLC (Total) 1L 2L ≥ 3L	170-190 10-30 80 80	151 29 51 70	Up to 39
Non-squamous NSCLC (Total) 1L 2L ≥ 3L	110-140 10-30 20-30 80	143 30 34 79	0
Gastroesophageal	20-60	51	Up to 9
TNBC	20-60	40	Up to 20
Pancreatic adenocarcinoma	10-60	31	Up to 29
UBC (Total) Initial UBC subjects Amendment 8 and beyond PD-L1 positive PD-L1 negative Non-evaluable for PD-L1	20-192 20-60 132 ≥ 70 50 12	60 60 0 0 0 0	Up to 132 0 Up to 132 ≥ 70 50 12
GBM (Total) MGMT negative	20-60 ≥ 10	20	Up to 40
Ovarian cancer (Total) Platinum sensitive	20-60 ≥ 10	46	Up to 14
Soft tissue sarcoma	20-60	20	Up to 40
SCLC	20-60	21	Up to 39
MSI-high cancers	20-60	57	Up to 3
HPV-positive tumors (Total) Cervical cancer	20-60 ≤ 10 [a]	22 10	Up to 38
Nasopharyngeal carcinoma	10-60	10	Up to 50
Total	**692-1,322**	**821**	**Up to 508**

GBM = glioblastoma multiforme; HCC = hepatocellular carcinoma; HPV = human papilloma virus; L = line; MGMT = O6-methylguanine-deoxyribonucleic acid methyltransferase promoter methylation; MSI = microsatellite instability; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1; SCCHN = squamous cell carcinoma of the head and neck; SCLC = small-cell lung cancer; TNBC = triple negative breast cancer; UBC = urothelial bladder cancer.

[a] A maximum of 10 cervical cancer subjects will be enrolled out of the initial 20 subjects in the HPV-positive tumors cohort. If the cohort is expanded beyond 20 subjects based on clinical activity, additional cervical cancer subjects may be enrolled.

3.1.1 Dose Escalation

MEDI4736 Dose-escalation Arm, Q2W Dosing

In the dose-escalation phase of the study, MEDI4736 will be administered Q2W, in sequential cohorts of 3-6 subjects each receiving one of 5 doses of MEDI4736 (0.1, 0.3, 1.0, 3.0, or 10 mg/kg) via intravenous (IV) infusion. Dose escalation will be considered completed once an MTD or OBD is identified or the top dose of 10 mg/kg is reached. Provided the MTD is not exceeded at the 10 mg/kg dose level, additional cohorts of 3-6 subjects using doses above 10 mg/kg of MEDI4736 Q2W may be explored based on emerging PK or pharmacodynamic data suggesting maximal suppression of sPD-L1 is not being maintained throughout the dosing interval or T-cell activation has not plateaued, respectively. The first cohort will enroll a minimum of 3 subjects, according to a standard 3+3 design. Subjects in the first cohort will receive a dose of 0.1 mg/kg MED4736. The first IV infusion for subjects in this cohort will be 4 hours in duration; subsequent infusions for subjects in this cohort and all infusions for the remaining cohorts will be approximately 60 minutes in duration. Subsequent cohorts will receive 0.3, 1.0, 3.0, or 10 mg/kg IV Q2W unless an MTD or OBD is identified before all dose-escalation cohorts are completed. Provided the MTD is not exceeded at the 10 mg/kg dose level, higher doses may be further explored based on clinical, safety, and PK/pharmacodynamic data generated from the study. Intermediate doses may be evaluated at the discretion of the sponsor based on available data. If ≥ 2 DLTs, as defined in Section 4.5.7, are observed in the first dose cohort, the starting dose will be de-escalated to half of the previous dose given (0.05 mg/kg) and will be administered Q3W. Refer to Section 4.5.6 for detailed dose-escalation procedures. A total of 20 subjects have been enrolled in the Q2W dose-escalation phase of the study, including 4 subjects in each of the 0.1 and 0.3 mg/kg cohorts, 3 subjects in each of the 1.0 and 3.0 mg/kg cohorts and 6 subjects in the 10 mg/kg cohort. The planned Q2W dose-escalation phase of the study is complete.

MEDI4736 Dose-escalation Arm, Q3W Dosing

Upon completion of dose escalation for the MEDI4736 Q2W dose-escalation arm, a separate dose-escalation arm of MEDI4736 administered Q3W will be initiated. This arm will be conducted in parallel with the dose-expansion phase (see below for description of dose expansion). The first cohort of 3-6 subjects will receive MEDI4736 via IV infusion Q3W at the highest dose level that has not exceeded the MTD or the OBD in the Q2W dose-escalation arm. MEDI4736 Q3W dose escalation may proceed with additional cohorts of 3-6 subjects dependent upon acceptable safety, PK/pharmacodynamic, and clinical data

according to the dose-escalation procedures described in Section 4.5.6. A total of 7 subjects have been enrolled in the 15 mg/kg Q3W dose-escalation arm and the planned Q3W dose-escalation phase of the study is complete.

3.1.2 Dose Exploration

A total of approximately 20 subjects with advanced cutaneous melanoma, uveal melanoma, pancreatic adenocarcinoma, NSCLC squamous histology, NSCLC non-squamous histology HCC, SCCHN, gastroesophageal cancer, or TNBC are being enrolled into the dose-exploration cohort at select sites in the United States. MEDI4736 will be administered Q4W, at a dose of 20 mg/kg MEDI4736 via IV infusion.

3.1.3 Dose Expansion

The dose-expansion phase of the study will be conducted following completion of dose escalation for the MEDI4736 Q2W dose-escalation arm and in parallel with the MEDI4736 Q3W dose-escalation arm. The 10 mg/kg dose administered Q2W was chosen to take into expansion.

A minimum of 20 subjects each with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, gastroesophageal cancer, TNBC, UBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, and HPV-positive cancers will be enrolled into tumor-specific expansion cohorts. In addition, a minimum of 10 subjects each with pancreatic adenocarcinoma or nasopharyngeal carcinoma will be enrolled. No more than 10 subjects with cervical cancer will be enrolled out of the 20 subjects in the HPV-positive cancers dose-expansion cohort. A minimum of 10 subjects without O^6-methylguanine-deoxynucleic acid (DNA) methyltransferase promoter methylation will be enrolled in the GBM cohort. Similarly, a minimum of 10 subjects with platinum sensitivity will be enrolled in the ovarian cancer cohort. Additional subjects, up to a total of 60 subjects in any of these dose-expansion cohorts may be enrolled if promising clinical activity is observed in that cohort. If the HPV-positive cancers, MSI-high cancers, GBM, ovarian cancer, or soft tissue sarcoma cohorts are expanded beyond 20 subjects each, enrollment may be prioritized to tumor sub-type(s) that showed promising clinical activity, at the sponsor's discretion. Approximately 110-140 subjects with non-squamous histology NSCLC will be enrolled including approximately 10-30 subjects who are treatment-naive, approximately 20-30 subjects who have received 1 prior line of therapy, and approximately 80 subjects who have received at least 2 prior lines of therapy. Approximately 170-190 subjects with squamous histology NSCLC will be enrolled including approximately 10-30 subjects who are treatment-naive,

approximately 80 subjects who have received 1 prior line of therapy, and approximately 80 subjects who have received at least 2 prior lines of therapy.

An evaluation of a possible correlation between clinical activity of MEDI4736 and potential biomarkers (eg, PD-L1 expression on tumor or sPD-L1) will be ongoing throughout the study. Initially, tumoral PD-L1 expression will be assessed on screening samples after enrollment on an ongoing basis. After the first 20-40 subjects in each of HCC, gastroesophageal cancer, TNBC, UBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, HPV-positive cancers, pancreatic adenocarcinoma, and nasopharyngeal carcinoma dose-expansion cohorts are enrolled, additional subjects in the applicable cohorts may be required to have tumoral PD-L1 expression as determined by prospective testing prior to enrollment. Under previous amendments of this protocol, a minimum of 5-10 SCCHN subjects were required to have tumoral PD-L1 expression. That requirement has been met and enrollment into the SCCHN cohort is complete. Tumoral PD-L1 expression as determined by prospective testing prior to enrollment will be required for the squamous and non-squamous NSCLC cohorts as described below in Table 3.1.3-1.

Table 3.1.3-1 NSCLC Dose-expansion Cohort PD-L1 Expression Requirements

Cohort	Total Planned Enrollment (n)	Tumoral PD-L1 Requirement (Under Amendment 7)
Squamous NSCLC (Total) 1L 2L ≥ 3L	170-190 10-30 80 80	Minimum of 80 PD-L1-positive Minimum of 10 PD-L1-positive Minimum of 35 PD-L1-positive Minimum of 35 PD-L1-positive
Non-squamous NSCLC (Total) 1L 2L ≥ 3L	110-140 10-30 20-30 80	All remaining subjects PD-L1-postive All remaining subjects PD-L1-positive All remaining subjects PD-L1-positive All remaining subjects PD-L1-positive

L = line; NSCLC = non-small cell lung cancer; PD-L1 = programmed death ligand 1.

Under Amendment 8 and beyond of this protocol, the UBC cohort will be expanded to evaluate the antitumor activity of MEDI4736 in subjects with PD-L1-positive UBC and validate the potential of PD-L1 expression (determined by IHC) to predict response to MEDI4736 treatment. Approximately 132 additional UBC subjects will be enrolled in this cohort in order to include a minimum of 70 PD-L1-positive subjects and 50 PD-L1-negative subjects, and approximately 12 subjects with non-evaluable PD-L1 status. [redacted]

[redacted] In addition to validating the currently proposed PD-L1 selection criteria (≥ 25% PD-L1 staining on tumor or immune cells), inclusion of patients with PD-L1 staining above and below this cutoff will enable exploratory analyses potentially leading to a refinement of PD-L1 status definitions or to the qualification of alternative biomarkers for selection of UBC subjects most likely to benefit from treatment with MEDI4736 in future clinical studies.

To ensure that all of the additional UBC subjects contribute to the biomarker validation, subjects must have measurable disease at baseline by blinded independent central review (BICR). PD-L1 status will be determined by a central testing laboratory and will be derived from a fresh tumor biopsy taken during screening or an available tumor sample taken from ≤ 6 months prior to study entry. The tumor sample (fresh and/or recent within 6 months prior to study entry) used for PD-L1 analysis must be shipped to, and confirmed as received by, the Sponsor or central vendor prior to the first dose of MEDI4736. It is highly recommended that efforts are taken to ensure presence of tumor cells within the tumor sample prior to shipping for PD-L1 analysis. The tumor PD-L1 status will be determined by IHC with PD-L1-positive samples defined as ≥ 25% tumor cell or immune cell staining and PD-L1-negative samples defined as < 25% tumor cell and immune cell staining. In cases where subjects have more than one tumor sample from ≤ 6 months prior to study entry available for testing, PD-L1 status will be derived from the most recent evaluable sample. PD-L1 status determined by IHC testing from tumor samples evaluated for screening into MedImmune Study D4190C00010 may be used if derived from a sample taken ≤ 6 months prior to study entry. Additional archival tumor tissue, from beyond 6 months prior to study entry is also required, if available.

As of 20Nov2015, 821 subjects have been treated in the dose-expansion phase of the study. Enrollment into dose-expansion cohorts may be discontinued at the discretion of the sponsor should emerging clinical or preclinical data suggest that continued treatment may not be beneficial to a given cohort.

All subjects will be evaluated regularly and their clinical status classified according to RECIST guidelines (v1.1; Eisenhauer et al, 2009) with modifications (see Section 5.2.6 for a description of disease evaluation) except for subjects with GBM who will have their clinical status classified according to the Response Assessment in Neuro-oncology (RANO) guidelines (Wen et al, 2010). Modification of RECIST as described may discourage early discontinuation of MEDI4736 and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy

analysis will be conducted primarily based on RECIST v1.1. All subjects will be followed indefinitely for survival until the sponsor closes the study or for the maximum duration per institutional standards. Adverse events and SAEs will be followed as per Section 6.4.

The endpoints to be measured in this study are described in Section 7.3.

3.2 Estimated Duration of Subject Participation

Subjects in the dose-escalation, dose-exploration, and dose-expansion phases will be treated for up to 12 months until confirmed progressive disease (PD), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur. In the event of PD, subjects may continue to receive MEDI4736 in the absence of clinical deterioration (see Section 5.2.6) and if investigators consider that subjects continue to receive benefit from treatment. Subjects who achieve and maintain disease control (DC; ie, CR, PR, or SD) or clinical benefit through to the end of the 12-month MEDI4736 treatment period will enter follow-up. Upon evidence of PD during follow-up, subjects will be re-administered MEDI4736 for up to another 12 months. Only one round of retreatment with MEDI4736 will be allowed. All subjects will be followed for survival and anticancer therapy indefinitely unless the sponsor decides to end the study.

3.3 Study-stopping Criteria

If the following occurs, administration of investigational product will be stopped and no additional subjects will be entered into the study:

- Any safety finding assessed as related to investigational product that, in the opinion of the sponsor in consultation with a MedImmune safety review committee (or equivalent), contraindicates further dosing of study subjects.

If any such safety findings occur, further administration of the investigational product will be stopped and no further subjects will be entered into the study. Thereafter the regulatory authorities and Institutional Review Boards (IRBs)/Independent Ethics Committees (IECs) will be notified and a prompt cumulative review of safety data and the circumstances of the event in question will be conducted (see Section 6.5). The findings will be shared with the regulatory authorities and the IRBs/IECs. If it is deemed appropriate by the sponsor after review by a MedImmune safety review committee (or equivalent), justification for stopping the study will be sent to the regulatory authorities and the IRBs/IECs as required.

Any subjects who have already received investigational product and are currently in the study at the time study-stopping criteria are met will continue to be followed by the investigator for safety (see Section 6.4.1).

Withdrawal criteria for individual subjects are provided in Section 4.2.3.

3.4 Rationale for Study Design and Doses

An open-label dose-escalation study with a dose-expansion arm is a common study design in early-phase oncology studies and is considered appropriate for a FTIH study.

The primary objective of the dose-escalation phase of this study is to determine the MTD or OBD of MEDI4736 in subjects with advanced melanoma, CRC, NSCLC, or RCC refractory to standard therapy or for which no standard therapy exists. This study population is appropriate for testing a FTIH compound with potential for significant toxicities. An unmet medical need exists for these patient populations given that they have exhausted alternative treatment options or available therapies. Moreover, subjects with less advanced disease still have options for life-prolonging therapy, and administration of an agent without proven benefit would be inappropriate.

The tumor types included in the dose-escalation phase are of interest for several reasons. There is a high unmet need for new treatment options in each of these diseases. Melanoma, NSCLC, and RCC are known to respond to immunotherapy (Hodi et al, 2010; Rosenblatt and McDermott, 2011; Topalian et al, 2012). Taken together with the proposed immunomodulatory mechanism of MEDI4736, there may be a greater chance of seeing antitumor activity in these malignancies.

The primary objective of the dose-expansion phase of this study is to determine the safety profile of MEDI4736 in subjects with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, pancreatic adenocarcinoma, UBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, HPV-positive cancers, and nasopharyngeal carcinoma. The dose-expansion phase will further evaluate the safety and preliminary antitumor activity of MEDI4736 at the MTD or OBD as assessed by RECIST v1.1 guidelines. In addition, under Amendment 8 of this protocol, the UBC cohort will be expanded to evaluate the antitumor activity of MEDI4736 in subjects with PD-L1-positive UBC and validate the potential for PD-L1 expression to predict response to MEDI4736 treatment.

The malignancies included in the dose-expansion phase were based on the greatest unmet medical need, tumoral expression of PD-L1, and underlying biology in these tumor types. Although, these tumor types have approved first-line treatments, further therapeutic options are limited with second- and third-line treatments generally providing short OS. These tumor types present an opportunity for an anti-PD-L1 antibody to demonstrate benefit.

Preliminary data from this study as well as emerging data from other antibodies targeting the PD-1/PD-L1 pathway suggest that subjects with multiple tumor types may benefit from treatment with an agent such as MEDI4736. Cancers that have historically shown responsiveness to immunotherapy may be likely to benefit from immune checkpoint blockade. Treatment of melanoma with immunotherapy is well established, with improvements in OS shown with anti-CTLA-4 (Hodi et al, 2010). Similarly, treatment of early stage bladder cancer with Bacillus Calmette-Guerin is well established and reduces the risk of recurrence (Sheley et al, 2000). While no longer considered to be a standard treatment, sarcoma was one of the first cancers to show response to immunotherapy with Coley's toxins (McCarthy, 2006) and recent reports suggest sarcoma may be responsive to PD-L1 targeting antibodies (Sagiv-Barfi et al, 2014). In addition to this early clinical approach, unpublished data from syngeneic mouse models of sarcoma suggest that PD-1/ PD-L1 targeting antibodies may have activity in this disease.

Cancers with viral and bacterial etiologies are known to express cell surface antigens which may be recognized by the immune system and immune checkpoint blockade may be advantageous in these diseases. Included in the expansion phase are cohorts designed to evaluate this hypothesis. The HPV -positive cancers cohort and nasopharyngeal carcinoma cohort will enroll subjects with HPV or Epstein bar virus associated cancers, respectively. Similarly, both SCCHN (HPV) and HCC (hepatitis B virus and hepatitis C virus [HCV]) have subpopulations with viral etiologies. Lastly, gastroesophageal cancer is associated with bacterial infection and may benefit from immunotherapy. For example, in a Phase 2 study in HCC, treatment with the anti-CTLA-4 antibody tremelimumab resulted in radiographic responses in 18% of subjects while demonstrating a decline in HCV load and an increase in anti-HCV immune response (Sangro et al, 2012). Tremelimumab has also demonstrated antitumor activity as monotherapy in gastroesophageal cancer and in combination with gemcitabine in pancreatic adenocarcinoma (Ralph et al, 2010; Aglietta et al, 2012).

Recent data suggest that NSCLC patients with a history of heavy smoking may be more prone to respond to an anti-PD-1/PD-L1 antibody. Specifically, higher ORR following treatment with MPDL3280A were observed in NSCLC subjects with a history of smoking as compared to those without a history of smoking (Soria et al, 2013). One potential explanation

for this observation is that heavy smoking may lead to a greater frequency of mutations within the tumor and subsequently a greater diversity of tumor associated antigens that are recognizable by the immune system. Considering the preliminary data presented by Soria et al, it is reasonable to extend the exploration of this hypothesis into additional tumor types known to be associated with smoking (NSCLC, SCLC, SCCHN, and bladder cancer). These same tumor types, along with melanoma, cervical cancer, MSI-high cancers, and gastroesophageal cancer are also known to have a high mutational burden (Alexandrov et al, 2013).

Based on early antitumor activity signals in this study as well as from similar agents, the dose-expansion phase of the study will further explore the safety and clinical activity of MEDI4736 in specific subpopulations of NSCLC to support future studies planned in this tumor type. Specifically, the expansion phase will test the hypothesis that MEDI4736 will result in at least a 10% ORR in subjects with squamous NSCLC who have received 1 prior line of therapy and with squamous and non-squamous NSCLC who have received at least 2 prior lines of therapy. In addition, the clinical activity of MEDI4736 will be explored in subjects who are treatment-naïve as a basis for potential future studies.

Tumor infiltrating lymphocytes are found in many tumors and are thought to be a marker of an immune response against the tumor. Cancers with high levels of infiltrating lymphocytes may benefit from checkpoint blockade. In TNBC and ovarian cancer, lymphocytic infiltration has been shown to be a strong prognostic factor (Loi et al, 2013; Sato et al, 2005; Leffers et al, 2009). Similarly, cancers with MSI are also known to harbor high levels of infiltrating lymphocytes targeting frame-shift peptides associated with MSI (Schwitalle et al, 2008). Ultimately, even in those patients with high levels of TILs, the underlying malignancy will usually recur and lead to death. This may suggest that although an immune response to the tumor has begun, there may be immune regulatory mechanisms hindering the antitumor response. These tumors may represent populations that could benefit from anti-PD-L1 therapy.

Preclinical evidence suggests that anti-PD-1/PD-L1 therapy may be beneficial in GBM, particularly in combination with radiotherapy (Zeng et al, 2013). Clinical data also show that immune checkpoint blockade with an anti-CTLA-4 MAb is active in patients with brain metastases, suggesting that immune recognition of cancer within the central nervous system (CNS) is possible. (Queirolo et al, 2014).

Current experience with immunotherapies suggests that only a subset of any given patient population is likely to benefit from treatment and that it might be beneficial to enrich the

patient population by selecting patients likely to respond to therapy. Independent data from multiple sources using different assays and scoring methods suggest that PD-L1 expression on tumor cells and/or tumor-infiltrating cells may be associated with greater clinical benefit in response to treatment with single agent anti-PD-1/PD-L1 agents:

- PD-L1 expression has been shown to correlate with clinical outcomes (ORR, progression-free survival [PFS], OS) in subjects with NSCLC treated with anti-PD-1/PD-L1 antibodies including pembrolizumab, nivolumab, atezolizumab, or MEDI4736 (Garon et al, 2015; Borghaei et al, 2015; Vansteenkiste et al, 2015; Besse et al, 2015; Rizvi et al, 2015).
- Similarly, PD-L1 expression has been shown to correlate with ORR, PFS, and OS in subjects with UBC treated with atezolizumab (Rosenberg et al, 2015).

[redacted]

The totality of the emerging data suggest that PD-L1 expression may improve the probability and/or quality of response to single agent PD-1/PD-L1 pathway inhibitors, and therefore may have merit as an enrichment tool. The tumor types included in the expansion phase are thought to express PD-L1 over a broad range of frequencies and will allow for an exploration of the correlation between tumor expression of PD-L1 and the clinical activity of MEDI4736. Access to fresh tumor biopsies and archival tumor tissue in the dose-expansion phase will support exploration of potential biomarkers of response, including PD-L1, for MEDI4736. Based on currently available data from patients treated with MEDI4736 and similar molecules, clinical outcomes in UBC appear to correlate with PD-L1 expression. Data from the recently presented Phase 2 study of atezolizumab in previously treated UBC suggest that patients with tumors defined as IC 2/3 by the Ventana SP142 IHC assay (ie, ≥ 5% of immune cells staining positive for PD-L1) , achieved higher ORR (27%) and improved OS compared to those patients with tumors defined as IC 1 (≥ 1% but < 5% immune cell staining; ORR = 10%) or IC 0 (< 1% immune cell staining; ORR = 9%). In this study population, 100 of 311 subjects (32%) were defined as IC 2/3, while 211 of 311 subjects (68%) were defined as IC 0 or IC 1. The data available from Study 1108 also support the hypothesis that PD-L1 expression may be useful as a selection strategy to identify UBC patients most likely to benefit from treatment with MEDI4736. Based on initial prevalence data from the study, it is estimated that approximately 60% of UBC subjects may be classified as PD-L1-positive as defined by ≥ 25% staining in either tumor cells or immune cells. Validation of a PD-L1 expression biomarker cutoff is warranted to allow for selection of UBC patients most likely to benefit from treatment with MEDI4736 alone and will inform ongoing registrational studies in this indication.

The study will also allow for retreatment with MEDI4736 upon evidence of PD. Demonstration of any clinical benefit with reinduction in the absence of significant AEs would suggest that future studies should include a similar treatment option.

The secondary endpoint of antitumor activity will be assessed according to RECIST v1.1 guidelines with modifications. Response to immunotherapy may differ from typical responses observed with cytotoxic chemotherapy including the following (Wolchok et al, 2009):

1. Response to immunotherapy may be delayed
2. Response to immunotherapy may occur after PD by conventional criteria
3. The appearance of new lesions may not represent PD with immunotherapy
4. Stable disease while on immunotherapy may be durable and represent clinical benefit

To account for these differences, the RECIST criteria will be modified so that PD must be confirmed at least 4 weeks after the initial assessment of PD in the absence of clinical deterioration. Treatment with MEDI4736 will continue between the initial assessment of progression and confirmation for progression. In addition, subjects may continue to receive MEDI4736 beyond confirmed PD in the absence of clinical deterioration (see Section 5.2.6) and if investigators consider that subjects continue to receive benefit from treatment. In the absence of clinical deterioration, RECIST criteria with such modifications may discourage the early discontinuation of MEDI4736 and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria.

The starting dose of 0.1 mg/kg to be evaluated in this FTIH study was selected to provide a potentially pharmacologically active dose with transient PD-L1 suppression and was approximately 1/30 of the maximum recommended starting dose (MRSD). [redacted]

The dose-escalation scheme of 0.1, 0.3, 1.0, 3.0, and 10 mg/kg MEDI4736 was designed to rapidly achieve dose levels at which clinical activity may be observed while maintaining an adequate safety margin. The range of doses selected was based on predicted PD-L1 suppression and considerable safety margins in relation to the NOAEL.

While both Q2W and Q3W dosing schedules are supported based on PK modeling data derived from the nonclinical and clinical studies performed to date, the Q2W dosing schedule will be taken into the dose-expansion phase first.

[redacted] This dosing regimen is expected to offer the opportunity to observe a clinical response in subjects with a variety of solid tumor malignancies.

[redacted]

[redacted]

4 STUDY PROCEDURES

4.1 Subject Participation and Identification

Study participation begins once written informed consent is obtained (see Section 10.3 for details). Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive voice/web response system [IVRS/IWRS]), and the screening evaluations may begin to assess study eligibility (inclusion/exclusion) criteria. The SID number will be used to identify the subject during the screening process and throughout study participation, if applicable.

A master log of all consented subjects will be maintained at the site and will document all screening failures (ie, subjects who are consented but do not meet study eligibility criteria) including the reason(s) for screening failure (see Section 9.1 for details).

4.2 Subject Selection and Withdrawal

The subjects in this study will be adults 18 years of age or older. Subjects in the dose-escalation phase will have advanced melanoma, RCC, NSCLC, or CRC refractory to standard therapy or for which no standard therapy exists. Subjects in the dose-exploration cohort will be adults with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, or pancreatic adenocarcinoma. Subjects in the dose-expansion phase of the study will be adults with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, pancreatic adenocarcinoma, UBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, HPV-positive cancers, or nasopharyngeal carcinoma. If approved first-line standard therapy is available, subjects in the dose-expansion phase must have failed, be intolerant to, be ineligible for, or have refused treatment.

The investigator (physician) or qualified designee will discuss the study with a subject/the legal representative of a subject who is considered a potential candidate for the study and provide the subject/legal representative with the study-specific informed consent form(s) (ICF[s]) approved by the IRB/IEC. The investigator or designee will address any questions and/or concerns that the subject/legal representative may have and, if there is continued interest, will secure written informed consent for participation in the study. Written informed consent and any locally-required authorization (eg, Health Insurance Portability and Accountability Act [HIPAA] authorization in the USA, European Union [EU] Data Privacy Directive authorization in the EU), will be obtained prior to conducting any protocol-specific

procedures, including screening evaluations or medication washouts. See Section 10.3 for additional details concerning informed consent.

4.2.1 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1. Written informed consent and any locally-required authorization (eg, HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations
2. In the dose-escalation phase: histologically- or cytologically-confirmed advanced melanoma, RCC, NSCLC, or CRC that is refractory to standard therapy and for which no standard therapy exists
3. In the dose-expansion phase: histologically or cytologically confirmed advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous and non-squamous histology, gastroesophageal cancer, TNBC, pancreatic adenocarcinoma, UBC, GBM, epithelial ovarian cancer, soft tissue sarcoma (excluding gastrointestinal stromal tumor), SCLC, MSI-high cancers, HPV-positive cancers, or nasopharyngeal carcinoma
4. HCC subjects must be of Child-Pugh class A (not amenable to or refractory to locoregional therapy). Subjects with HCC associated with hepatitis B virus must be receiving adequate antiviral therapy
5. UBC cohort: Subjects must have histologically or cytologically confirmed inoperable or metastatic transitional cell (including transitional cell and mixed transitional cell/non-transitional cell histologies) carcinoma of the urothelium (including the urinary bladder, ureter, urethra, and renal pelvis).
    a. Subjects must have received and have progressed or are refractory to at least 1 but not more than 2 prior lines of systemic therapy for inoperable or metastatic disease, including a standard platinum-based regimen. Interval progression between 2 lines of therapy defines separate lines of therapy. Prior definitive chemoradiation for locally advanced disease, adjuvant treatment, or neoadjuvant treatment will be considered a prior line of therapy, provided that progression has occurred < 12 months from therapy [for chemoradiation and adjuvant treatment] or < 12 months from surgery [for neoadjuvant treatment].
6. Subjects with histologically or cytologically documented NSCLC must present with Stage IIIB/ Stage IV disease (according to version 7 of the International Association for the Study of Lung Cancer Staging Manual in Thoracic Oncology), or with recurrent or progressive disease following multimodal therapy (radiation therapy, surgical resection, or definitive chemoradiation therapy) for locally advanced disease
    a. For advanced stage NSCLC, maintenance therapy following platinum doublet-based chemotherapy is not considered as a separate regimen of therapy.
    b. Prior platinum containing neoadjuvant chemotherapy for operable disease, adjuvant chemotherapy for completely resected disease or definitive chemoradiation therapy given for locally advanced disease is not considered a separate regimen of therapy.

c. For first-line therapy NSCLC cohorts: Subjects must not have received prior chemotherapy or systemic anti-neoplastic therapy (eg, tyrosine kinase inhibitor [TKI], MAb therapy) for advanced disease. Prior surgery and/or localized irradiation are permitted.

d. For second-line therapy NSCLC cohorts: Subjects without known sensitizing epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements must have experienced disease progression or recurrence following one prior platinum based doublet chemotherapy for advanced disease. Subjects with sensitizing EGFR mutations or ALK rearrangements must have experienced disease progression or recurrence following either a TKI therapy or prior platinum based doublet chemotherapy for advanced disease.

e. For third-line or greater therapy NSCLC cohorts: Subjects must have experienced disease progression or recurrence after both a platinum-doublet based chemotherapy regimen and at least 1 additional systemic therapy for advanced disease. For subjects with sensitizing EGFR mutations or ALK rearrangements, the additional therapy must include a TKI therapy. Additional therapies are defined as agents that are US FDA- or European Medicine Agency-approved for use after a prior regimen, given as monotherapy or in combination; or vinorelbine- or gemcitabine-containing regimens given as part of locally accepted standard-of-care, for subjects who are not candidates for docetaxel.

f. For subjects in the Q4W dose-exploration cohort, subjects are eligible if they meet any of the criteria for first-line, second-line, or third-line or greater therapy as described in 5c, 5d, or 5e above.

7. Subjects with SCCHN must have disease that is either metastatic or recurrent and deemed to be incurable by the investigator (subjects who refuse radical resection for recurrent disease are eligible).
8. MSI-high cancers must have defective DNA mismatch repair by either:
   a. High-frequency microsatellite instability with changes detected in 2 or more panels of microsatellite markers (BAT-25, BAT-26, NR-21, NR-24 and MONO-27); OR,
   b. Immunohistochemical analysis demonstrating absence of protein expression of any 1 or more of the following proteins: MLH1, MSH2, MSH6, PMS2.
9. Subjects with HPV-positive cancers are eligible if they have a confirmed HPV-positive tumor by local laboratory. Subjects with HPV-positive SCCHN are only eligible for the SCCHN specific cohort. No more than 10 subjects with cervical cancer will initially be enrolled in this cohort
10. GBM cohort: Subjects with GBM must not have significant edema or shift from midline by intracranial imaging, or be symptomatic due to edema. A minimum of 10 subjects without O^6-methylguanine-DNA methyltransferase promoter methylation will be enrolled in the GBM cohort
11. Epithelial ovarian cancer cohort: A minimum of 10 subjects with platinum sensitivity will be enrolled in the ovarian cancer cohort
12. If an approved first-line standard therapy is available, subjects must have failed, be intolerant to, be ineligible for, or have refused treatment

13. Progressive disease as assessed by the investigator or treatment naïve at the time of study entry
14. Tumoral PD-L1 expression requirements are as follows:
    a. HCC, gastroesophageal cancer, TNBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, HPV-positive cancers, pancreatic adenocarcinoma, and nasopharyngeal carcinoma dose-expansion cohorts: after the first 20-40 subjects in each cohort are enrolled, additional subjects in the applicable cohorts may be required to have tumoral PD-L1 expression as determined by prospective testing prior to enrollment
    b. Under previous versions of this protocol, a minimum of 5-10 SCCHN subjects were required to have tumoral PD-L1 expression. That requirement has been met, and enrollment into this cohort is complete
    c. NSCLC (squamous and non-squamous) dose-expansion cohorts:
        - Non-squamous NSCLC: all remaining subjects to be enrolled will be required to have tumoral PD-L1 expression as determined by prospective testing prior to enrollment
        - Squamous NSCLC: A minimum of 10 subjects in the first-line therapy cohort, and a minimum of 35 subjects in each of the second-line therapy and third-line or greater therapy cohorts will be required to have tumoral PD-L1 expression as determined by prospective testing prior to enrollment
    d. UBC cohort:
        - Subjects must consent to provide an archived tumor specimen from within 6 months prior to study entry (ie, from subject signing consent to participate in the study) for PD-L1 IHC analysis. If not available, subjects must have at least 1 lesion amenable to biopsy and consent to provide a pre-treatment fresh biopsy; tumor lesions planned for biopsy should not be lesions used as RECIST target lesions. Tumor tissue for PD-L1 analysis must be shipped to, and confirmed as received by, the Sponsor or designated central vendor prior to the first dose of investigational product. However, subjects may be dosed before PD-L1 results are known. It is highly recommended that efforts are taken to confirm presence of tumor cells within the tumor sample prior to shipping for PD-L1 analysis. In addition to the tumor tissue required for PD-L1 analysis, subjects in the UBC cohort must also provide additional older archival tissue regardless of age, if available.
15. Age $\geq$ 18 years at time of study entry
16. Females of childbearing potential who are sexually active with a nonsterilized male partner must use 2 methods of contraception, at least one of which must be highly effective, from screening, and must agree to continue using such precautions for 90 days after the final dose of MEDI4736; 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 drug treatment 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
    a. Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or

postmenopausal (defined as 12 months with no menses without an alternative medical cause)

b. Subjects must use 2 acceptable methods of effective contraception, at least one of which is highly effective, as described in Table 4.2.1-1

c. Female subjects should also refrain from breastfeeding throughout this period

17. Nonsterilized males who are sexually active with a female partner of childbearing potential must use a male condom with spermicide and another highly effective method of contraception (see Table 4.2.1-1) from Day 1 and for 90 days after receipt of the final dose of investigational product. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period
18. Eastern Cooperative Oncology Group (ECOG) status of 0 or 1
19. Adequate organ and marrow function as defined below (without growth factor or transfusion support within 28 days prior to first dose of investigational product):
    a. Hemoglobin $\geq$ 9 g/dL
    b. Absolute neutrophil count $\geq$ 1,500/mm^3
    c. Platelet count $\geq$ 100,000/mm^3
    d. AST and ALT $\leq$ 2.5 $\times$ institutional upper limit of normal (ULN); for subjects with HCC or liver metastases, AST or ALT $\leq$ 5 $\times$ ULN
    e. Bilirubin $\leq$ 1.5 $\times$ ULN; for subjects with HCC or subjects with documented/suspected Gilbert's disease, bilirubin $\leq$ 3 $\times$ ULN
    f. Creatinine clearance $\geq$ 50 mL/min (or $\geq$ 30 mL/min for subjects with UBC) as determined by the Cockcroft-Gault equation (Cockcroft and Gault, 1976) or by 24-hour urine collection for determination of creatinine clearance
20. Subjects must have at least 1 measurable lesion per RECIST v1.1 guidelines or per RANO guidelines (Wen et al, 2010) for subjects with GBM
    a. A previously irradiated lesion can be considered a target lesion if the lesion is well defined, measurable per RECIST v1.1, and there is objective evidence of interval increase in size
    b. For subjects in the UBC cohort, measurable disease per RECIST v1.1 must be confirmed by BICR prior to enrollment
21. Available unstained archived tumor tissue sample in sufficient quantity to allow for pharmacodynamic analyses. Note: a biopsy must be performed for all subjects for which suitable archived tumor sample is not available (eg, recently diagnosed subjects or diagnosed with fine needle aspiration). In addition to the tumor tissue requirements specified in inclusion criterion 14d, subjects in the UBC cohort must also provide additional older archival tissue regardless of age, if available. (See inclusion criterion 14d for tissue requirements for the UBC cohort.)
22. Life expectancy $\geq$ 16 weeks
23. At least 1 lesion amenable to biopsy (dose-expansion phase only, excluding GBM subjects) as described in Section 5.2.7.2. See inclusion criterion 14d for tissue requirements for the UBC cohort.

24. Willingness to provide consent for biopsy samples (dose-expansion phase only). Tumor biopsies will be required for all subjects as described in Section 5.2.7.2. Tumor lesions planned for biopsy should not be lesions used as RECIST target lesions. Note: biopsies are optional for subjects with GBM. If a biopsy is not performed for GBM subjects, an archival tissue sample will be required for study entry. Note: for subjects in the UBC cohort, this requirement does not apply if an archival tumor sample from within 6 months prior to study entry has been provided
25. In the dose-exploration cohort: histologically or cytologically confirmed advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous and non-squamous histology, gastroesophageal cancer, TNBC, or pancreatic adenocarcinoma

Table 4.2.1-1 Highly Effective Methods of Contraception (< 1% Failure Rate)

Barrier/Intrauterine Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a]	Etonogestrel implants; eg, Implanon or Norplan • Intravaginal device; eg, ethinylestradiol and etonogestrel • Medroxyprogesterone injection: e.g. Depo-Provera • Normal and low dose combined oral contraceptive pill • Norelgestromin/ethinylestradiol transdermal system • Cerazette (desogestrel)

Note: A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective (eg, 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).

[a] This is also considered a hormonal method.

4.2.2 Exclusion Criteria

Any of the following would exclude the subject from participation in the study:

1. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study
2. Receipt of any immunotherapy, BRAF inhibitor (in cutaneous melanoma and uveal melanoma subjects), or investigational anticancer therapy within 4 weeks prior to the first dose of MEDI4736; in the case of MAbs (for investigational use or immunotherapy), 6 weeks prior to the first dose of MEDI4736
3. Any prior Grade ≥ 3 irAE while receiving immunotherapy, including anti-CTLA-4 treatment, or any unresolved irAE > Grade 1.
4. For all subjects, prior exposure to any anti-PD-1 or anti-PD-L1 antibody. For subjects in the UBC cohort, prior treatment with immunotherapy agents including, but not limited to, tumor necrosis factor receptor superfamily agonists or checkpoint inhibitors or natural

killer (NK) cell inhibitors including agents targeting KIR, PD-1, PD-L1, CTLA-4, OX40, CD27, CD137 (4-1BB), CD357 (GITR), and CD40. Prior treatment with Bacillus Calmette-Guerin therapy is permitted.

5. Any concurrent chemotherapy, immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable.
   Note: Local treatment of isolated lesions for palliative intent is acceptable (eg, by local surgery or radiotherapy)
6. Current or prior use of immunosuppressive medication within 28 days before the first dose of MEDI4736, with the exceptions of intranasal, topical, and inhaled corticosteroids or systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent (2 mg/day of dexamethasone or equivalent for subjects with GBM). Subjects with GBM must be on a stable dose of steroids for ≥ 7 days prior to study entry and prior to baseline imaging
7. Active or prior documented autoimmune disease within the past 2 years
   Note: Subjects with vitiligo, Grave's disease, Hashimoto's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded
8. Active or prior documented inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis)
9. History of primary immunodeficiency
10. History of organ transplant that requires use of immunosuppressives
11. Known allergy or reaction to any component of the MEDI4736 formulation.
12. Untreated CNS metastatic disease, leptomeningeal disease, or cord compression. Note: Subjects previously treated for CNS metastases that are radiographically and neurologically stable for at least 42 days and do not require corticosteroids (of any dose) for symptomatic management for at least 14 days prior to the first dose of MEDI4736 are not excluded.
13. Other invasive malignancy within 2 years except for noninvasive malignancies such as cervical carcinoma in situ, non-melanomatous carcinoma of the skin or ductal carcinoma in situ of the breast that has/have been surgically cured. Cancer subjects with incidental histologic findings of prostate cancer that, in the opinion of the investigator, is not deemed to require active therapy (eg, incidental prostate cancer identified following cystoprostatectomy that is tumor/node/metastasis stage ≤ pT2N0) may be enrolled, pending discussion and approval with the study physician.
14. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to National Cancer Institute's (NCI's) Common Terminology Criteria for Adverse Events (CTCAE) (NCI CTCAE v4.03) Grade 0 or 1, or to levels dictated in the inclusion/exclusion criteria with the exception of alopecia. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by MEDI4736 may be included (eg, hearing loss) after consultation with the MedImmune medical monitor.
15. Major surgical procedure (as defined by the investigator) within 30 days prior to the first dose of MEDI4736 or still recovering from prior surgery
16. Females who are pregnant or lactating

17. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, severe active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirement or compromise the ability of the subject to give written informed consent
18. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results
19. Known history of tuberculosis
20. Subjects who are known to be human immunodeficiency virus (HIV) positive
21. Subjects who are known to be hepatitis B or C positive, except for subjects with HCC
22. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving MEDI4736
23. Subjects with pancreatic adenocarcinoma must not have more than 50% of the liver parenchyma replaced by tumor
24. Subjects with HCC must not have a history of bleeding from esophageal varices, unless the varices have been treated with no active bleeding within 30 days prior to the first dose of MEDI4736
25. Prior participation in clinical studies that include MEDI4736 alone or in combination, where the study has registrational intent and the analyses for the primary endpoint have not yet been completed

4.2.3 Withdrawal Criteria

Permanent discontinuation of investigational product: An individual subject will not receive any further investigational product if any of the following occur in the subject in question:

1. Withdrawal of consent or lost to follow-up
2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing
3. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
4. Pregnancy or intent to become pregnant
5. Any AE that meets criteria for discontinuation as defined in Appendix 15
6. Adverse event related to MEDI4736 that is Grade ≥ 3, with the exception of toxicities that do not meet criteria for discontinuation as defined in Appendix 15
7. Dose-limiting toxicity (See Section 4.5.7 for definition of DLT)
8. Grade ≥ 3 infusion reaction
9. Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits
10. Initiation of alternative anticancer therapy including another investigational agent

11. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with MEDI4736

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment. Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study (see Section 4.7).

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 6.4, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

Withdrawal of consent: If consent is withdrawn, the subject will not receive any further investigational product or further study observation. Note that the subject may be offered additional tests or tapering of treatment to withdraw safely.

Lost to follow-up: Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed (as defined in Section 4.8) such that there is insufficient information to determine the subject's status at that time.

- Note: Subjects who refuse continuing participation in the study, including phone contact, should be documented as "withdrawal of consent" rather than "lost to follow-up." Investigators should document attempts to re-establish contact with missing subjects throughout the study period. If contact with a missing subject is re-established, the subject should not be considered lost to follow-up and any evaluations should resume according to the protocol.

4.2.4 Replacement of Subjects

Subjects in the dose-escalation cohorts are considered evaluable if they receive 2 doses of MEDI4736 or they discontinue MEDI4736 due to DLTs. Nonevaluable subjects in the dose-escalation cohorts will be replaced in the same dose cohort. Subjects enrolled in the dose-expansion or dose-exploration cohorts will not be replaced.

4.3 Treatment Assignment

Each subject who meets the eligibility criteria will be assigned open-label investigational product. Investigational product (MEDI4736) must be administered within 1 business day after the investigational product is assigned. If there is a delay in the administration of investigational product such that it will not be administered within the specified timeframe, the study monitor must be notified *immediately*.

4.4 Blinding

This study is not blinded.

4.5 Study Medications

4.5.1 Investigational Products

MedImmune will provide the investigator(s) with adequate quantities of investigational product using designated distribution centers. MEDI4736 will be stored at 2-8°C (36-46°F) in a secure area with restricted access.

MEDI4736: [redacted]

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune according to the investigational site policy.

4.5.1.1 Investigational Product Preparation

The dose of investigational product for administration must be prepared by the investigator's or site's designated investigational product manager using aseptic technique. Commercially available WFI and 0.9% (w/v) saline will be supplied by each site. Total in-use storage time from reconstitution of MEDI4736 to start of administration should not exceed 4 hours at room temperature or 24 hours at 2-8°C (36-46°F). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. MEDI4736 does not contain preservatives and any unused portion must be discarded.

Reconstitution of investigational product

MEDI4736 requires reconstitution prior to use. The reconstitution should be performed with 4.0 mL sterile WFI for each vial with the liquid added gently to the side of the vial to minimize product foaming. The vial should be gently rotated or swirled for 5 minutes or until dissolution is complete. The vial should not be shaken or vigorously agitated. Reconstituted MEDI4736 should stand undisturbed at room temperature for a minimum of 5 minutes or until the solution clarifies. The reconstituted solution should appear clear or slightly opalescent. A thin layer of bubbles on the liquid surface is considered normal.

Preparation of doses less than 1.0 mg/kg MEDI4736 for administration with a syringe

For IV doses less than 1.0 mg/kg, administration will be performed using a polypropylene syringe and IV administration set. Each dose will be administered as an admixture of MEDI4736 and 0.9% (w/v) saline prepared to a set volume. The delivery volume for each dose level is listed in Table 4.5.1.1-1. The preparation volume will include additional volume of admixture to allow for purging the lines of the administration set.

Table 4.5.1.1-1 Preparation of MEDI4736 Doses Less Than 1.0 mg/kg to Dose for Administration by Syringe

Dose (mg/kg)	Delivery Volume (mL)
0.05	2
0.10 to 0.29	4
0.30 to 0.89	12
0.90 to 0.99	30

The dose preparation procedure is as follows:

1. Determine from Table 4.5.1.1-1 the correct delivery volume needed.
2. Calculate the amount of admixture to prepare using the formula below:
3. Preparation Volume (mL) =
4. Delivery Volume (mL) + Hold-up Volume of Administration Set (mL)
5. Calculate the concentration of MEDI4736 in the admixture using the formula below:
6. Final Dose Concentration (mg/mL) =
7. Dose (mg/kg) × Subject Weight (kg) ÷ Delivery Volume (mL)
8. Determine the volume of reconstituted MEDI4736 (mL) to be prepared in 0.9% (w/v) saline required for the calculated concentration:
9. Volume of MEDI4736 to be Diluted (mL) =

10. Final Dose Concentration (mg/mL) × Preparation Volume (mL) ÷ Drug Product Concentration (nominal 50 mg/mL)
11. Determine the volume of 0.9% (w/v) saline (mL) used to dilute MEDI4736:
12. Volume of 0.9% (w/v) Saline (mL) =
13. Preparation Volume (mL) - Volume of MEDI4736 to be Diluted (mL)

The admixture should be prepared in a separate sterile container. Following preparation, the admixture must be mixed by gentle swirling or inversion. The admixture should then be inspected to ensure the solution is clear and then drawn up into the syringe. Intravenous lines are then purged and the specified delivery volume is administered, using a 0.2-µm in-line filter. Subjects in the first cohort will receive the initial infusion over approximately 4 hours. All remaining infusions for these subjects and other study subjects will be approximately 60 minutes in duration. Disconnect the IV line when the correct volume has been delivered.

Example:

1. For a dose of 0.3 mg/kg, the Delivery Volume will be 12 mL.
2. The administration lines to be used have a hold-up volume of approximately 10 mL. The volume of admixture to prepare is 22 mL (12 mL + 10 mL)
3. The Final Dose Concentration of MEDI4736 for a subject weighing 100 kg and dosed at 0.3 mg/kg will be 2.5 mg/mL.
4. (0.3 mg/kg × 100 kg ÷ 12 mL)
5. The volume of reconstituted MEDI4736 required will be 1.1 mL.
6. (2.5 mg/mL × 22 mL ÷ 50 mg/mL)
7. The volume of 0.9% (w/v) saline required to dilute MEDI4736 will be 20.9 mL.
8. (22 mL - 1.1 mL)

After gentle mixing of the admixture in the syringe by gentle inversion the lines are purged and 12 mL is administered over the specified infusion time.

Preparation of MEDI4736 doses greater than or equal to 1.0 mg/kg and less than or equal to 30 mg/kg for administration with an IV bag

No incompatibilities have been observed between MEDI4736 and polyethylene, polyolefin copolymers, or polyvinylchloride. Doses greater than or equal to 1.0 mg/kg will be administered using a 250 mL IV bag containing 0.9% (w/v) saline and delivered through an IV administration set. The volume of reconstituted MEDI4736 to add to the IV bag is calculated as follows:

Volume of MEDI4736 (mL) =

Dose (mg/kg) × Subject Weight (kg) ÷ MEDI4736 Concentration (nominal 50 mg/mL)

Subject weight at baseline should be used for dosing calculations unless there is a ≥ 10% change in weight in which case the dosing day weight should be used. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard. An additional volume of 0.9% (w/v) saline 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. Following preparation of the dose, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes, using a 0.2-µm in-line filter. Flush the IV line with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

Example: For a subject weighing 80 kg and dosed at 10 mg/kg, 16 mL [10 mg/kg × 80 kg divided by 50 mg/mL] of MEDI4736 is to be diluted in a 250 mL IV bag containing 0.9% (w/v) saline. First, 16 mL of saline is removed from the IV bag, and then 16 mL of MEDI4736 is added to the bag. The bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag and the diluted MEDI4736 is administered as described above.

4.5.2 Other Study Medications

No other study medications are specified for use in this clinical protocol.

4.5.3 Treatment Regimen

Subjects will be treated in a dose-escalation phase, dose-exploration cohort, or a dose-expansion phase of the study.

4.5.3.1 Dose Escalation

MEDI4736 Q2W Dose-escalation Arm

Subjects enrolled in the Q2W dose-escalation arm will receive one of 5 doses of MEDI4736 (0.1, 0.3, 1.0, 3.0, or 10 mg/kg) via IV infusion Q2W ± 3 days. Provided the MTD is not exceeded at the 10 mg/kg dose level, additional cohorts of 3-6 subjects using doses above 10 mg/kg of MEDI4736 Q2W may be initiated based on PK or pharmacodynamic data suggesting maximal suppression of sPD-L1 is not being maintained throughout the dosing interval or T-cell activation has not plateaued, respectively. The rules for dose escalation described in Section 4.5.6 would apply in this setting. Intermediate doses may be evaluated at

the discretion of the sponsor based on available data. Dose modification for toxicities will be allowed as described in Appendix 15.

Subjects will continue MEDI4736 Q2W treatment for 12 months or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur (Figure 4.5.3.1-1). In the event of confirmed PD, subjects may continue to receive MEDI4736 in the absence of clinical deterioration (see Section 5.2.6) and if investigators consider that subjects continue to receive benefit from treatment.

Subjects who have achieved and maintained DC (ie, CR, PR, or SD) or clinical benefit through to the end of the 12-month Q2W treatment period will enter follow-up and be assessed according to the procedures outlined in Table 5.1-3. Upon evidence of PD during follow-up, subjects will be re-administered MEDI4736 at the dose previously received or at 10 mg/kg, the dose chosen for the expansion phase via IV infusion Q2W (Appendix 13). Subjects may continue MEDI4736 Q2W retreatment for up to 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Only one round of retreatment with MEDI4736 will be allowed. Subjects who have confirmed PD during the 12-month Q2W initial treatment or retreatment period and cannot continue to receive MEDI4736 will enter follow-up for 90-day safety assessments and survival follow-up (see Appendix 14 for schedule of procedures).

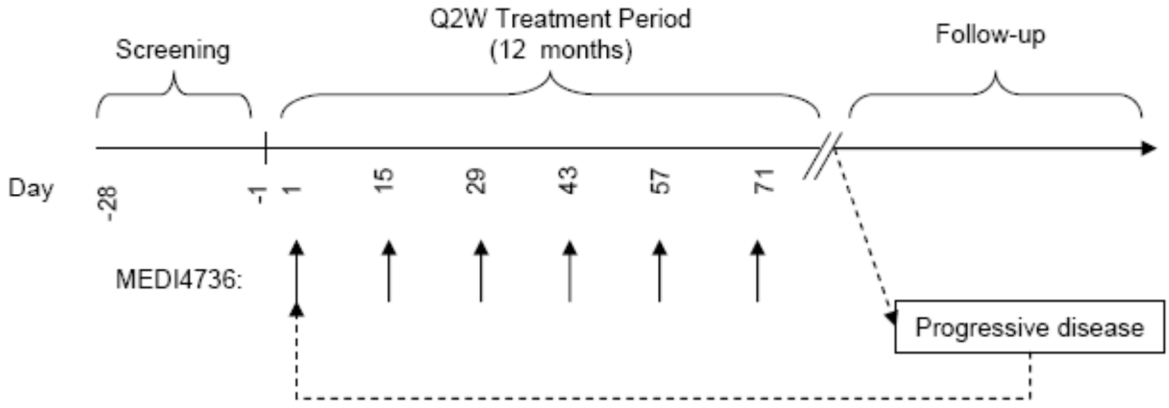

Figure 4.5.3.1-1 Dosing Schema for MEDI4736 Q2W Dose-escalation Cohorts

Q2W = every 2 weeks.

MEDI4736 Q3W Dose-escalation Arm

Upon the completion of dose escalation for the Q2W dose-escalation arm, a separate dose-escalation arm of MEDI4736 administered Q3W will be initiated. This Q3W dose-escalation arm will be carried out in parallel to the dose-expansion phase. The first cohort of subjects will receive MEDI4736 Q3W ± 3 days at the highest dose level that does not exceed the MTD or the OBD in the Q2W dose-escalation arm. Higher doses of MEDI4736 may be explored based upon acceptable safety, PK/pharmacodynamic, and clinical data following the rules for dose escalation described in Section 4.5.6.

Subjects will continue MEDI4736 Q3W treatment for 12 months or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur (Figure 4.5.3.1-2). In the event of confirmed PD, subjects may continue to receive MEDI4736 in the absence of clinical deterioration (see Section 5.2.6) and if investigators consider that subjects continue to receive benefit from treatment.

Subjects who have achieved and maintained DC (ie, CR, PR, or SD) or clinical benefit through the end of the 12-month Q3W treatment period will enter follow-up and be assessed according to the procedures outlined in Table 5.1-3. Upon evidence of PD during follow-up, subjects will be re-administered MEDI4736 at the highest dose previously received via IV infusion Q3W (Appendix 13). Subjects may continue MEDI4736 Q3W retreatment for up to 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Only one round of retreatment with MEDI4736 will be allowed. Subjects who have confirmed PD during the 12-month Q3W initial treatment or retreatment period and cannot continue to receive MEDI4736 will enter follow-up for 90-day safety assessments and survival follow-up (see Appendix 14 for schedule of procedures).

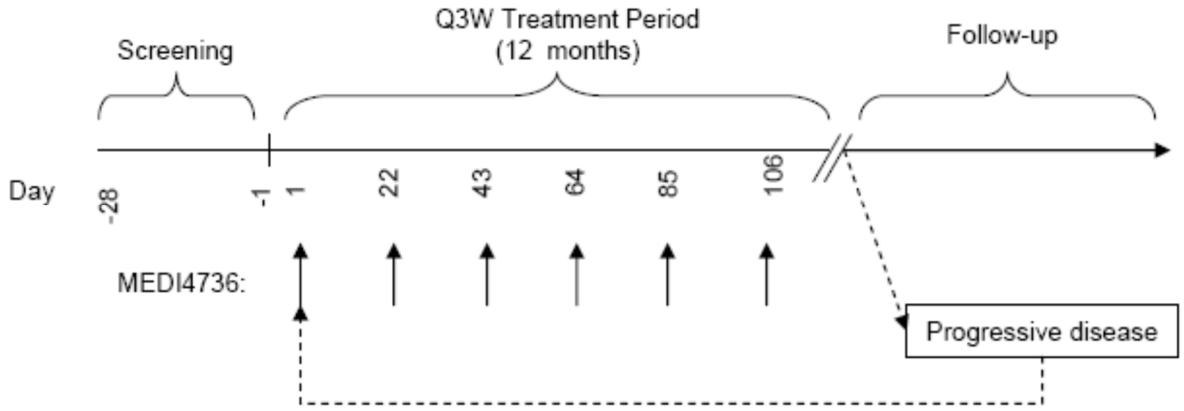

Figure 4.5.3.1-2 Dosing Schema for MEDI4736 Q3W Dose-escalation Cohorts

Q3W = every 3 weeks.

4.5.3.2 Dose Exploration

The dose-exploration cohort of the study will be conducted in parallel with the MEDI4736 Q2W dose-expansion phase.

Subjects with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC or pancreatic adenocarcinoma, will receive MEDI4736 Q4W via IV infusion at 20 mg/kg.

Treatment in the dose-exploration cohort will continue on a Q4W schedule for 12 months or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or other reasons to discontinue treatment occur (Figure 4.5.3.2-1). In the event of confirmed PD, subjects may continue to receive MEDI4736 in the absence of clinical deterioration (see Section 5.2.6) and if investigators consider that subjects continue to receive benefit from treatment.

Subjects who have achieved and maintained DC (ie, CR, PR, or SD) or clinical benefit through the end of the 12-month Q4W treatment period will enter follow-up and be assessed according to the procedures outlined in Table 5.1-3. Upon evidence of PD during follow-up, these subjects will be re-administered MEDI4736 at 20 mg/kg via IV infusion Q4W (Table 5.1-2). Rebaseline will be required using the screening visit assessments with the exception of consent, collecting the pathology report, and collecting an archival tumor sample. In addition subject must not have met discontinuation criteria. Subjects may continue MEDI4736 Q4W retreatment for up to 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Only one round of retreatment with

MEDI4736 will be allowed. Subjects who have confirmed PD during the 12-month Q4W initial treatment or retreatment period and cannot continue to receive MEDI4736 will enter follow-up for 90-day safety assessments and survival follow-up (see Appendix 14 for schedule of procedures).

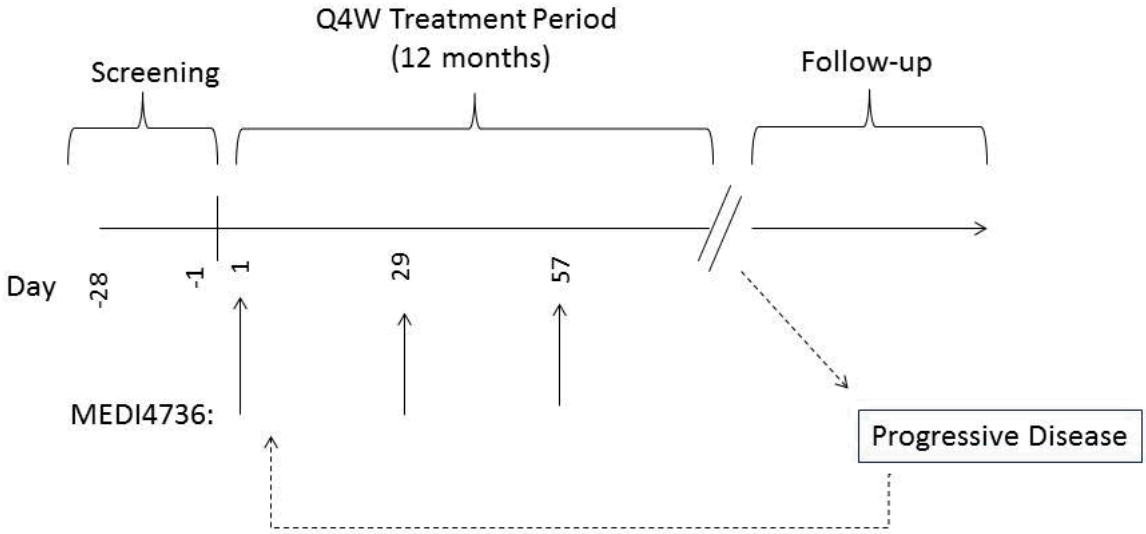

Figure 4.5.3.2-1 Dosing Schema for MEDI4736 Q4W Dose-exploration Cohort

Q4W = every 4 weeks.

4.5.3.3 Dose Expansion

The dose-expansion phase of the study will be conducted following completion of the MEDI4736 Q2W dose-escalation arm and in parallel with the MEDI4736 Q3W dose-escalation arm and Q4W dose-exploration cohort.

Subjects with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, pancreatic adenocarcinoma, UBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, HPV-positive cancers, or nasopharyngeal carcinoma will receive MEDI4736 Q2W via IV infusion at the 10 mg/kg Q2W, the dose selected for the expansion phase of the study.

Treatment in the dose-expansion phase will continue on a Q2W schedule for 12 months or until confirmed PD, initiation of alternative cancer therapy, unacceptable toxicity,

withdrawal of consent, or other reasons to discontinue treatment occur (Figure 4.5.3.3-1). In the event of confirmed PD, subjects may continue to receive MEDI4736 in the absence of clinical deterioration (see Section 5.2.6) and if investigators consider that subjects continue to receive benefit from treatment.

Subjects who have achieved and maintained DC (ie, CR, PR, or SD) or clinical benefit through the end of the 12-month Q2W treatment period will enter follow-up and be assessed according to the procedures outlined in Table 5.1-3. Upon evidence of PD during follow-up, these subjects will be re-administered MEDI4736 at the dose previously received via IV infusion Q2W (Appendix 13). Subjects may continue MEDI4736 Q2W retreatment for up to 12 months with the same treatment guidelines followed during the initial 12-month treatment period. Only one round of retreatment with MEDI4736 will be allowed. Subjects who have confirmed PD during the 12-month Q2W initial treatment or retreatment period and cannot continue to receive MEDI4736 will enter follow-up for 90-day safety assessments and survival follow-up (see Appendix 14 for schedule of procedures).

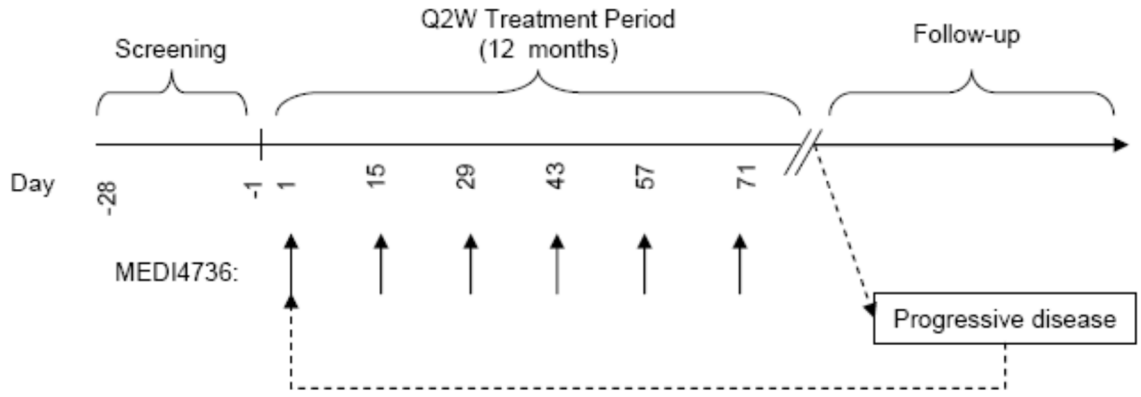

Figure 4.5.3.3-1 Dosing Schema for MEDI4736 Q2W Dose-expansion Cohorts

Q2W = every 2 weeks.

4.5.4 Treatment Administration

The first day of dosing is considered Day 1. Subjects in the first dose-escalation cohort will receive the first dose of MEDI4736 as an IV infusion over 4 hours and subsequent doses as an IV infusion over approximately 60 minutes (± 5 minutes). In the remaining dose-escalation and expansion cohorts, MEDI4736 will be administered as an IV infusion over approximately 60 minutes (± 5 minutes). When a syringe is used for the infusion, the syringe should be disconnected when the correct volume has been infused. When an IV bag

is used for the infusion, the IV line will be flushed with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered (unless prohibited by institutional practice).

Since the compatibility of MEDI4736 with other IV medications and solutions, other than normal saline (0.9% [w/v] Sodium Chloride for Injection), is not known, the MEDI4736 solution should not be infused through an IV line in which other solutions or medications are being administered. The date, start time, interruption, and completion time of MEDI4736 administration must be recorded in the source documents.

4.5.5 Monitoring of Dose Administration

Subjects will be monitored during and after the first infusion of MEDI4736 with assessment of vital signs within an hour prior to the start of the infusion, every 15 minutes (± 5 minutes) during the infusion, at the end of infusion (+ 5 minutes) and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) postinfusion, followed by a 3-hour (± 15 minutes) period of observation. For subsequent doses (at dose levels of 10 mg/kg or less), the 3-hour observation period will not be required unless a subject experiences an infusion-related reaction or a higher dose level is being tested. The 3-hour observation period, however, will be required for the first 4 doses for any dose level > 10mg/kg (Q2W or Q3W) and for subjects in the 20 mg/kg Q4W dose-exploration cohort.

Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered prior to infusion at the discretion of the investigator for primary prophylaxis against infusion-related reactions. In the event of Grade ≤ 2 infusion-related reaction, the infusion rate of MEDI4736 may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. In subjects experiencing Grade ≤ 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. If a subject experiences an infusion-related reaction, acetaminophen and/or an antihistamine (eg, diphenhydramine) and/or corticosteroid or equivalent medications per institutional standard may be administered prior to subsequent infusions at the discretion of the investigator for secondary prophylaxis of infusion-related reactions. If the infusion-related reaction is Grade 3 or higher in severity, treatment with MEDI4736 will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study

site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

4.5.6 Dose Escalation

In the dose-escalation phase, the first dose of MEDI4736 will be administered to all subjects in the first cohort as a 0.1 mg/kg infusion given over 4 hours. Subsequent infusions (2nd and 3rd doses, etc) for the first cohort will be given over approximately 60 minutes Q2W. The doses for subsequent cohorts will be 0.3, 1.0, 3.0, or 10 mg/kg, administered over approximately 60 minutes as an IV infusion Q2W unless an MTD or OBD is identified before all dose-escalation cohorts are completed. Higher doses may be further explored based on clinical, safety, and PK/pharmacodynamic data generated from the study. If 2 or more DLTs are observed in the first dose cohort, the dose will be de-escalated to half of the starting dose (0.05 mg/kg) and will be given Q3W.

Upon completion of dose escalation for the MEDI4736 Q2W dose-escalation arm, a separate Q3W dose-escalation arm will be initiated in parallel with the dose-expansion phase. The dose planned for the first Q3W escalation cohort is the dose that is the equivalent dosing rate (in average mg/kg/week) to the OBD or highest dose tested if an OBD was not identified. A lower dose may be used pending review of available data. For example, if dose escalation proceeds to 10 mg/kg Q2W, the planned starting dose in the Q3W dose escalation will be 15 mg/kg Q3W.

If an MTD is reached prior to completing the Q2W dose escalation, the Q3W starting dose will be the equivalent dosing rate to the Q2W MTD. For example, if an MTD is identified at 3.0 mg/kg Q2W, the starting dose in the Q3W dose escalation will be approximately 4.5 mg/kg Q3W. The Q3W dose escalation will proceed based upon on available data. Additional MEDI4736 Q3W cohorts with 3-6 subjects each may be initiated based on acceptable clinical, safety, and PK/pharmacodynamic data following the rules for dose escalation described below. Because the DLT evaluation period for this study includes 2 doses of MEDI4736, the timing of any toxicities observed during the Q2W escalation will be important in determining the maximum dose level to be evaluated in the Q3W escalation. If DLTs defining the Q2W MTD are observed prior to the second dose of MEDI4736, the Q3W dose escalation may not proceed past the Q2W MTD dose level. However, if the DLTs defining the Q2W MTD are observed after the second dose of MEDI4736, the Q3W dose escalation may proceed beyond the Q2W MTD.

Rules for dose escalation are as follows:

1. The MTD will be determined based on the assessment of DLT (as defined in Section 4.5.7) during the DLT evaluation period, which is defined as the period from administration of the first dose of MEDI4736 until the planned administration of the third dose. Subjects are considered evaluable for assessment of DLT if they receive 2 full assigned doses of MEDI4736, or the subject experiences any DLT. Nonevaluable subjects will be replaced in the same dose cohort.
2. A minimum of 3 subjects will be enrolled in each dose cohort.
3. The administration of MEDI4736 to the first and second subjects of each cohort will be separated by at least 24 hours.
4. Dose escalation to the next dose level is permitted only after the subject(s) enrolled in the current dose cohort have competed the DLT observation period and all safety data have been reviewed by a study-specific dose-escalation committee.
5. If 1 of the 3 subjects in any dose cohort experiences a DLT, that dose cohort will be expanded to a total of 6 subjects. If no more than 1 of 6 subjects in the cohort experiences a DLT, dose escalation may proceed.
6. If 2 or more subjects in a dose cohort experience a DLT during the DLT evaluation period, the MTD will be exceeded and no further subjects will be enrolled into that dose cohort. If this occurs, the preceding dose cohort will be evaluated for the MTD and a total of 6 subjects will be treated at the preceding dose. If no more than 1 of 6 subjects experiences a DLT at the preceding dose, then that dose level will be the MTD.
7. At the discretion of the sponsor, dose escalation may be stopped before an MTD is reached. In this case, the OBD may be chosen based on an assessment of PK, pharmacodynamic, biomarker, safety, and response data. An MTD does not have to be reached to expand a dose cohort if the available data demonstrate that a lower dose level may provide antitumor activity while minimizing potential risk.
8. Upon completion of the Q2W dose escalation, the cohort with either the highest dose level shown to be well tolerated or the OBD will be expanded to a total of 6 subjects (if not already done due to observation of a DLT).
9. A separate, Q3W dose escalation will be initiated following the completion of dose escalation for the Q2W dose-escalation arm and at the same time as the dose-expansion phase. Dose escalation will begin with the highest dose level that has not exceeded the MTD or the OBD in the Q2W dose-escalation arm and proceed as per the rules outlined above.
10. Upon completion of the Q3W dose escalation, the cohort with either the highest dose level that does not exceed the MTD or the OBD will be expanded to a total of 6 subjects (if not already done due to observation of a DLT).

4.5.7 Dose-limiting Toxicity

Dose-limiting toxicities will be evaluated during the dose-escalation phase. The period for evaluating DLTs will be from the time of first administration of MEDI4736 until the planned administration of the third dose of MEDI4736. Subjects who do not remain on the study up

to this time for reasons other than DLT will be replaced with another subject at the same dose level. Grading of DLTs will be according to the NCI CTCAE v4.03.

A DLT will be defined as any Grade 3 or higher treatment-related toxicity that occurs during the DLT evaluation period, including

- Any Grade ≥ 3 colitis
- Any Grade ≥ 3 irAE including rash, pruritus, or diarrhea that does not downgrade to Grade ≤ 2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids

The definition excludes the following conditions:

- Grade 3 decrease in lymphocyte count or increase in GGT that downgrades to Grade ≤ 2 within 7 days after onset of the event and resolves to Grade ≤ 1 or baseline within 14 days
- Grade 3 endocrinopathy that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and the following criterion is met:
  - The subject is asymptomatic
- Grade 3 inflammatory reaction attributed to a local antitumor response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes, etc)

Immune-related AEs are defined as AEs of immune nature (ie, 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.

4.5.8 Dose Modification for Toxicity Management

Based on the mechanism of action of MEDI4736 leading to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study. Potential irAEs may be similar to those seen with the use of ipilimumab and nivolumab, and may include immune-mediated enterocolitis, dermatitis, pneumonitis, hepatitis (hepatotoxicity), neurotoxicity, and endocrinopathies (Hodi et al, 2010; Brahmer et al, 2012; Topalian et al, 2012; Wolchok et al, 2013). Subjects should be monitored for signs and symptoms of irAEs in any organ. In the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis.

All toxicities will be graded according to NCI CTCAE v4.03.

Treatment 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. Dose reductions are not permitted. Dose modification and management guidelines are provided in Appendix 15. Dosing may continue despite concurrent vitiligo of any AE grade.

4.5.9 Treatment Compliance

Investigational product is administered by study site personnel, who will monitor subject compliance.

4.6 Concomitant Medications

4.6.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments (eg, acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as "excluded" as listed in Section 4.6.2.

4.6.2 Excluded Concomitant Medications

Subjects must be instructed not to take any medications, including over-the-counter products, without first consulting with the investigator.

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

1. Any investigational anticancer therapy
2. Any concurrent chemotherapy, radiotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable. Note: Local treatment of isolated lesions for palliative intent is acceptable (eg, by local surgery or radiotherapy)
3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses beyond 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor alpha (TNF-α) blockers. Use of immunosuppressive medications for the management of investigational product-related AEs and in subjects with contrast allergies is acceptable. In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. Temporary courses of corticosteroids for treatment of underlying or concurrent illness or in the setting of palliative radiotherapy may be permitted upon discussion with the medical monitor.

4. Live attenuated vaccines within 30 days of MEDI4736 dosing

4.7 Subject Completion

An individual subject will be considered to have completed the study if the subject was followed up through the end of the study as defined in Section 4.8, regardless of the number of doses of investigational product that was received.

Subjects will be considered not to have completed the study if consent was withdrawn or the subject was lost to follow-up (see Section 4.2.3).

4.8 End of the Study

The end of the study ("study completion") is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study or the date the study is closed by the sponsor, whichever occurs first. All materials or supplies provided by the sponsor will be returned to the sponsor or designee upon study completion, as directed by the site monitor. The investigator will notify the IRB/IEC when the study has been completed.

5 STUDY PROCEDURES

5.1 Schedule of Study Procedures

All subjects who are assigned an SID number and receive any investigational product will be followed according to the protocol regardless of the number of doses received, unless consent is withdrawn. The investigator must notify the sponsor or designee of deviations from protocol visits or evaluations and these evaluations, if applicable, must be rescheduled or performed at the nearest possible time to the original schedule. Protocol deviations will be recorded on the source document with an explanation for the deviation and any study-specific case report forms (CRFs) or logs designated for capturing protocol deviations, if applicable for the study. The investigator must comply with the applicable requirements related to the reporting of protocol deviations to the IRB/IEC.

Subjects/legal representatives will be instructed to call study personnel to report any abnormalities during the intervals between study visits and to come to the study site if medical evaluation is needed and the urgency of the situation permits. For emergency and other unscheduled visits to a medical facility other than the study site, medical records will be obtained by the investigator and made available to the sponsor or designee during monitoring visits.

Schedules of study procedures for the screening and treatment period are presented in Table 5.1-1 for Q2W or Q3W dosing schedules and Table 5.1-2 for Q4W dosing schedule. Subjects in retreatment using the Q4W dosing schedule will follow the same schedule as initial treatment. A schedule of follow-up study procedures for subjects who have completed MEDI4736 treatment and achieved DC (until confirmed PD) and subjects who have discontinued MEDI4736 due to toxicity in the absence of PD is presented in Table 5.1-3. A schedule of retreatment for subject in dose-escalation and dose-expansion is presented in Appendix 13. A schedule of follow-up study procedures and description of each visit for subjects who have discontinued MEDI4736 treatment due to confirmed PD is presented in Appendix 14. A description of the study procedures is included in Section 5.2. The sponsor may stop the collection of an exploratory laboratory evaluation at any time based on available data.

Table 5.1-1 Schedule of Study Procedures: Screening and Treatment Period

Evaluation	Screening Day -28 to Day -1	Treatment Period (12 Months)											
		Dose 1						Dose 2 (± 3 days)		Odd-numbered Doses (after Dose 1; ± 3 days)	Even-numbered Doses (after Dose 2; ± 3 days)	After 6 Weeks (Day 43 ± 7 days)	After 12 Weeks and 16 Weeks (Days 85 and 113) Then Every 8 Weeks (± 7 days)
		Days						Days					
		1	2 (Dose-escala-tion only)	3 (Dose-escala-tion only)	5 ± 1 (Dose-escala-tion only)	10 ± 1	15 ± 1 (for Q3W)	1	8 ± 1				
Written informed consent/assignment of SID number	X												
Verify eligibility criteria	X	X											
Pain questionnaire (dose-expansion phase only)	X	X								X (Doses 3 and 5 only)		X	X
EORTC QLQ-C30 and cancer-specific modules (dose-expansion phase only)	X	X								X (Doses 3 and 5 only)		X	X
FACT-BL (UBC subjects only)	X	X								X (Doses 3 and 5 only)		X	X
Collect pathology report (if available)	X												
Medical history	X												
Smoking history	X												
Hepatitis B and C; HIV	X												
Serum βhCG	X												

Table 5.1-1 Schedule of Study Procedures: Screening and Treatment Period

Evaluation	Screening Day -28 to Day -1	Treatment Period (12 Months)											
		Dose 1						Dose 2 (± 3 days)		Odd-numbered Doses (after Dose 1; ± 3 days)	Even-numbered Doses (after Dose 2; ± 3 days)	After 6 Weeks (Day 43 ± 7 days)	After 12 Weeks and 16 Weeks (Days 85 and 113) Then Every 8 Weeks (± 7 days)
		Days						Days					
		1	2 (Dose-escala-tion only)	3 (Dose-escala-tion only)	5 ± 1 (Dose-escala-tion only)	10 ± 1	15 ± 1 (for Q3W)	1	8 ± 1				
Urine hCG or serum βhCG		X						X		X	X		
Kit assignment and MEDI4736 administration		X						X		X	X		
Protocol/Safety Evaluations													
Physical examination	X	X						X		X	X		
Vital signs [a]	X	X						X		X	X		
Postinfusion observation [a]		X						X		X	X		
Weight	X	X						X		X	X		
Electrocardiogram, Q2W dose-escalation arm [b]	X	X								X (every 4th dose)			
Electrocardiogram, Q3W dose-escalation arm [b]	X	X								X (every 3rd dose)			
Electrocardiogram, Q2W dose-expansion [b,c]	X	X								X (every 12 weeks starting at Dose 3)			

Table 5.1-1 Schedule of Study Procedures: Screening and Treatment Period

Evaluation	Screening Day -28 to Day -1	Treatment Period (12 Months)											
		Dose 1						Dose 2 (± 3 days)		Odd-numbered Doses (after Dose 1; ± 3 days)	Even-numbered Doses (after Dose 2; ± 3 days)	After 6 Weeks (Day 43 ± 7 days)	After 12 Weeks and 16 Weeks (Days 85 and 113) Then Every 8 Weeks (± 7 days)
		Days						Days					
		1	2 (Dose-escala-tion only)	3 (Dose-escala-tion only)	5 ± 1 (Dose-escala-tion only)	10 ± 1	15 ± 1 (for Q3W)	1	8 ± 1				
AE/SAE assessment	X	X	X	X	X	X	X	X		X	X		
Concomitant medications	X	X						X		X	X		
ECOG performance status	X	X						X		X	X		
Laboratory Evaluations													
Hepatitis B and C viral titers (only HCC subjects with hepatitis B or C)	X									X			
Serum chemistry	X	X						X		X	X		
Thyroid function tests (TSH and free T3 and T4)	X	X						X		X	X		
Hematology	X	X[d]			X	X		X		X	X		
Urinalysis	X	X						X		X	X		
Coagulation parameters	X							X		X	X		
Pharmacokinetic assessment, Q2W dose-escalation arm		X[e]		X	X	X		X[e]	X		X[e]		

Table 5.1-1 Schedule of Study Procedures: Screening and Treatment Period

Evaluation	Screening Day -28 to Day -1	Treatment Period (12 Months)											
		Dose 1						Dose 2 (± 3 days)		Odd-numbered Doses (after Dose 1; ± 3 days)	Even-numbered Doses (after Dose 2; ± 3 days)	After 6 Weeks (Day 43 ± 7 days)	After 12 Weeks and 16 Weeks (Days 85 and 113) Then Every 8 Weeks (± 7 days)
		Days						Days					
		1	2 (Dose-escalation only)	3 (Dose-escalation only)	5 ± 1 (Dose-escalation only)	10 ± 1	15 ± 1 (for Q3W)	1	8 ± 1				
Pharmacokinetic assessment, Q3W dose-escalation arm		X[e]		X	X	X	X	X[e]	X		X[e]		
Pharmacokinetic assessment, Q2W dose-expansion arm		X[e]						X[e]		X (every 12 weeks starting at Dose 3)			
Pharmacokinetic assessment, Q2W UBC cohort		X[f]								X (Dose 3, 7, and 13 [Day 29, 85, and 169])			
Immunogenicity assessment dose-escalation arms		X								X (Dose 3 only)	X (begin after Dose 4)		
Immunogenicity assessment dose-expansion arms		X								X (every 12 weeks starting at Dose 3)			
Immunogenicity assessment UBC cohort		X								X (Dose 3, 7, and 13 [Day 29, 85, and 169])			

Table 5.1-1 Schedule of Study Procedures: Screening and Treatment Period

Evaluation	Screening Day -28 to Day -1	Treatment Period (12 Months)											
		Dose 1						Dose 2 (± 3 days)		Odd-numbered Doses (after Dose 1; ± 3 days)	Even-numbered Doses (after Dose 2; ± 3 days)	After 6 Weeks (Day 43 ± 7 days)	After 12 Weeks and 16 Weeks (Days 85 and 113) Then Every 8 Weeks (± 7 days)
		Days						Days					
		1	2 (Dose-escala-tion only)	3 (Dose-escala-tion only)	5 ± 1 (Dose-escala-tion only)	10 ± 1	15 ± 1 (for Q3W)	1	8 ± 1				
sPD-L1 concentration dose-escalation arms	X	X[e]		X	X	X	X	X	X		X		
sPD-L1 concentration dose-expansion arms [c]		X[e]						X		X (every 12 weeks starting at Dose 3)			
Flow cytometric analysis - absolute cell counts, immune cell subsets, activation markers dose-escalation arms	X	X[d]		X	X	X		X			X		
Flow cytometric analysis- absolute cell counts, immune cell subsets, activation markers dose-expansion arms [c]	X	X				X		X			X [h]		
Circulating soluble factors dose-escalation arms	X	X [g]	X		X	X		X [g]		X [g]	X [g]		

Table 5.1-1 Schedule of Study Procedures: Screening and Treatment Period

Evaluation	Screening Day -28 to Day -1	Treatment Period (12 Months)											
		Dose 1						Dose 2 (± 3 days)		Odd-numbered Doses (after Dose 1; ± 3 days)	Even-numbered Doses (after Dose 2; ± 3 days)	After 6 Weeks (Day 43 ± 7 days)	After 12 Weeks and 16 Weeks (Days 85 and 113) Then Every 8 Weeks (± 7 days)
		Days						Days					
		1	2 (Dose-escala-tion only)	3 (Dose-escala-tion only)	5 ± 1 (Dose-escala-tion only)	10 ± 1	15 ± 1 (for Q3W)	1	8 ± 1				
Circulating soluble factors dose-expansion arms	X	X				X [c]		X [c]			X [c]		
PBMC collection (immunodiversity, flow cytometry, or functional assessment) dose-escalation arms	X			X	X	X		X			X		
Anticancer/testis antigen antibodies dose-escalation arms	X									X			
Anticancer/testis antigen antibodies dose-expansion arms [c]	X									X			
Circulating tumor cells (dose escalation and TNBC for dose expansion)		X						X		X			
miRNA/mRNA analysis dose-escalation arms	X			X		X		X				X	

Table 5.1-1 Schedule of Study Procedures: Screening and Treatment Period

Evaluation	Screening Day -28 to Day -1	Treatment Period (12 Months)											
		Dose 1						Dose 2 (± 3 days)		Odd-numbered Doses (after Dose 1; ± 3 days)	Even-numbered Doses (after Dose 2; ± 3 days)	After 6 Weeks (Day 43 ± 7 days)	After 12 Weeks and 16 Weeks (Days 85 and 113) Then Every 8 Weeks (± 7 days)
		Days						Days					
		1	2 (Dose-escala-tion only)	3 (Dose-escala-tion only)	5 ± 1 (Dose-escala-tion only)	10 ± 1	15 ± 1 (for Q3W)	1	8 ± 1				
miRNA/mRNA dose-expansion arms	X					X [c]		X [c]		X [c]		X [c]	
Archival tumor tissue sample [i]	X												
Confirm HPV status by central lab (HPV-positive cancers only)	X												
Disease Evaluations													
Disease assessment	X [j]											X	X
Submission of baseline imaging for BICR (UBC cohort only)	X												
Tumor biopsy (dose-expansion phase only) [i]	X											X [c]	

Table 5.1-1 Schedule of Study Procedures: Screening and Treatment Period

Evaluation	Screening Day -28 to Day -1	Treatment Period (12 Months)											
		Dose 1						Dose 2 (± 3 days)		Odd-numbered Doses (after Dose 1; ± 3 days)	Even-numbered Doses (after Dose 2; ± 3 days)	After 6 Weeks (Day 43 ± 7 days)	After 12 Weeks and 16 Weeks (Days 85 and 113) Then Every 8 Weeks (± 7 days)
		Days						Days					
		1	2 (Dose-escala-tion only)	3 (Dose-escala-tion only)	5 ± 1 (Dose-escala-tion only)	10 ± 1	15 ± 1 (for Q3W)	1	8 ± 1				

AE = adverse event; βhCG = beta human chorionic gonadotropin; BICR = blinded independent central review; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer quality-of-life questionnaire; FACT-BL = Functional Assessment of Chronic Illness Therapy-bladder; HCC = hepatocellular carcinoma; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; HPV = human papilloma virus; IHC = immunohistochemistry; miRNA = micro ribonucleic acid; mRNA = messenger ribonucleic acid; PBMC = peripheral blood mononuclear cell; PD-L1 = programmed death ligand 1; Q2W = every 2 weeks; Q3W = every 3 weeks; SAE = serious adverse event; SID = subject identification; sPD-L1 = soluble programmed death ligand 1; TNBC = triple negative breast cancer; TSH = thyroid-stimulating hormone; UBC = urothelial bladder cancer.

Note: all samples are collected predose unless otherwise indicated.

[a] Vital signs every 15 minutes (± 5 minutes) during MEDI4736 administration, at the end of infusion (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post end of infusion, followed by a 3-hour (± 15 minutes) period of observation. For subsequent doses (at dose levels of 10 mg/kg or less), the 3-hour observation period will not be required unless a subject experiences an infusion-related reaction or a higher dose level is being tested.

[b] ECGs will be collected during screening, on Dose 1, Day 1 (within an hour prior to start of infusion, within 30 minutes post-end of infusion, and 3 hours [± 15 minutes] post-end of infusion) and within an hour prior to start of infusion on remaining dosing days indicated. Digital ECGs will be collected at selected sites. All other sites will perform ECGs per their institution's standard.

[c] Not required for subjects in the UBC cohort.

[d] Predose (for both dose-escalation and dose-expansion subjects) and 3 hours (± 15 minutes) post end of infusion (for dose-escalation subjects only).

[e] Predose and post dose (+ 5 minutes) post end of infusion. For Cohort 1 subjects only, an additional sample will be taken 2 hours after start of infusion.

[f] End of infusion (+ 5 minutes).

[g] Predose and 2 hours (± 15 minutes) post end of infusion.

[h] Sample collected every other even dose (ie, every 8 weeks starting at Dose 4).

[i] For subjects in the UBC cohort, either archival tumor tissue from within 6 months prior to study entry or a fresh biopsy is required for PD-L1 IHC testing. Additional older archival tissue regardless of age is also required, if available.

[j] Disease assessments performed as part of standard of care prior to subjects signing informed consent may be used for screening if obtained within 28 days before the first dose of investigational product.

Table 5.1-2 Q4W Schedule of Study Procedures: Screening and Treatment Period

Procedure	Screening	Dose 1			Dose 2	Odd-numbered Doses (after Dose 1; ± 3 Days)	Even-numbered Doses (after Dose 2; ± 3 Days)	Weeks 6, 12, 16, Then Every 8 Weeks (± 7 Days)
		Day 1	Day 2	Day 15 ± 1 Days	Day 1 ± 3 Days			
Written informed consent/assignment of SID number	X							
Verify eligibility criteria	X							
Collect pathology report (if available)	X							
Medical history	X							
Smoking history	X							
Hepatitis B and C; HIV	X							
Serum βhCG	X							
Urine hCG or serum βhCG		X			X	X	X	
Physical examination (including weight)	X	X		X	X	X	X	
Vital signs [a]	X	X	X	X	X	X	X	
Electrocardiogram [b]	X	X				X (every other odd dose)		
AE/SAE assessment	X	X	X	X	X	X	X	
Concomitant medications	X	X		X	X	X	X	

Table 5.1-2 Q4W Schedule of Study Procedures: Screening and Treatment Period

Procedure	Screening	Dose 1			Dose 2	Odd-numbered Doses (after Dose 1; ± 3 Days)	Even-numbered Doses (after Dose 2; ± 3 Days)	Weeks 6, 12, 16, Then Every 8 Weeks (± 7 Days)
		Day 1	Day 2	Day 15 ± 1 Days	Day 1 ± 3 Days			
ECOG performance status	X	X			X	X	X	
Hepatitis B and C viral titers (only HCC subjects with hepatitis B or C)	X					X		
Serum chemistry	X	X		X	X	X	X	
Thyroid function tests (TSH and free T3 and T4)	X	X		X	X	X	X	
Hematology	X	X		X	X	X	X	
Urinalysis	X	X		X	X	X	X	
Coagulation parameters	X	X		X	X	X	X	
Pharmacokinetic assessment		X [c]		X	X [c]	X [d,e]	X [d,e]	
Immunogenicity		X			X		X	
sPD-L1 concentration	X	X [c]		X	X	X [e]	X [e]	
Circulating soluble factors	X	X		X	X	X		
Archival tumor tissue sample	X							
Disease assessment	X [f]							X
Tumor biopsy	X							X (Week 6 ± 7 Days only)

Table 5.1-2 Q4W Schedule of Study Procedures: Screening and Treatment Period

Procedure	Screening	Dose 1			Dose 2	Odd-numbered Doses (after Dose 1; ± 3 Days)	Even-numbered Doses (after Dose 2; ± 3 Days)	Weeks 6, 12, 16, Then Every 8 Weeks (± 7 Days)
		Day 1	Day 2	Day 15 ± 1 Days	Day 1 ± 3 Days			
Kit assignment and MEDI4736 administration		X			X	X	X	
Postinfusion observation		X			X	X	X	

AE = adverse event; βhCG = beta human chorionic gonadotropin; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; Q4W = every 4 weeks; SAE = serious adverse event; SID = subject identification; sPD-L1 = soluble programmed death ligand 1; TSH = thyroid-stimulating hormone.

Note: all samples are collected predose unless otherwise indicated.

[a] Vital signs every 15 minutes (± 5 minutes) during MEDI4736 administration, at the end of infusion (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post end of infusion, followed by a 3-hour (± 15 minutes) period of observation (for the first 4 doses only). For subsequent doses (starting at Dose 5), the 3-hour observation period will not be required unless a subject experiences an infusion-related reaction or a higher dose level is being tested.

[b] ECGs will be collected during screening, on Dose 1, Day 1 (within an hour prior to start of infusion, within 30 minutes post-end of infusion, and 3 hours [± 15 minutes] post-end of infusion) and within an hour prior to start of infusion on remaining dosing days indicated. ECGs will be performed per their institution's standard.

[c] Predose and post dose (+ 5 minutes) post end of infusion.

[d] Predose and post dose (+ 5 minutes) post end of infusion for first 6 months (Doses 3-6).

[e] Sampling changes to even doses (ie every 8 weeks) only starting at Dose 6. Predose sampling only after Dose 6.

[f] Disease assessments performed as part of standard of care prior to subjects signing informed consent may be used for screening if obtained within 28 days before the first dose of investigational product.

Table 5.1-3 Schedule of Study Procedures: Follow-up for Subjects Who Have Completed MEDI4736 Treatment and Achieved Disease Control (Until Confirmed Progressive Disease) and Subjects Who Have Discontinued MEDI4736 Due to Toxicity in the Absence of Confirmed Progressive Disease

Evaluation	End of Treatment[a]	Time Since Last Dose of MEDI4736								
		Days (± 3)		Months (± 1 week)						12 Months and Every 3 Months (± 2 weeks)
		14	30	2	3	4	6	8	10	
Protocol/Safety Evaluations										
Pain questionnaire (dose-expansion phase only)	X		X	X		X	X	X	X	X [b]
EORTC QLQ-C30 and cancer-specific modules (dose-expansion phase only)	X		X	X		X	X	X	X	X [b]
FACT-BL (UBC subjects only)	X		X	X		X	X	X	X	X [b]
Physical examination	X		X							
Vital signs	X		X							
Weight	X		X							
Electrocardiogram [c,d]	X		X							
AE/SAE assessment	X	X	X	X	X					
Concomitant medications	X	X	X							
ECOG performance status	X		X							
Subsequent anticancer therapy				X	X	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted				X	X	X	X	X	X	X
Laboratory Evaluations										
Hepatitis B and C viral titers (only HCC subjects with hepatitis B or C)	X		X		X		X			
Hematology	X		X							
Serum chemistry	X		X							
Thyroid function tests (TSH, and free T3 and T4)	X		X							
Coagulation parameters	X		X							
Urinalysis	X		X							

Table 5.1-3 Schedule of Study Procedures: Follow-up for Subjects Who Have Completed MEDI4736 Treatment and Achieved Disease Control (Until Confirmed Progressive Disease) and Subjects Who Have Discontinued MEDI4736 Due to Toxicity in the Absence of Confirmed Progressive Disease

Evaluation	End of Treatment[a]	Time Since Last Dose of MEDI4736								
		Days (± 3)		Months (± 1 week)						12 Months and Every 3 Months (± 2 weeks)
		14	30	2	3	4	6	8	10	
Pharmacokinetic assessment	X [d]		X [d]		X					
Immunogenicity assessment	X [d]		X [d]		X		X [d]			
sPD-L1 concentration [d]	X		X		X					
Flow cytometric analysis - absolute cell counts, immune cell subsets, activation markers (Q2W and Q3W subjects only) [d]	X				X					X [b]
Circulating soluble factors [d]	X		X		X					X [b]
PBMC collection (immunodiversity, flow cytometry, or functional assessment; Q2W and Q3W subjects only) [d]	X				X					X [b]
Anticancer/testis antigen antibodies (Q2W and Q3W subjects only) [d]	X				X					X [b]
Circulating tumor cells (dose escalation and TNBC for dose expansion)	X		X		X					X [b]
miRNA/mRNA analysis (Q2W and Q3W subjects only) [d]	X		X							
Disease Evaluation										
Disease assessment	X			X		X	X	X	X	X

Table 5.1-3 Schedule of Study Procedures: Follow-up for Subjects Who Have Completed MEDI4736 Treatment and Achieved Disease Control (Until Confirmed Progressive Disease) and Subjects Who Have Discontinued MEDI4736 Due to Toxicity in the Absence of Confirmed Progressive Disease

Evaluation	End of Treatment[a]	Time Since Last Dose of MEDI4736								
		Days (± 3)		Months (± 1 week)						12 Months and Every 3 Months (± 2 weeks)
		14	30	2	3	4	6	8	10	

AE = adverse event; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer quality-of-life questionnaire; ECG = electrocardiogram; FACT-BL = Functional Assessment of Chronic Illness Therapy-bladder; HCC = hepatocellular carcinoma; miRNA = micro ribonucleic acid; mRNA = messenger ribonucleic acid; PBMC = peripheral blood mononuclear cell; Q2W = every 2 weeks; Q3W = every 3 weeks; SAE = serious adverse event; sPD-L1= soluble programmed death ligand 1; TNBC = triple negative breast cancer; TSH = thyroid-stimulating hormone; UBC = urothelial bladder cancer.

[a] End of treatment is defined as the last planned dosing visit within the 12-month treatment period. For subjects who discontinue treatment prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue. All required procedures may be completed within ± 7 days of the endo of treatment visit. Note: repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

[b] Stop evaluation at 12 months.

[c] Digital ECGs will be collected at select sites. All other sites will perform ECGs per their institution's standard.

[d] Not required for subjects in the UBC cohort.

5.1.1 Screening

All screening procedures must be performed within 28 days before the first dose of investigational product (Day -28 to Day -1), unless otherwise specified. The screening evaluations may be carried out over more than one visit. Written informed consent and any locally required privacy act document authorization must be obtained prior to performing any protocol-specific procedures, including screening evaluations. Disease assessments performed as part of standard of care prior to subjects signing informed consent may be used for screening if obtained within 28 days before the first dose of investigational product.

5.1.2 Treatment Period

Includes subjects who will be receiving the first infusion of MEDI4736 and subjects who are being retreated with MEDI4736 following evidence of PD in follow-up. If the subject has completed any safety laboratory tests or ECOG evaluation within 72 hours of Day 1, they will not need to be repeated.

5.1.3 End of Treatment

End of treatment is defined as the last planned dosing visit within the 12-month dosing period. For subjects who discontinue MEDI4736 prior to 12 months, end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

5.1.4 Post-treatment Follow-up

Post-treatment follow-up assessments for subjects who have completed the MEDI4736 12-month treatment and achieved DC (until confirmed PD) and subjects who have discontinued MEDI4736 due to toxicity in the absence of PD are shown in Table 5.1-3. Assessments for subjects who have discontinued MEDI4736 treatment due to confirmed PD are presented in Appendix 14.

5.2 Description of Study Procedures

5.2.1 Medical History and Physical Examination, Electrocardiogram, Weight, and Vital Signs

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the prestudy grade or below.

Physical examinations will be performed on study days noted in Section 5.1, and will include assessments of the head, eyes, ears, nose, and throat, respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, and endocrine systems; and height (at screening only).

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on study days noted in Section 5.1. On MEDI4736 treatment days, vital signs will be measured within an hour prior to start of MEDI4736 administration, every 15 minutes (± 5 minutes) during MEDI4736 administration, at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) postinfusion, followed by a 3-hour (± 15 minutes) period of observation. For subsequent doses (at dose levels of 10 mg/kg or less), the 3-hour observation period will not be required unless a subject experiences an infusion-related reaction or a higher dose level is being tested. The 3-hour observation period, however, will be required for the first 4 doses for any dose level > 10 mg/kg (Q2W or Q3W) and for subjects in the 20 mg/kg Q4W dose-exploration cohort.

All electrocardiograms (ECGs) recorded during the study will be obtained in triplicate (all 3 within a 5-minute time period at least 1 minute apart). Approximately 150 subjects at select sites will have ECGs collected digitally for central analysis. All other sites will perform ECGs per their institution's standards. All ECGs will be recorded at 25 mm/second. All 12-lead ECGs should be recorded while the subject is in the supine position. A 12-lead ECG will be recorded for all subjects on study days noted in Section 5.1. The same method of assessment should be used throughout the study. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case. On Dose 1, Day 1, ECGs will be recorded within an hour prior to start of infusion, within 30 minutes post end of infusion, and 3 hours (± 15 minutes) post end of infusion. Further ECGs will be performed within an hour prior to start of infusion on remaining dosing days according to the schedule of study procedures (Section 5.1) and when clinically indicated, eg, in the event of a cardiac AE. As described in Section 5.1, ECGs are not required for subjects in the UBC cohort, unless clinically indicated.

Paper tracings will be used for local management, but a digital copy of ECGs at select sites will be held centrally by a central ECG provider, and the data from this review will be stored for analysis during or at the end of the study. The independent review will not replace the local review by the investigator or other medically–qualified designee. Clinical interpretation and management of subjects for all ECGs will be done locally.

5.2.2 Clinical Laboratory Tests

Clinical laboratory safety tests including serum pregnancy tests will be performed in a licensed clinical laboratory. Urine pregnancy tests may be performed at the site using a licensed test (dipstick). Abnormal laboratory results should be repeated as soon as possible (preferably within 24 to 48 hours).

A Laboratory Manual will be provided to the sites that specifies the procedures for collection, processing, storage, and shipment of samples, as well as laboratory contact information, specific to this clinical research study.

The following clinical laboratory tests will be performed (see Section 5.1 for the schedule of tests):

Serum Chemistry

- Calcium
- Chloride
- Magnesium
- Potassium
- Sodium
- Bicarbonate
- AST
- ALT
- Alkaline phosphatase (ALP)
- Total bilirubin
- GGT
- Lactic dehydrogenase
- Uric acid
- Creatinine
- Blood urea nitrogen
- Glucose
- Albumin
- Total protein
- Triglycerides
- Cholesterol

Note for serum chemistries: Tests for AST, ALT, ALP, and total bilirubin must be conducted concurrently and assessed concurrently

Hematology

- White blood cell (WBC) count with differential
- Red blood cell (RBC) count
- Hematocrit
- Hemoglobin
- Platelet count
- Mean corpuscular volume
- Mean corpuscular hemoglobin concentration

Urinalysis

- Color
- Appearance
- Specific gravity
- pH
- Protein
- Glucose
- Ketones
- Blood
- Bilirubin
- Microscopy including WBC/high power field (HPF), RBC/HPF

Pregnancy Test (females of childbearing potential only)

- Urine hCG
- Serum βhCG

Other Safety Tests

- Coagulation tests: prothrombin time, partial thromboplastin time, fibrinogen
- Hepatitis B surface antigen, hepatitis C antibody
- HIV-1 antibody
- Thyroid function tests: TSH, free T3 and free T4
- Hepatitis B and C viral titers (only HCC subjects with hepatitis B or C)

5.2.3 Pharmacokinetic Evaluation and Methods

Measurement of MEDI4736 concentrations in serum will be performed using a validated immunoassay.

Details for collection, aliquoting, storage, and shipment of serum samples for PK evaluations are presented in a separate Laboratory Manual.

Blood samples for measurement of MEDI4736 concentrations in serum will be collected in samples taken according to the schedules presented in Section 5.1.

5.2.4 Immunogenicity Evaluation and Methods

Presence of ADA will be assessed in samples taken according to the schedule presented in Section 5.1. Samples will be measured for the presence of ADA by MedImmune using a validated bridging immunoassay. Tiered analysis will be performed to include screening, confirmatory and titer assay components and positive-negative cut points will be employed that were statistically determined from drug naive validation samples. Samples will be collected for assessing the neutralization capacity in the future.

5.2.5 Biomarker Evaluation and Methods

Blood samples will be collected and analyzed to evaluate protein, nucleic acid, and cellular biomarkers that relate to MEDI4736 treatment according to the schedule presented in Section 5.1.

[redacted]

[redacted]

Other biomarkers may be evaluated as determined by additional data. Details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

5.2.6 Disease Evaluation and Methods

Tumor assessments will be based on RECIST v1.1 guidelines (Eisenhauer et al, 2009) with modifications for all subjects, except those with GBM who will be evaluated based on RANO guidelines (Wen et al, 2010), and will be performed during screening and treatment according to the schedule presented in Section 5.1. Modification of RECIST as described may discourage the early discontinuation of MEDI4736 and provide a more complete

evaluation of its antitumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted primarily based on RECIST v1.1. This assessment schedule also applies to those subjects who continue to receive MEDI4736 beyond confirmed PD, and those subjects who re-enter treatment upon evidence of PD during follow-up. For those subjects who discontinue MEDI4736 as a result of confirmed PD, disease evaluation will be performed at the end of treatment visit if clinically appropriate (ie, in the absence of rapidly deteriorating clinical status). For those subjects who enter follow-up after discontinuing MEDI4736 as a result of toxicity or having achieved DC, disease evaluation will be performed at the end of treatment visit, every 2 months for 1 year, and every 3 months thereafter until the end of the study or confirmed PD. Additional disease assessments may be performed as clinically indicated.

All imaging assessments, including unscheduled visit scans, will be collected on an ongoing basis and sent to the sponsor or designee for storage. The centralized storage of imaging data is intended for BICR of disease assessments. At the discretion of the sponsor, a BICR of all scans used in the assessment of tumors by RECIST v1.1 and/or irRECIST will be conducted. Guidelines for imaging collection and storage will be provided in a separate charter. The management of subjects will be based solely upon the results of the assessment conducted by the investigator based on RECIST v1.1. Note: subjects who were assessed by immune-related response criteria (irRC) under older versions of this protocol will continue to be assessed by irRC.

The tumor assessment performed at 6 weeks after initiation of MEDI4736 will not be used to document antitumor efficacy or make decisions regarding subject participation in the study unless observed disease progression is accompanied by rapidly deteriorating clinical status. This is an exploratory disease assessment only and will be used to evaluate the kinetics of tumor response to MEDI4736. However, the investigator and/or subject may decide at any time that it is in the subject's best interest to discontinue from the study.

Tumor assessments may include the following evaluations: physical examination (with photograph and measurement of skin lesions as applicable); computed tomography (CT) or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis; and CT or MRI scan of the brain. Computed tomography or MRI scan of the brain will be performed only at screening or if the subject is neurologically symptomatic. Subjects with GBM should use MRI with contrast for tumor assessments. The preferred method of disease assessment is CT with contrast except for subjects with GBM. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments.

5.2.6.1 RECIST v 1.1

Physical examination

- Lesions detected by physical examination will only be considered measurable if superficial, eg, skin nodules and palpable lymph nodes. Documentation by color photography including ruler is recommended for estimating the size of skin lesions.

CT scan with contrast of the chest, abdomen, and pelvis

- CT scans should be performed with contiguous cuts in slice thickness of 5 mm or less. Spiral CT should be performed using a 5-mm contiguous reconstruction algorithm.

MRI scans

- MRI of the abdomen and pelvis is acceptable for measurement of lesions provided that the same anatomical plane is used for serial assessments. If possible, the same imaging device should be used for serial evaluations. In case of MRI, measurements will be preferably performed in the axial (transverse) plane on contrast-enhanced T1-weighted images. However, there are no specific sequence recommendations.

Measurability of Tumor Lesions

Tumor lesions will be categorized as follows:

- **Measurable Lesions -** Must be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:
- 10 mm by CT scan (irrespective of scanner type) and MRI (no less than double the slice thickness and a minimum of 10 mm).
- 10 mm caliper measurement by clinical exam (when superficial).
- Malignant lymph nodes are 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).
- **Nonmeasurable Lesions -** Nonmeasurable lesions are defined as 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). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.
- **Target Lesions -** All lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target

lesions. 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.

- **Non-target Lesions -** It is possible to record multiple nontarget lesions involving the same organ as a single item on the case record form (eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

Response Criteria

Evaluation of Target Lesions

- **Complete Response -** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be "0" if there are target nodes).
- **Partial Response -** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease -** At least a 20% increase in the sum of 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 progression.)
- **Stable Disease -** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **Complete Response -** 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).
- **Non-complete response/Non-progressive disease -** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease -** Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in non-measurable disease comparable in magnitude to the increase that would be required to declare PD for measurable disease. Examples include an increase in a pleural effusion from 'trace' to 'large,' an increase in lymphangitic disease from localized to widespread.

Appearance of New Lesions

The appearance of new lesions is considered PD according to RECIST v 1.1 guidelines. Considering the unique response kinetics that have been observed with immunotherapy, new lesions may not represent true disease progression. In the absence of rapid clinical deterioration, subjects may continue to receive MEDI4736 if investigators consider that subjects continue to benefit from treatment (see Section 3.4 for a discussion of immunotherapy response kinetics).

Evaluation of Overall Response with Modifications

Confirmation of CR and PR is required by a repeat assessment no less than 4 weeks from the date of first documentation. Progressive disease should be confirmed, preferably at the next scheduled disease assessment, and no less than 4 weeks from the first documentation of PD, in the absence of clinical deterioration. Treatment with MEDI4736 will continue between the initial assessment of PD and confirmation for PD. In addition, subjects may continue to receive MEDI4736 beyond confirmed PD in the absence of clinical deterioration and if investigators consider that subjects continue to receive benefit from treatment. In the absence of clinical deterioration, such modifications to the RECIST or RANO criteria may discourage the early discontinuation of MEDI4736 and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria. Table 5.2.6.1-1 provides overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions.

Table 5.2.6.1-1 Evaluation of Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response (or no non-target lesion)	No	Complete response
No target lesion [a]	Complete response	No	Complete response
Complete response	Not evaluable [b]	No	Partial response
Complete response	Non-complete response / non-progressive disease	No	Partial response
Partial response	Non-progressive disease and not evaluable (or no non-target lesion) [b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable (or no non-target lesion) [b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion [a]	Not all evaluated	No	Not evaluable

Table 5.2.6.1-1 Evaluation of Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
No target lesion [a]	Non-complete response / non-progressive disease	No	Non-complete response / non-progressive disease
Progressive disease	Any	Yes/No	Progressive disease
Any	Progressive disease	Yes/No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion [a]	Unequivocal progressive disease	Yes/No	Progressive disease
No target lesion [a]	Any	Yes	Progressive disease

[a] Defined as no target lesion at baseline.

[b] Not evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment.

5.2.6.2 Revised RANO Criteria

All measurable and nonmeasurable lesions should be assessed using the same techniques as at baseline. Ideally, subjects should be imaged on the same MRI scanner, or at least with the same magnet strength, for the duration of the study to reduce difficulties in interpreting changes.

MRI Scans

Specific lesions must be evaluated serially, and comparative analysis of changes in the area of contrast enhancement, as well as the nonenhancing component, should be performed. The product of the maximal cross-sectional enhancing diameters will be used to determine the size of the contrast-enhancing lesions.

Minimum sequences required:

- Pre-contrast T1, T2/ fluid attenuated inversion recovery (FLAIR)
- Post-contrast T1, with two orthogonal planes (or a volume acquisition) recommended
- Recommended slice thickness $\leq$ 5 mm with no gap

Measurability of Tumor Lesions

Tumor lesions are categorized as follows:

- Measurable disease is defined as bidimensionally contrast enhancing lesions with clearly defined margins by CT or MRI scan, with two perpendicular diameters of at least 10 mm, visible on two or more axial slices that are preferably, at most, 5 mm apart with 0-mm skip.

- Nonmeasurable disease is defined as either unidimensionally measurable lesions, masses with margins not clearly defined, or lesions with maximal perpendicular diameters less than 10 mm. Subjects without measurable disease, such as those who undergo a gross total resection, cannot respond and can only achieve SD as their best radiographic outcome.
  - There are two types of non-target lesions
    - Enhancing (T1 with contrast)
    - Non-enhancing (T2/FLAIR)
  - These are assessed subjectively. Some rules are recommended for objective assessment of progression eg, if a nonmeasurable enhancing lesion becomes measurable, AND either has absolute increase of > 5 mm OR > 25% in sum of products of diameter

Response Criteria

Evaluation of Target Lesions

- Complete response - Requires all of the following: complete disappearance of all enhancing measurable and nonmeasurable disease sustained for at least 4 weeks; no new lesions; stable or improved non-enhancing (T2/FLAIR) lesions; patients must be off corticosteroids (or on physiologic replacement doses only); and stable or improved clinically. Note: Subjects with nonmeasurable disease only, cannot have a CR; the best response possible is SD.
- Partial response - Requires all of the following: 50% decrease compared with baseline in the sum of products of perpendicular diameters of all measurable enhancing lesions sustained for at least 4 weeks; no progression of nonmeasurable disease; no new lesions; stable or improved nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan; the corticosteroid dose at the time of the scan evaluation should be no greater than the dose at time of baseline scan; and stable or improved clinically. Note: Subjects with nonmeasurable disease only, cannot have a PR; the best response possible is SD.
- Stable disease - Requires all of the following: does not qualify for CR, PR, or progression; stable nonenhancing (T2/FLAIR) lesions on same or lower dose of corticosteroids compared with baseline scan. In the event that the corticosteroid dose was increased for new symptoms and signs without confirmation of disease progression on neuroimaging, and subsequent follow-up imaging shows that this increase in corticosteroids was required because of disease progression, the last scan considered to show SD will be the scan obtained when the corticosteroid dose was equivalent to the baseline dose.
- Progression - Defined by any of the following: 25% increase in sum of the products of perpendicular diameters of enhancing lesions compared with the smallest tumor measurement obtained either at baseline (if no decrease) or best response, on stable or increasing doses of corticosteroids; significant increase in T2/FLAIR nonenhancing

lesion on stable or increasing doses of corticosteroids compared with baseline scan or best response after initiation of therapy not caused by comorbid events (eg, radiation therapy, demyelination, ischemic injury, infection, seizures, postoperative changes, or other treatment effects); any new lesion; clear clinical deterioration not attributable to other causes apart from the tumor (eg, seizures, medication adverse events, complications of therapy, cerebrovascular events, infection) or changes in corticosteroid dose; failure to return for evaluation as a result of death or deteriorating condition; or clear progression of nonmeasurable disease.

Evaluation of Enhancing Non-target Lesions

- Complete response - All enhancing non-target lesions have disappeared completely
- Incomplete response/SD - Enhancing lesions present; stable or decreased in size
- Progressive disease - Unequivocal progression
- Unable to assess - Unable to evaluate enhancing lesions because of technical factors

Evaluation of T2/FLAIR Lesion Response

- Improved - Signal abnormality decreased
- Unchanged - Unchanged compared to prior imaging
- Worse - Unequivocal worsening/progression of signal abnormality
- Unable to assess - Unable to evaluate non-enhancing lesions because of technical factors

5.2.7 Archival Tumor Samples and Tumor Biopsies

5.2.7.1 Archival Tumor Samples

Archival tumor samples are required for all subjects and adequate tissue for biomarker analysis must be deemed available during the screening period. This will be waived for subjects who have no archived sample because no previous biopsy has been performed (eg, recently diagnosed or diagnosed with fine needle aspiration); however a biopsy must be performed for all subjects for which suitable archived tumor sample is not available. Subjects in the UBC cohort must provide either a fresh tumor biopsy during screening or an archived tumor specimen from within 6 months prior to study entry (ie, from subject signing consent to participate in the study) for PD-L1 IHC analysis. In addition, UBC subjects must provide additional archival tumor tissue regardless of age if available. Formalin fixed paraffin embedded (FFPE) tumor samples will be collected for IHC and additional correlative markers (eg, tumor mutation analysis, RNA analysis, and immunodiversity). If a tumor block

cannot be provided for this study, then only freshly prepared unstained sections should be provided as described in the Laboratory Manual.

5.2.7.2 Tumor Biopsies

Image-guided core needle tumor biopsy will be performed according to institutional practice during screening and again 6 weeks after initiation of MEDI4736 (if clinically appropriate, ie, repeat biopsy after 6 weeks does not pose unacceptable medical risk to a subject as determined by the investigator) for subjects in the dose-exploration cohort and dose-expansion phase of the study. For subjects in dose-expansion, tumor biopsies resulting in adequate tissue for analysis will be required during screening for 10 subjects each enrolled in the pancreatic adenocarcinoma and nasopharyngeal carcinoma cohorts; 20 subjects enrolled in the advanced cutaneous melanoma, uveal melanoma, HCC, gastroesophageal cancer, SCCHN, TNBC, UBC, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, and HPV-positive cancers cohorts; and for all subjects enrolled in the NSCLC squamous histology and NSCLC non-squamous histology cohorts. If more than 10 subjects are enrolled in the pancreatic adenocarcinoma or nasopharyngeal carcinoma cohorts; more than 20 subjects are enrolled in the HCC, gastroesophageal cancer, SCCHN, TNBC, UBC, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, or HPV-positive cancers cohorts, either a fresh biopsy during screening or archival tissue from less than 6 months prior to enrollment will be required. For all subjects in the UBC cohort enrolled under Amendment 8 and beyond, either a fresh biopsy during screening or archival tissue from less than 6 months prior to enrollment will be required for PD-L1 IHC analysis. Tumor biopsies at 6 weeks after initiation of MEDI4736 are strongly encouraged for all subjects with the exception of subjects in the UBC cohort. For subjects entering retreatment, tumor biopsies during rebaseline and at 6 weeks after initiation of retreatment are encouraged, if clinically feasible with the exception of subjects in the UBC cohort. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions. Additional tumor biopsies are permitted as clinically indicated and if feasible (eg, for mixed responses or upon PD). If clinically practical, at each time point, subjects will undergo 4 core biopsies. The first and third core biopsies will be placed in formalin and processed for FFPE, while the second and fourth core biopsies (fourth biopsy, if available) will be immediately frozen in liquid nitrogen or equivalent method and then stored at -60°C or below. In exceptional cases, excisional or punch biopsies are permitted and may be substituted for the required core biopsies if sufficiently large (4 mm or greater in diameter).

Tumor biopsies will be stored at MedImmune or an appropriate vendor selected by MedImmune. Core biopsies may be used for correlative studies such as IHC, tumor mutation

analysis, RNA analysis, proteomic analysis, and immunodiversity. Additional details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

5.2.8 Patient-reported Outcomes Assessments

The pain questionnaire, European Organisation for Research and Treatment of Cancer quality-of-life questionnaire (EORTC QLQ-C30), and cancer-specific modules are self-administered questionnaires and are to be completed by the subject without the assistance of the investigational site personnel. All questionnaires should be completed before any other study procedures are conducted at the visit. Patient-reported outcome questionnaires need to be administered at screening visit, Day 1 of Dose 1, 3, and 5, and at the same visit as the disease assessment by physical examination and CT scans, before other clinical procedures. If subjects get scans at an outside facility or missed a scheduled data collection, PRO questionnaires need to be administered at the next visit. It takes about 15-20 minutes for subjects to complete all 3 questionnaires and the subjects are asked to only fill out questionnaires that have been validated to be relevant to their specific type of cancer; hence the burden to the subject is moderate. When the subject completes the questionnaires, study coordinators need to review the questionnaires for missing responses and then ask subject to date and sign at places specified in the questionnaires. Note: subjects who began treatment under older versions of this protocol prior to implementation of PRO assessments will not be required to complete the questionnaires. Subjects will not be required to complete questionnaires if unavailable in their native language. Subjects in the dose-exploration cohort are not required to complete PRO assessments.

5.2.8.1 Pain Questionnaire

A pain questionnaire (Appendix 2) containing one question is used: “On a scale ranging from 0 (absent) to 10 (worst imaginable), please rate the severity of your pain in the last 24 hours.”

5.2.8.2 EORTC QLQ-C30 and Cancer-specific Modules

The EORTC QLQ-C30 is a 30-item self-administered questionnaire (Appendix 3). There are 9 multiple-item scales: 5 scales that assess aspects of functioning (physical, role, cognitive, emotional, and social); 3 symptom scales (fatigue, pain, and nausea and vomiting); and a global health status/quality of life scale. There are 5 single-item measures assessing additional symptoms commonly reported by cancer patients (dyspnea, loss of appetite, insomnia, constipation, and diarrhea) and a single item concerning perceived financial impact of the disease. All but 2 questions have 4-point scales: “Not at all,” “A little,” “Quite a bit,” and “Very much.” The 2 questions concerning global health status and quality of life have

7-point scales with ratings ranging from "Very poor" to "Excellent." For each of the 15 domains (9 multiple-item scales, 6 single-item scales), final scores are transformed such that they range from 0-100 whereas higher scores indicate greater functioning, greater quality of life, or greater level of symptom (Aaronson et al, 1993).

Triple Negative Breast Cancer

For TNBC subjects, a disease-specific 23-item self-administered questionnaire for breast cancer was developed (EORTC QLQ-BR23; Appendix 4) to be used in conjunction with the EORTC QLQ-C30. It incorporates 4 functional scales (body image, sexual functioning, sexual enjoyment, and future perspective) and 4 symptom scales (arm symptoms, breast symptoms, systemic therapy side-effects, and upset by hair loss). Both questionnaires are widely used with cancer patients (Montazeri, 2008; Nagel et al, 2001; Svensson et al, 2010; Park et al, 2010).

The EORTC QLQ-BR23 contains 3 items that ask about sexual functioning. Although some subjects may view this as a highly personal issue area, for women with breast cancer sexuality can be greatly impacted. The developers of this standardized questionnaire included these items when the questionnaire was developed and require that they be retained. Subjects can skip these questions if they do not feel comfortable to answer.

Lung Cancer

For NSCLC and SCLC subjects, a disease-specific 13-item self-administered questionnaire for lung cancer was developed (EORTC QLQ-LC13; Appendix 5) to be used in conjunction with the EORTC QLQ-C30 (Bergman et al, 1994). It comprises both multi-item and single-item measures of lung cancer-associated symptoms (ie, coughing, hemoptysis, dyspnea, and pain) and side effects from conventional chemotherapy and radiotherapy (ie, hair loss, neuropathy, sore mouth, and dysphagia).

Gastroesophageal Cancer

For gastroesophageal cancer subjects, a disease-specific 22-item self-administered questionnaire for gastroesophageal cancer was developed (EORTC QLQ-STO22; Appendix 6) to be used in conjunction with the EORTC QLQ-C30 (Blazeby, et al 2004). It comprises both multi-item and single-item measures of gastroesophageal cancer-associated symptoms (ie, dysphagia, pain, reflux, eating, anxiety) and side-effects from conventional chemotherapy and radiotherapy (ie, dry mouth, taste, body image, and hair loss).

Pancreatic Adenocarcinoma

For pancreatic adenocarcinoma subjects, a disease-specific 26-item self-administered questionnaire for pancreatic adenocarcinoma was developed (EORTC QLQ-PAN26; Appendix 7) to be used in conjunction with the EORTC QLQ-C30 (Fitzsimmons and Johnson, 1998; Fitzsimmons et al, 2005). The module comprises 26 questions assessing pain, dietary changes, jaundice, altered bowel habit, emotional problems related to pancreatic adenocarcinoma, and other symptoms such as cachexia, indigestion, flatulence, dry mouth, and taste changes.

Head and Neck Cancer

For head and neck cancer, a disease-specific 35-item self-administered questionnaire for head and neck cancer was developed (EORTC QLQ-H&N35; Appendix 9) to be used in conjunction with the EORTC QLQ-C30 (Bjordal et al, 1994; Bjordal et al, 1999; Bjordal et al, 2000). It comprises both multi-item and single-item measures of head and neck cancer-associated symptoms (ie, pain, swallowing, senses, speech, social eating, social contact, sexuality) and side-effects from conventional chemotherapy and radiotherapy.

The EORTC QLQ-H&N35 contain items that ask about sexual functioning. Although some subjects may view this as a highly personal issue area, for those with head and neck cancer sexuality can be greatly impacted. The developers of this standardized questionnaire included these items when the questionnaire was developed and require that they be retained. Subjects can skip these questions if they do not feel comfortable to answer.

Hepatocellular Cancer

For HCC, a disease-specific 18-item self-administered questionnaire for HCC was developed (EORTC QLQ-HCC18; Appendix 8) to be used in conjunction with the EORTC QLQ-C30 (Blazeby et al, 2004). It comprises multi-item scales assessing fatigue, body image, jaundice, nutrition, pain, and fever, with 2 single-items addressing sexual interest and abdominal swelling.

The EORTC QLQ-HCC18 contains items that ask about sexual functioning. Although some subjects may view this as a highly personal issue area, for those with head and neck cancer or HCC sexuality can be greatly impacted. The developers of this standardized questionnaire included these items when the questionnaire was developed and require that they be retained. Subjects can skip these questions if they do not feel comfortable to answer.

Melanoma

With the exception for uveal melanoma, subjects are only required to complete the EORTC QLQ-C30 questionnaire. For uveal melanoma subjects, since most of the metastasis are in liver, the liver cancer module EORTC QLQ-HCC18 (Appendix 8), will be used to collect subject reported liver metastasis related symptoms in conjunction with the EORTC QLQ C30.

Glioblastoma Multiforme

For subjects with GBM, a disease-specific, 20-item self-administered questionnaire for brain cancer was developed (EORTC QLQ-BN20 [Osoba et al, 1996; Taphoorn et al, 2010; Maringwa et al, 2011]; Appendix 10) to be used in conjunction with the EORTC QLQ-C30. It includes 4 symptom scales (future uncertainty, visual disorder, motor dysfunction, and communication deficit) and 7 symptom items (headaches, seizures, drowsiness, hair loss, itching skin, weakness of both legs, and bladder control). The EORTC QLQ-C30 and the EORTC QLQ-BN20 have been used in a number of brain cancer clinical trials (Taphoorn et al, 2005; Keime-Giubert et al, 2007; Grabenbauer et al, 2009; Chinot et al, 2011; Flechl et al, 2012).

Ovarian Cancer

For subjects with ovarian cancer, a disease-specific, 28-item self-administered questionnaire for women with ovarian cancer was developed (EORTC QLQ-OV28; Appendix 11) to be used in conjunction with the EORTC QLQ-C30. It includes 7 items on abdominal/gastrointestinal symptoms, 3 items on peripheral neuropathy, 7 items on other chemotherapy side effects, 2 items on hormonal/menopausal symptoms, 2 items on body image, and 3 items on attitude toward disease and treatment (Cull et al, 2001; Greimela et al, 2003).

The EORTC QLQ-OV28 contains 4 items that ask about sexual functioning. Although some subjects may view this as a highly personal issue area, for women with ovarian cancer sexuality can be greatly impacted. The developers of this standardized questionnaire included these items when the questionnaire was developed and require that they be retained. Subjects can skip these questions if they do not feel comfortable answering them.

5.2.8.3 FACT-BL

For subjects with bladder cancer, a disease-specific, 39-item self-administered questionnaire for bladder cancer was developed (Functional Assessment of Chronic Illness Therapy-

bladder [FACT-BL]; Appendix 12). Of the 39 questions, 27 come from the Functional Assessment of Chronic Illness Therapy-General (FACT-G) and 12 questions are specific to bladder cancer. All questions inquire about the subject's health-related quality of life during the past week. The FACT-BL (version 4) covers the domains of physical well-being, social/family well-being, emotional well-being, functional well-being as well as urinary, bowel, and sexual function (Cella et al, 1993).

The FACT-BL contains 3 items that ask about sexual functioning; one of these items is for men only. Although some subjects may view this as a highly personal issue area, for people with bladder cancer sexuality can be greatly impacted. The developers of this standardized questionnaire included these items when the questionnaire was developed and require that they be retained. Subjects can skip these questions if they do not feel comfortable answering them.

5.2.9 Estimate of Volume of Blood to be Collected

Q2W or Q3W Dosing Schedule

A total of 45 mL will be required for all screening tests, which may be conducted over 1 or more days during screening. No more than 51 mL of blood will be drawn on any visit day after screening. Approximately 179 mL of blood will be collected at all visits related to the first dose. The total volume to be collected will depend on the number of doses administered and the length of follow-up. Subjects in the first cohort in the dose-escalation phase will have an additional 3.5-mL blood sample drawn for PK at 2 hours after the start of the first infusion.

Q4W Dosing Schedule

Approximately 28 mL will be required for all screening tests. No more than 33 mL of blood will be drawn on any visit day after screening. Approximately 56 mL of blood will be collected at all visits related to the first dose. The total volume to be collected will depend on the number of doses administered and the length of follow-up.

6 ASSESSMENT OF SAFETY

6.1 Safety Parameters

6.1.1 Adverse Events

The International Conference on Harmonisation (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

> Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this 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 product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition that did not worsen from baseline is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

6.1.2 Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- This term refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that may have led to death.
- Requires inpatient hospitalization or prolongation of existing hospitalization
- In general, hospitalization signifies that the subject has been detained (usually involving at least an overnight stay) at the hospital or emergency ward for observation and/or treatment that would not have been appropriate in an outpatient setting.
- Results in persistent or significant disability/incapacity
- The term disability means a substantial disruption of a person's ability to conduct normal life functions.

- Is a congenital anomaly/birth defect in offspring of the subject
- Is an important medical event that may jeopardize the subject or may require medical intervention to prevent one of the outcomes listed above.
- Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

6.1.3 Other Events of Special Interest

Adverse events of special interest are events of scientific and medical interest specific to the further understanding of the MEDI4736 safety profile and require close monitoring and rapid communication by the investigator to the sponsor. MEDI4736 AESIs may be serious or non-serious. The rapid reporting of these AESIs allows ongoing analysis of these events in order to characterize and understand them in association with the use of this investigational product.

Adverse events of special interest 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 irAE is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an 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 study physician.

Adverse events of special interest observed with MEDI4736 include:

- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy/neuromuscular toxicity (ie, events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)

- Endocrinopathy (ie, events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)

Further information on these risks (eg, presenting symptoms) can be found in Appendix 15.

6.1.3.1 Pneumonitis

Pneumonitis has been reported in association with use of anti-PD-L1/anti-PD-1 antibodies (Brahmer et al 2012). Initial work-up should include a high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is recommended.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the MEDI4736 Investigator's Brochure. Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Appendix 15.

6.1.3.2 Hypersensitivity Reactions

Hypersensitivity reactions as well as infusion-related reactions have been reported with anti-PD-L1 and anti-PD-1 therapy (Brahmer et al 2012). As with the administration of any foreign protein and/or other biologic agents, reactions following the infusion of MAbs can be caused by various mechanisms, including acute anaphylactic (IgE-mediated) and anaphylactoid reactions against the MAb, and serum sickness. Acute allergic reactions may occur, may be severe, and may result in death. Acute allergic reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness.

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Appendix 15.

6.1.3.3 Hepatic Function Abnormalities (Hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1 (Brahmer et al 2012). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 MAbs (eg, ipilimumab). The clinical manifestations of

ipilimumab-treated patients included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN **and concurrent** increase in bilirubin to greater than 2 × ULN (ie, Hy's law cases). Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (eg, cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product.

If the underlying diagnosis for the hepatic function abnormality is known (including progression of pre-existing disease such as primary or metastatic malignancy), the diagnosis should be recorded as an AE/SAE.

If the underlying diagnosis for the hepatic function abnormality remains unknown, the term "hepatic function abnormal" should be used to report the AE/SAE.

Hepatic function abnormality of unknown etiology, or which is considered attributable to investigational product, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to MedImmune Patient Safety using the SAE Report Form, even if the event is considered to be non-serious (see Section 6.4.2.2 for contact information). The investigator will review the data with the medical monitor. The investigator should then use clinical judgment to establish the cause based on local standard of care and follow the subject by conducting testing as clinically indicated.

6.2 Assessment of Safety Parameters

6.2.1 Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.03.

The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild)	An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.
Grade 2 (moderate)	An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.
Grade 3 (severe)	An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.
Grade 4 (life threatening)	An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).
Grade 5 (fatal)	Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

6.2.2 Assessment of Relationship

6.2.2.1 Relationship to Investigational Product

The investigator is required to provide an assessment of relationship of AEs and SAEs to the investigational product.

An event will be considered “not related” to use of the investigational product if any of the following tests are met:

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)

- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

Individual AE/SAE reports will be considered "related" to use of the investigational product if the "not related" criteria are not met.

"Related" implies that the event is considered to be "associated with the use of the drug" meaning that there is "a reasonable possibility" that the event may have been caused by the product under investigation (ie, there are facts, evidence, or arguments to suggest possible causation).

6.2.2.2 Relationship to Protocol Procedures

The investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes nontreatment-emergent SAEs (ie, SAEs that occur prior to the administration of investigational product) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (eg, blood collection, washout of an existing medication). The following guidelines should be used by investigators to assess the relationship of SAEs to the protocol:

Protocol related: The event occurred due to a procedure/intervention that was described in the protocol for which there is no alternative etiology present in the subject's medical record.

Not protocol related: The event is related to an etiology other than the procedure/ intervention that was described in the protocol (the alternative etiology must be documented in the study subject's medical record).

6.3 Recording of Safety Parameters

6.3.1 Recording of Adverse Events and Serious Adverse Events

Adverse events will be recorded on the CRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to MedImmune Patient Safety. See Section 6.1.2 for the definition of SAEs, and Section 6.2.1 and Section 6.2.2 for guidelines for assessment of severity and relationship, respectively. If an

AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

6.3.2 Recording of Other Events of Special Interest

Hepatic Function Abnormality

Events of hepatic function abnormality (as defined in Section 6.1.3.3) should be recorded according to the definitions of AE and SAE (Section 6.1.1 and Section 6.1.2, respectively):

- If an event of hepatic function abnormality is considered to be related to a pre-existing condition and does not represent a worsening of this condition and/or is considered to be within the range of normal physiological fluctuation for the subject, the event does not meet the definition of an AE and does not need to be recorded as such.
- If a definitive diagnosis for an underlying condition unrelated to the investigational product is established for an event of hepatic function abnormality, the diagnosis should be recorded as an AE/SAE per Section 6.3.1.
- If no definitive diagnosis is determined for an event of hepatic function abnormality, the term "hepatic function abnormal" should be used to report the AE/SAE per Section 6.3.1.

6.4 Reporting Requirements for Safety Parameters

6.4.1 Study Reporting Period and Follow-up for Adverse Events

The reporting period for AEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of MEDI4736 or until the initiation of alternative anticancer therapy.

New (nonserious) AEs that start after the reporting period has ended will not be collected. All AEs that start during the reporting period will be followed to resolution through the end of subject participation in the study.

6.4.2 Reporting of Serious Adverse Events

6.4.2.1 Study Reporting Period and Follow-up for Serious Adverse Events

The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of MEDI4736. After submitting an initial SAE report for a subject (to MedImmune Patient Safety), the investigator is required to follow the subject proactively and provide further information on the subject's condition to MedImmune Patient Safety.

At any time after completion of the study, if an investigator or qualified designee becomes aware of an SAE that is suspected by the investigator or qualified designee to be related to investigational product, the event must be reported to MedImmune Patient Safety.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

6.4.2.2 Notifying the Sponsor of Serious Adverse Events

Within 24 hours of identifying an SAE, regardless of the presumed relationship to the investigational product, the investigator or qualified designee must complete the SAE Report Form and fax it to MedImmune Patient Safety.

MedImmune contact information:

Patient Safety
MedImmune
One MedImmune Way
Gaithersburg, MD 20878
USA
Fax: +1 301-398-4205

The sponsor is responsible for reporting certain SAEs as expedited safety reports to applicable regulatory authorities, ethics committees, and participating investigators, in accordance with ICH Guidelines and/or local regulatory requirements (see Section 6.4.2.3). The sponsor may be required to report certain SAEs to regulatory authorities within 7 calendar days of being notified about the event; therefore, it is important that investigators submit additional information requested by the sponsor as soon as it becomes available.

Investigators should provide all available information at the time of SAE Report Form completion. Investigators should not wait to collect additional information to fully document the event before notifying MedImmune Patient Safety of an SAE. When additional information becomes available, investigators should submit a follow-up SAE Report Form (separate from the initial report form) with the new information. Any follow-up information to an SAE also needs to be provided to MedImmune Patient Safety within 24 hours of learning of the new information.

6.4.2.3 Safety Reporting to Investigators, Institutional Review Boards or Independent Ethics Committees, and Regulatory Authorities

The sponsor is responsible for reporting all applicable SAEs to regulatory authorities, investigators, and IRBs/IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of an investigational product or that would be sufficient to consider changes in the administration of the investigational product or in the overall conduct of the study.

For all investigators located in the European Economic Area, the sponsor will be responsible for reporting suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities including the European Medicines Agency, investigators, and IRBs/IECs, as applicable, in accordance with national regulations in the countries where the study is conducted. Suspected unexpected serious adverse reactions will be submitted within 7 days for fatal and life-threatening events and within 15 days for other serious events, unless otherwise required by national regulations.

For all other investigators, the sponsor will prepare an expedited report for all SAEs that are unexpected and potentially related to the investigational product, and copies will be distributed to all concerned regulatory authorities, investigator(s), and IRBs/IECs according to applicable laws and regulations. The investigational site also will forward a copy of all expedited reports to the site's applicable IRB/IEC. Investigators must also submit safety information provided by the sponsor to the IRB/IEC as detailed in Section 10.1 and Section 10.2.

6.4.3 Other Events Requiring Immediate Reporting

6.4.3.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with the investigational product, with or without associated AEs/SAEs, is required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE CRF (see Section 6.3.1). 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 reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.4.3.2 Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 6.1.3) 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 MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information), unless a definitive underlying diagnosis for the abnormality (eg, cholelithiasis and bile duct obstruction) that is unrelated to investigational product has been confirmed.

- 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. If the etiology of the event remains unconfirmed and/or is considered related to investigational product (see Section 6.2.2.1), a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by the internal safety governance bodies (see Section 6.5) to determine whether continued dosing of current study subjects and/or study entry should be interrupted, whether the protocol will be modified, or whether the study will be discontinued permanently. Review and approval by the internal safety governance bodies is required for resumption of subject dosing or study entry in the event that the study is interrupted. Where applicable, regulatory authorities and IRBs/IECs will be notified of any actions taken with the study.

6.4.3.3 Pregnancy

Pregnancy in a female subject who has received investigational product is required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information).

Subjects who become pregnant during the study period must not receive additional doses of investigational product but will not be withdrawn from the study. After obtaining the subject's consent, the pregnancy will be followed for outcome of the mother and child (including any premature terminations) and should be reported to MedImmune Patient Safety after outcome.

Should the investigator become aware of a pregnancy in the partner of a male study subject who has received investigational product(s) this should be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety or designee using the Safety Fax Notification Form. The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

6.4.3.4 Events Meeting Study-stopping Criteria

Events that meet any of the study-stopping criteria (Section 3.3), with or without associated AEs or SAEs, are required to be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 6.4.2.2 for contact information). The occurrence of these events does not automatically make an AE serious, but if the consequences of the event are serious, for example death or hospitalization, the event is serious and must be reported as an SAE (see Section 6.3.1 and Section 6.4.2).

6.5 Safety Management During the Study

The MedImmune medical monitor has primary responsibility for the ongoing medical review of safety data throughout the study. This includes review of SAEs and timely review of AEs and "other events" reported during the study. MedImmune Patient Safety is responsible for the receipt, immediate review, investigation, and follow-up of SAEs and other immediately reportable events (eg, overdose and pregnancies) reported from the clinical study sites.

A study-specific Dose Escalation Committee will provide ongoing safety surveillance of the study, with regularly scheduled reviews of safety and other relevant data. This committee will be responsible for dose-escalation decisions and making recommendations regarding further conduct of the study. The Dose Escalation Committee includes the MedImmune medical monitor for the study, the MedImmune Patient Safety physician for the study, and the principal investigator from each actively enrolling study site. This committee will review data, including all AEs, laboratory parameters, PK and pharmacodynamic data, following the full enrollment of any dose-escalation cohort and completion of the DLT evaluation period. This committee will also review data at other time points in response to AEs assessed as medically relevant by the medical monitor. Dose-escalation decisions and outcomes of reviews of safety and other relevant data will be communicated to the internal safety governance bodies. The sponsor will notify sites when enrollment into each dose cohort has been completed and when enrollment into the next dose cohort is permitted.

The MedImmune Safety Review Team (SRT) provides safety surveillance, guidance, and oversight for all clinical development studies of MEDI4736 in which MedImmune has

sponsor accountabilities. The SRT reviews protocol-specific safety data at regularly scheduled meetings and ad hoc meetings, and provides oversight for individual study protocol safety committees, such as those specified for early-phase dose-escalation studies. Based on review of safety data, the SRT may recommend suspension of enrollment or subject dosing in clinical studies, request modification of study documents, or take other actions as deemed necessary.

7 STATISTICAL CONSIDERATIONS

7.1 General Considerations

Data will be provided in data listings sorted by treatment group and subject number. Tabular summaries will be presented by treatment group. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics, including mean, standard deviation, median, minimum, and maximum. Confidence intervals (CIs) will be two-sided, unless otherwise stated. Details of endpoint analyses will be described in the Statistical Analysis Plan.

7.2 Analysis Populations

The DLT Evaluable Population includes all subjects enrolled in the dose-escalation phase who receive at least 2 doses of MEDI4736 and complete the safety follow-up through the DLT evaluation period (defined as the time period from the first administration of MEDI4736 until the planned administration of the third dose of MEDI4736) or experience any DLT. The DLT Evaluable Population will be used for the MTD evaluation.

The As-treated Population includes all subjects who receive any treatment with MEDI4736. The As-treated Population will be used to evaluate baseline characteristics as well as all endpoints for the safety and efficacy profiles, unless otherwise specified.

The full analysis set (FAS) includes all subjects from the As-treated Population who have baseline disease assessment with measurable disease per BICR and at least 24 weeks follow-up at the time of the data cutoff (ie, dosed at least 24 weeks prior to the time of the data cutoff). This is the primary analysis population for the analysis of efficacy endpoints using the BICR data.

The PD-L1-positive FAS includes those PD-L1-positive subjects in the FAS as defined by an IHC assay developed by Ventana. The PD-L1-negative FAS includes those PD-L1-negative subjects in the FAS as defined by an IHC assay developed by Ventana. The definition for a

subject whose PD-L1 status is PD-L1 positive or negative may be specific for each tumor type, as described below.

- For NSCLC and SCCHN cohorts, positive for PD-L1 as defined by ≥ 25% tumor cell membrane for PD-L1 at any intensity. A subject's PD-L1 status will be determined from a fresh tumor biopsy obtained during screening and/or available archival tumor samples.
- For the UBC cohort, positive for PD-L1 is defined as ≥ 25% tumor cell membrane or ≥ 25% immune cell staining. A subject's PD-L1 status will be derived from a fresh tumor biopsy taken during screening and/or available tumor samples taken from ≤ 6 months prior to study entry. In cases where multiple samples are available, a subject's PD-L1 status will be derived from the most recent tumor sample (prior to first dose of study treatment) with a quantifiable result. If all samples taken ≤ 6 months prior to the study entry are non-evaluable by IHC, PD-L1 status may be derived form an older archival sample.

7.3 Endpoints

7.3.1 Primary Endpoints

For the dose-escalation phase, the primary objective is to determine the MTD or OBD, and safety profile of MEDI4736 in subjects with advanced melanoma, RCC, NSCLC, and CRC refractory to standard therapy or for which no standard therapy exists.

Endpoints related to this objective include an evaluation of DLTs, overall safety, and parameters related to the MTD or OBD. The MTD evaluation will be based on the DLT Evaluable Population. The OBD will be determined based upon analysis of all available subject data, including safety, PK, pharmacodynamic, biomarker, and response data.

For the dose-expansion phase, the primary objectives are:

- To determine the safety profile of MEDI4736 in subjects with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC, pancreatic adenocarcinoma, UBC, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, HPV-positive cancers, or nasopharyngeal carcinoma.
- To evaluate the antitumor activity of MEDI4736 in subjects with non-squamous NSCLC who have received 2 or more prior lines of therapy and subjects with squamous NSCLC who have received 1 prior lines of therapy and 2 or more prior lines of therapy.
- To evaluate the antitumor activity of MEDI4736 in subjects with PD-L1-positive UBC.

Endpoints for safety profile include assessments of AEs, SAEs, laboratory evaluations, vital signs, and physical examinations. The occurrence of AEs, abnormal laboratory values, and

SAEs reported from the signing of an ICF through 90 days after the last dose of MEDI4736 will be summarized and/or listed for all subjects who received at least one dose of MEDI4736 (As-treated Population). Any SAEs occurring after 90 days after the last dose of MEDI4736 that, in the opinion of the investigator, are related to study drug will also be reported and summarized and/or listed. Adverse events and SAEs will be graded according to the NCI CTCAE v4.03 and described by system organ class using the Medical Dictionary for Regulatory Activities (MedDRA) preferred term, severity, and relationship to MEDI4736.

The primary endpoint of antitumor activity for the NSCLC and UBC cohorts is objective response (OR), which is defined as a best overall response (BoR) of CR or PR according to RECIST v1.1 as determined by BICR. BoR is defined as the best response (in the order of CR, PR, SD, PD, and not evaluable) among all overall responses recorded from the start of treatment until objective documentation of PD (per RECIST v1.1 as assessed by BICR), or the last evaluable disease assessment in the absence of PD prior to initiation of subsequent anticancer therapy or discontinuation from the study, whichever occurs first. The best overall response of CR or PR must be confirmed, which means a response of CR/PR is recorded at a visit and confirmed by repeat imaging no less than 4 weeks after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visits. The ORR is defined as the proportion of subjects with OR. The 95% CI of ORR will be estimated using the exact probability method.

For NSCLC, the ORR (based on RECIST v1.1 by BICR) along with its 95% CI will be provided for all NSCLC subjects in each line by histology and for the subpopulation in the ≥ second-line squamous NSCLC subjects who have tumoral PD-L1 expression as determined by prospective testing prior to enrollment.

For UBC, the primary analysis of ORR based on RECIST v1.1 by BICR will be performed for all UBC subjects (second-or greater line of therapy) in the PD-L1-positive FAS enrolled in the entire study. The primary endpoint for UBC cohort in PD-L1-positive subgroup is considered to be met if the lower-limit of the exact 2-sided 95% CI for ORR excludes a historical response rate of 10% or less (Bellmunt et al, 2009). An analysis of ORR for all UBC subjects in the PD-L1-positive FAS enrolled under Amendment 8 and beyond will be conducted as a supportive analysis.

If the primary endpoint for the PD-L1-positive subgroup of the UBC cohort is met, the ORR based on RECIST v1.1 by BICR along with its 95% CI will be also provided for all UBC subjects (second-or greater line of therapy) in the FAS (regardless of PD-L1 status) enrolled in the entire study. The primary endpoint for UBC cohort in all-comers is considered to be

met if the lower-limit of the exact 2-sided 95% CI for ORR excludes a historical response rate of 10% or less (Bellmunt et al, 2009). In addition, the ORR based on RECIST v1.1 by BICR along with its 95% CI will be provided for all UBC subjects (second- or greater line of therapy) in the PD-L1-negative FAS enrolled in the entire study and in the PD-L1-negative FAS enrolled under Amendment 8 and beyond. The primary analysis for UBC cohort will occur at least 24 weeks after the last PD-L1-positive UBC subject's first dose of study treatment. The analyses of ORR per BICR described above for the UBC cohort will be repeated for the UBC subjects (second- or greater line of therapy) in the PD-L1-positive FAS, the PD-L1-negative FAS and the FAS (regardless of PD-L1 status) enrolled in the entire study.

In order to validate the potential of PD-L1 expression to predict response to MEDI4736 treatment, the ORR per BICR for UBC subjects in the PD-L1-positive FAS and the PD-L1-negative FAS enrolled under Amendment 8 and beyond will be compared using one-sided Fisher's exact test with a significance level of 5%. The difference in the ORR along with the exact 2-sided 90% CI will be estimated based on Chan and Zhang's method based on score statistics (Chan and Zhang, 1999). A multivariate logistic regression analysis may be conducted to assess the difference after adjusting for important baseline characteristics. An odds ratio with its associated profile likelihood 90% CI will be provided.

Additional analysis of ORR as determined by the investigator according to RECIST v1.1 will be conducted in the same manner as those described for the BICR-assessed ORR. The investigator's recorded measurements and assessments for target, non-target, and new lesions according to RECIST v1.1 will be used to derive the overall response and progression programmatically.

For the dose-exploration cohort, the primary objective is to determine the safety profile of MEDI4736 in subjects with advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous histology, NSCLC non-squamous histology, gastroesophageal cancer, TNBC and pancreatic adenocarcinoma using a Q4W dosing schedule. Endpoints for safety profile including assessments of AEs, SAEs, laboratory evaluations, vital signs, and physical examinations will be summarized in the same manner as those described above for dose-expansion phase.

7.3.2 Secondary Endpoints

7.3.2.1 Pharmacokinetics

Individual MEDI4736 concentrations will be tabulated by dose cohort along with descriptive statistics. Noncompartmental PK data analysis will be performed for data obtained from each

dose cohort with scheduled PK sample collection. If data allow, descriptive statistics of noncompartmental PK parameters (area under the curve, C_{max}, systemic clearance, half-life) will be provided.

A population PK model will be developed using a non-linear mixed-effects modeling approach in subjects treated with MEDI4736. The impact of physiologically-relevant subject characteristics (covariates) and disease characteristics on PK will be evaluated. The relationship between MEDI4736 blood exposure and response or safety will be evaluated. Any such analysis will be described in a separate population PK/pharmacodynamic analysis plan and the results for this exploratory analysis will be reported separately from the main study report.

7.3.2.2 Immunogenicity

The immunogenic potential of MEDI4736 will be assessed by summarizing the number and percentage of subjects who develop detectable ADAs. The impact of ADAs on PK will be assessed if data allow. Samples will be collected for evaluating neutralizing capacity of ADAs in the future.

7.3.2.3 Antitumor Activity

Assessments of antitumor activity will be based on the ORR (except for subgroups of NSCLC and UBC cohorts where OR is considered the primary endpoint), DCR, duration of response (DR), progression-free survival (PFS), and OS. RECIST v1.1 (Eisenhauer et al, 2009) will be used to determine tumor response (see Section 5.2.6).

The ORR is defined in Section 7.3.1. The DCR is defined as the proportion of subjects with CR, PR, or SD (subjects achieving SD will be included in the DCR if they maintain SD for ≥ 12 weeks). Disease control rate will be analyzed in a manner similar to ORR. The 95% CI of DCR will be estimated using the exact probability method. Duration of response will be defined as the duration from the first documentation of objective response to the first documented disease progression or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of data cutoff for analysis, DR will be censored at the last tumor assessment date. The DR will only be evaluated for the subgroup of subjects with an objective response using the Kaplan-Meier method (Kaplan and Meier, 1958).

Progression-free survival will be measured from the start of treatment with MEDI4736 until the documentation of disease progression or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of data cutoff for analysis, PFS

will be censored at the last tumor assessment date. Progression-free survival will be evaluated using the Kaplan-Meier method. Overall survival will be determined as the time from the start of treatment with MEDI4736 until death. For subjects who are alive at the time of data cutoff for analysis or lost to follow-up, OS will be censored on the last date when subjects are known to be alive. The OS will be evaluated using the Kaplan-Meier method (Kaplan and Meier, 1958).

Separate analyses of efficacy endpoints will be performed based on BICR assessment (if BICR data are available) and investigator assessment.

7.3.3 Exploratory Endpoints

Descriptive statistics will be the primary methods used for the exploratory analyses. Depending on the nature of the data, geometric mean and other appropriate statistical summaries might be used as well. It is hypothesized that MEDI4736 will induce measurable changes in the immune status of subjects. Among the variables to be examined in the exploratory analyses to assess these changes are:

[redacted]

7.4 Subgroup Analysis

In the dose-expansion phase, the antitumor activity by baseline PD-L1 expression (positive vs negative), line of therapy, ECOG performance status, and metastatic site at baseline, when practical and appropriate, will be assessed in each as well as across all disease cohorts.

In assessment of antitumor activity in the UBC population, subjects will be also be analyzed by baseline hemoglobin levels (≤ 10 g/dL vs > 10 g/dL), baseline creatinine clearance levels (< 60 mL/min vs ≥ 60 mL/min), PD-L1 subgroups defined based on tumor cell staining only, and PD-L1 subgroups defined based on immune cell staining only.

7.5 Interim Analysis

For the UBC cohort, the first interim analysis will be conducted after approximately 30 PD-L1-positive UBC subjects are enrolled and followed for at least 12 weeks. The efficacy analysis will be based on investigator RECIST data.

The second interim analysis for the UBC cohort will be conducted after approximately a minimum of 60 PD-L1-positive second- or greater line UBC subjects are enrolled in the entire study and followed for at least 16 weeks. The primary efficacy analysis population for this analysis will be based on the treated PD-L1-positive UBC subjects (second- or greater

line) with measurable disease at baseline per BICR who have had an opportunity of being followed up for at least 16 weeks by the interim analysis. The analysis will be primarily based on RECIST v1.1 by BICR, and additional analysis based on investigator RECIST data will be conducted as supportive.

The purpose of those interim analyses for the UBC cohort will be for early evaluation of efficacy and safety data for internal program decision and/or potential interactions with regulatory agencies on future development. Additional data cut-offs for the UBC cohort may also take place before the primary analysis of ORR to support interactions with the regulatory authorities. The enrollment will not be interrupted or terminated for efficacy based on the interim analysis.

7.6 Sample Size and Power Calculations

[redacted]

Dose-escalation Phase

The number of subjects required will depend upon the toxicities observed as the study progresses. Up to approximately 50 evaluable subjects (3+3 subjects per dose cohort) could be required during the dose-escalation phase if the separate Q3W escalation is implemented upon completion of dose escalation for the MEDI4736 Q2W dose-escalation arm. More subjects may be enrolled to investigate intermediate doses for MTD evaluation if DLTs are observed in either the 3.0 or 10 mg/kg dose cohort. In addition, more subjects may be enrolled if doses higher than 10 mg/kg Q2W are evaluated during dose escalation. Non-evaluable subjects will be replaced in the same dose cohort. Table 7.6-1 provides the probability of dose escalation to the next higher level for each underlying true DLT rate. For example, for a common toxicity that occurs in 10% of subjects, there is a greater than 90% probability of escalating to the next higher dose level. Conversely, for a toxicity that occurs with a rate of 60%, the probability of escalating to the next higher dose level is less than 10%.

Table 7.6-1 Probability of Escalation for Different True Underlying Dose-limiting Toxicity Rate at a Given Dose Level

True underlying DLT rate	10%	20%	30%	40%	50%	60%	70%	80%	90%
Probability of escalating dose	0.91	0.71	0.49	0.31	0.17	0.08	0.03	0.009	0.001

DLT = dose-limiting toxicity.

Dose-exploration Phase

Approximately 20 subjects will be enrolled in the dose-exploration cohort of the study to determine the safety of 20 mg/kg Q4W dose schedule. [redacted]

Dose-expansion Phase

A minimum of approximately 692 subjects will be enrolled in the dose-expansion phase as follows. Additional subjects, described in each cohort below, may be enrolled if promising clinical activity is observed in any of these cohorts.

- Advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, gastroesophageal cancer, TNBC, UBC (initial cohort enrolled prior to Amendment 8), GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, and HPV-positive cancers cohorts: A minimum of 20 subjects will be enrolled in each of these 13 disease cohorts. The sample size is chosen to obtain a preliminary assessment of antitumor activity in terms of DCR for each disease cohort. The DCR will be estimated by the proportion of subjects with CR, PR, or SD ≥ 12 weeks in each disease cohort and its 80% CI will be estimated by the exact probability method [redacted] Additional subjects, up to a total of 60 subjects in any of these dose-expansion cohorts may be enrolled if promising clinical activity is observed in that cohort. If the HPV-positive cancers, MSI-high cancers, GBM, ovarian, or soft tissue sarcoma cohorts are expanded beyond 20 subjects, enrollment may be prioritized to tumor sub-type(s) that showed promising clinical activity, at the sponsor's discretion.

Table 7.6-2 [redacted]

[redacted]							
[redacted]							

Table 7.6-2 [redacted]

[redacted]							
[redacted]							
[redacted]							

- Pancreatic adenocarcinoma and nasopharyngeal carcinoma cohorts: A minimum of 10 subjects will be enrolled in each of these cohorts. The DCR will be estimated by the proportion of subjects with CR, PR, or SD ≥ 12 weeks in each cohort and its 80% CI will be estimated by the exact probability method (Table 7.6-3). Additional subjects, up to a total of 60 subjects in either of these 2 cohorts may be enrolled if promising clinical activity is observed in that cohort.

Table 7.6-3 [redacted]

[redacted]				
[redacted]				
[redacted]				

- NSCLC: Preliminary data from the dose-escalation phase of this study as well as data from other antibodies targeting the PD-1/PD-L1 pathway suggest that subjects with NSCLC may benefit from treatment with an agent such as MEDI4736. As a result, a minimum of approximately 110 subjects in the non-squamous histology NSCLC cohort and 170 subjects in the squamous histology NSCLC cohort will be enrolled from among specific subpopulations of NSCLC as outlined below.
  - For the non-squamous NSCLC cohort, the enrollment will include approximately 10 subjects who are treatment naïve, approximately 20 subjects who have received 1 prior line of therapy, and approximately 80 subjects who have received at least 2 prior lines of therapy. Additional subjects, up to a total of 30 each for the first-line and second-line therapy groups, may be enrolled.
  - For the squamous NSCLC cohort, the enrollment will include approximately 10 subjects who are treatment naïve, approximately 80 subjects who have received 1 prior line of therapy, and approximately 80 subjects who have received at least 2 prior lines of therapy. Additional subjects, up to a total of 30 for the first-line therapy group, may be enrolled.
  - The minimum sample sizes of 10 and 20 subjects were chosen to provide a preliminary assessment of ORR for MEDI4736 as first-line therapy for both squamous and non-squamous NSCLC and second-line therapy for non-squamous NSCLC, respectively, similar to the aforementioned other cohorts in other tumor types.

- The sample size of 80 subjects for MEDI4736 as third or greater-line therapy in non-squamous NSCLC and as second-line therapy as well as third or greater-line therapy for squamous NSCLC, respectively, was chosen to provide a formal statistical testing of the following hypothesis

$$H_0: ORR \leq 10\% \text{ vs } H_1: ORR > 10\%$$

[redacted]

In order to have the estimation with reasonable precision for ORR in the NSCLC subpopulation with subjects who have tumoral PD-L1 expression, all remaining subjects in the non-squamous NSCLC dose-expansion cohort will be required to have tumoral PD-L1 expression as determined by prospective testing prior to enrollment. In the squamous NSCLC dose-expansion cohort, a minimum of 80 subjects in the squamous NSCLC dose-expansion cohorts (a minimum of 10 subjects in the first-line therapy, a minimum of 35 subjects in each of the second-line therapy and third-line or greater therapy cohorts) will be required to have tumoral PD-L1 expression as determined by prospective testing prior to enrollment. Table 7.6-4 provides the estimated ORR and its 95% confidence interval (CI) in squamous NSCLC subjects based on the exact binomial distribution.

Table 7.6-4 Estimated ORR and 95% CI in Squamous NSCLC Subjects with Tumoral PD-L1 Expression

Category	N = 35 [a]			N = 70 [b]			N = 80 [b]		
Number of CR/PR observed	7	9	11	18	21	25	20	24	28
Estimated ORR	20%	25.7%	31.4%	25.7%	30%	35.7%	25%	30%	35%
Lower limit of 95% CI	8.4%	12.5%	16.9%	16.0%	19.6%	24.6%	16.0%	20.3%	24.7%
Upper limit of 95% CI	36.9%	43.3%	49.3%	37.6%	42.1%	48.1%	35.9%	41.3%	46.5%

CI = confidence interval; CR = complete response; NSCLC = non-small cell lung cancer; ORR = objective response rate; PD-L1 = programmed death ligand 1; PR = partial response.

[a] Subjects from either second-line therapy or third-line or greater therapy squamous NSCLC

[b] Subjects from the second-line therapy and third-line or greater therapy squamous NSCLC cohorts pooled together

- UBC: Under Amendment 7, approximately 60 UBC subjects were enrolled. Under Amendment 8 and beyond, approximately 132 additional UBC subjects with inoperable or metastatic disease (second- or greater line) will be enrolled, which includes approximately 70 PD-L1-positive and 50 PD-L1-negative subjects, assuming a PD-L1-positive prevalence of 60% and approximately 10% of subjects with tumor samples non-evaluable for PD-L1 (based on preliminary data from the initial UBC cohort of this study; see Section 1.2.3).

Of 192 UBC subjects enrolled in the study, it is expected that there will be approximately 100 PD-L1-positive subjects in the second- or greater line of treatment (approximately 30 enrolled under Amendment 7 and approximately 70 enrolled under Amendment 8 and beyond). [redacted] when the ORR is expected to be in the 17% to 33% range (Plimack et al, 2015; Rosenberg et al, 2015), a total of 100 subjects would provide a width of < 9% between the observed ORR and its lower limit of the exact 95% CI [redacted]

Table 7.6-5 [redacted]

[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

The prevalence of PD-L1 status for UBC subjects will be monitored through the study. After a total of approximately 132 subjects are enrolled under Amendment 8 and beyond, the enrollment of only PD-L1-positive subjects may continue to ensure a minimum total of 70 PD-L1-positive subjects are enrolled.

With 70 PD-L1-positive and 50 PD-L1-negative UBC subjects enrolled under Amendment 8 and beyond to validate the potential of PD-L1 expression to predict response to MEDI4736 treatment, [redacted] The response rate for the PD-L1-negative group is assumed to be similar to that observed with chemotherapy in a second-line UBC population (Bellmunt et al, 2009).

8 DIRECT ACCESS TO SOURCE DOCUMENTS

The study will be monitored by the sponsor or designee on a regular basis throughout the study period. During monitoring visits, the investigator will provide direct access to all source documentation relevant to the subject's participation in the study. Source documentation includes, but is not limited to, the subject's clinic and/or office chart, hospital chart, ICFs, treatment notes, laboratory reports, pharmacy records, radiographs, recorded data from automated instruments, and any other records maintained to conduct and evaluate the clinical study. The investigator must also ensure that direct access to study documents be made available for study-related audits, IRB/IEC review, or regulatory inspection.

9 QUALITY CONTROL AND QUALITY ASSURANCE

9.1 Data Collection

As part of the responsibilities assumed by participating in the study, the investigator agrees to maintain adequate and accurate case histories for the subjects treated under this protocol. Case histories include CRFs and supporting data including, but not limited to, signed and dated ICFs, progress notes, hospital charts, nurse's notes, diary cards or other worksheets provided to subjects, laboratory reports, ECG strips, etc.

Subject demographics and key/essential disease baseline characteristics thought to affect outcome, ie, stratification variables and other prognostic factors, may be collected, as available, for all subjects who provide written informed consent. For subjects who provided informed consent and were not entered into the study, the reason the subject was not entered, ie, did not meet one or more inclusion criteria, met one or more exclusion criteria, or other (eg, lost to follow-up, consent withdrawn), may also be collected.

9.2 Study Monitoring

The primary source document for this study will be the subject's medical record. If separate research records are maintained by the investigator(s), both the medical record and the research records will be monitored/audited for the purposes of the study.

The investigator and institutions involved in the study will permit study-related monitoring and provide direct access to all study records and facilities. Adequate time and space for monitoring visits should be made by the investigator or other investigator site staff.

The monitor will visit study facilities at periodic intervals, in addition to maintaining necessary contact through telephone, e-mail, and letter, to ensure that the study is conducted and documented in accordance with the protocol, GCP, and applicable regulations. The monitor will assess subject enrollment and informed consent procedures; investigational product storage, dispensing, administration and accountability; compliance with protocol procedures; completeness and accuracy of data entered onto validated data collection instruments (paper CRF or electronic data screen) against original source documents; the continued acceptability of the facilities and qualifications of the site staff; and the occurrence of AEs/SAEs. All aspects of the study will be carefully monitored for compliance with the protocol, applicable regulatory requirements, GCP, and the site's standard operating procedures.

The monitor will discuss the conduct and progress of the study with the investigator and other site staff. The investigator must cooperate with the monitor to ensure that corrective action is taken to resolve any problems noted in the course of the monitoring, and that the preventative measures are put into place to prevent recurrence of issues. In cases where compliance is not achieved, shipment(s) of investigational product to the investigator will be discontinued and study participation by that investigator will be terminated.

9.3 Audit and Inspection of the Study

During and after the study, the sponsor or its representative may conduct audits of any data and any facility participating in the study. The investigator and institutions involved in the study will permit such study-related audits and provide direct access to all study records and facilities. The investigator must maintain a comprehensive and centralized filing system of all study-related documentation that is suitable for inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The investigator agrees to participate in audits conducted at a convenient time in a reasonable manner.

Government regulatory authorities may also perform inspections either during or after the study. In the event of an inspection by any regulatory authority, the investigator should promptly notify the sponsor. The investigator agrees to cooperate fully with inspections conducted by regulatory authorities and to allow representatives of the regulatory authority access to all study records. The investigator will forward to the sponsor a copy of any inspection records received.

10 ETHICS

10.1 Regulatory Considerations

The study will be conducted in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC that approves this study to be conducted in its territory. Good clinical practice is defined as a standard for the design, conduct, performance, monitoring, auditing, recording, analysis, and reporting of clinical studies in a way that provides assurance that the data and reported results are credible and accurate, and that the rights, safety, and well-being of study subjects are protected.

Per GCP, the protocol will be reviewed and approved by the IRB or IEC of each participating center prior to study initiation. Serious adverse events regardless of causality will be reported to MedImmune Patient Safety or designee, and the investigator will keep the IRB/IEC informed as to the progress of the study.

The investigator will explain the nature of the study and will inform the subject/legal representative that participation is voluntary and that the subject can withdraw or be withdrawn from the study at any time. Written informed consent will be obtained from each subject/legal representative prior to the screening procedures to determine if study eligibility criteria are met. A copy of the signed ICF(s) will be given to every subject/legal representative, and the original(s) will be maintained with the subject's records.

10.2 Institutional Review Board or Independent Ethics Committee

A list of IRB/IEC members or a Statement of GCP Compliance should be obtained by the investigator and provided to the sponsor.

Any documents that the IRB/IEC may need to fulfill its responsibilities, such as protocol amendments, and information concerning subject recruitment, payment, or compensation procedures, or information from the sponsor will be submitted to the IRB/IEC. The

IRB/IEC's written unconditional approval of the study protocol, the ICF(s), and any other written materials to be provided to subjects will be in the possession of the investigator and the sponsor before the study is initiated. The IRB/IEC's unconditional approval statement will be transmitted by the investigator to the sponsor prior to shipment of investigational product supplies to the site. This approval must refer to the study by exact protocol title and number, and should identify the documents reviewed and the date of review.

Protocol modifications or changes may not be initiated without prior written IRB/IEC approval except when necessary to eliminate immediate hazards to the subjects or when the change(s) involves only logistical or administrative aspects of the study. Such modifications will be submitted to the IRB/IEC and written verification that the modification was submitted should be obtained.

The IRB/IEC must be informed by the investigator of ICF changes or revisions of other documents originally submitted for review; serious and/or unexpected adverse experiences occurring during the study (as applicable according to local regulations); new information that may affect adversely the safety of the subjects or the conduct of the study; an annual update and/or request for re-approval; and when the study has been completed.

10.3 Informed Consent

Freely given informed consent will be obtained and documented for all subjects under this protocol (or a subject's legal representative, if the subject is unable to provide informed consent) in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the ICH guidelines on GCP, any applicable laws and requirements, and any conditions required by a regulatory authority and/or IRB/IEC.

Information should be given in both oral and written form, and subjects or their legal representatives must be given ample opportunity to inquire about details of the study. Written informed consent will additionally be obtained for the conduct of certain protocol-specified procedures including consent for biopsy of tumor tissue in the dose-expansion phase of the study using separate ICFs. If the study will enroll subjects who are unable to give written informed consent, such as incapacitated subjects, informed consent will be obtained according to the site's standard operating procedures.

The ICF(s) generated by the investigator must be approved by the IRB/IEC and be acceptable to the sponsor. Informed consent forms must be written so as to be understood by the prospective subject/legal representative. Informed consent will be documented by the use of a written ICF(s) approved by the IRB/IEC and signed and dated by the subject or the

subject's legal representative, and by the person who conducted the informed consent discussion. The signature confirms the consent is based on information that has been understood. Each subject's signed ICF(s) must be kept on file by the investigator for possible inspection by the sponsor or its designated monitors, auditors, or regulatory agency representatives. The subject or the subject's legal representative should receive a copy of the signed and dated written ICF(s) and any other written information provided to the subject, and should receive copies of any signed and dated consent form updates and any amendments to the written information provided to subjects.

10.4 Withdrawal of Consent for Continued Study Participation

Data and Samples Obtained for the Main Study

Study data are protected by the use of a subject identification number, which is a number specific to the subject. The investigator is in control of the information that is needed to connect a study sample to a subject. A subject's consent to the use of data does not have a specific expiration date, but the subject may withdraw consent at any time by notifying the investigator. If consent is withdrawn, any data collected prior to that time may still be given to and used by the sponsor but no new data or samples will be collected unless specifically required to monitor safety of the subject.

Samples Obtained for Genetic Research or Future Research

Samples obtained for genetic research or future research will be labeled with a sample identification number but will not be labeled with personal identifiers such as the subject's name. A file linking this sample identification number with the SID number will be kept in a secure place at the sponsor with restricted access. If the subject withdraws consent for participating in the genetic research or future research, this link will allow the sponsor to locate the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

If the subject consents to have his/her samples used for genetic research or future research, this additional research may not start immediately and may start at any time during the storage period. The subject's sample(s) including any specimens of extracted DNA will be stored by the sponsor with similar samples from other subjects at a secure central laboratory. The subject's samples will not be kept for more than 25 years after the end of the study in which they were collected. If the subject chooses not to allow his/her study samples to be

used for genetic research or future research, the samples will be destroyed by the sponsor once they are no longer required for the main study.

If consent is withdrawn after a sample has been taken but before the subject's sample is sent to the sponsor for genetic research or future research, the investigator will arrange to have it destroyed. If consent is withdrawn after the subject's sample(s) have been sent to the sponsor for genetic research or future research, the sponsor and the investigator will ensure that these sample(s) are destroyed unless the sample identification number has been removed and the subject can no longer be linked to any sample(s). However, if the subject's sample(s) have already been used for research, the sponsor is not required to destroy results of this research. In this case only the remaining sample(s) will be destroyed.

11 DATA HANDLING AND RECORD KEEPING

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a subject's identification number or coded number and age. All study records, source medical records, and code sheets or logs linking a subject's name to an SID number will be kept in a secure location. Study records such as CRFs may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject/legal representative, except as specified in the ICF(s) (eg, necessary for monitoring by regulatory authorities or the sponsor of the clinical study). The investigator must also comply with all applicable privacy regulations (eg, HIPAA 1996, EU Data Protection Directive 95/46/EC).

Study documents (including subject records, copies of data submitted to the sponsor, study notebook, and pharmacy records) must be kept secured in accordance with the specific data retention periods that are described in the clinical study site agreement and based upon local requirements. Study documents must not be destroyed without prior written approval of the sponsor.

12 FINANCING AND INSURANCE

Financing and insurance are addressed in the individual site contracts.

13 PUBLICATION POLICY

Publication by the site of any data from this study must be carried out in accordance with the clinical study site agreement.

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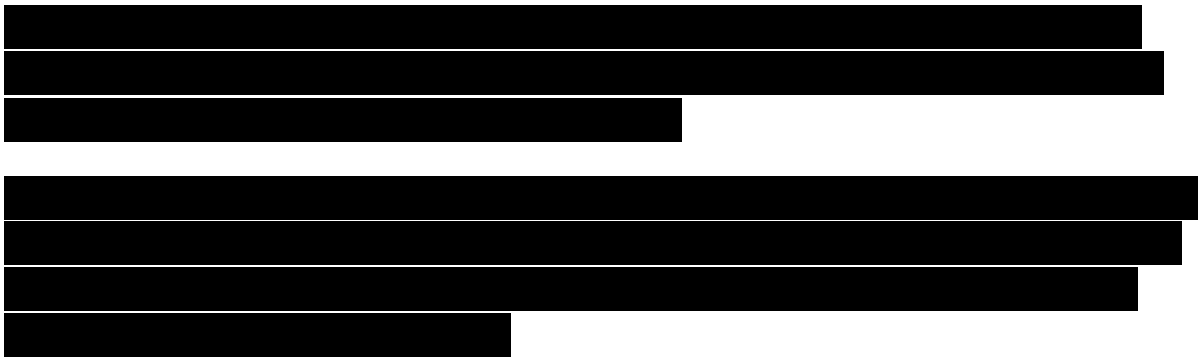

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15 SUMMARY OF PROTOCOL AMENDMENTS AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

Protocol Amendment 1, 11Jul2012

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Major changes to the protocol are summarized below.

Section 3.1 (Overview of Study Design): The section was updated to reflect that the first cohort will enroll a minimum of 3 subjects and that all subjects in this cohort will receive the initial dose as a 4-hour infusion. If 2 or more DLTs are observed in this cohort, the starting dose will be de-escalated as previously described. The estimated number of subjects was changed to 110.

Section 4.5.1.1 (Investigational Product Preparation): The section was updated to reflect that the first cohort will enroll a minimum of 3 subjects and that all subjects in this cohort will receive the initial dose as a 4-hour infusion.

Section 4.5.5 (Monitoring of Dose Administration): The frequency of monitoring of vital signs during all infusions was changed to every 15 minutes (± 5 minutes). After the infusion, subject vital signs will be assessed at the end of infusion (± 5 minutes) and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) postinfusion, followed by a 3-hour period of observation.

The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

Section 4.5.6 (Dose Escalation): The rules for dose escalation were modified so that the definition of the DLT evaluation period is the time from the first dose of MEDI4736 until the administration of the third dose. Subjects are evaluable for assessment of DLTs if they receive 2 full assigned doses of MEDI4736. The section was also modified to reflect that all dose cohorts will include more than 1 subject.

Section 4.5.7 (Dose-limiting Toxicity): The period for evaluating DLTs is from the time of first administration of MEDI4736 until the administration of the third dose of MEDI4736.

The DLT definition was modified so that any Grade ≥ 3 colitis is a DLT, as is any Grade ≥ 3 irAE of rash, pruritus, or diarrhea that does not downgrade to Grade ≤ 2 within 3 days after onset despite maximal supportive care including systemic corticosteroids. Previously stated exclusions remain valid.

Section 5.1 (Schedule of Study Procedures): Tables 5.1-1 and 5.1-2 were modified to add the post-infusion observation to protocol/safety evaluations.

Section 5.1.2 (Treatment Period), Section 5.1.3 (Maintenance Period for Subjects in the Expansion Phase Who Achieve Disease Control), and Section 5.2.1 (Medical History and Physical Examination, Electrocardiogram, Weight, and Vital Signs): The interval of vital signs monitoring during all infusions was changed to every 15 minutes (± 5 minutes). Postinfusion monitoring includes vital signs assessment at the end of infusion (± 5 minutes), at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) postinfusion, followed by a 3-hour period of observation.

Section 7.2 (Analysis Populations): The definition of the DLT Evaluable Population was modified so that the DLT evaluation period is defined as the time period until the administration of the third dose of MEDI4736.

Section 7.5 (Sample Size and Power Calculations): The sample size was modified to reflect a total of up to approximately 110 evaluable subjects and up to approximately 50 subjects in the dose-escalation phase.

Protocol Amendment 2, 24Jul2012

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. Major changes to the protocol are summarized below.

1. Section 5.1 (Schedule of Study Procedures): Table 5.1-1 was modified to schedule the first IM assessment during treatment on the day of the Dose 3 infusion. The IM assessment was added per FDA request in order to capture potential early onset of ADA.
2. Section 5.1.2.9 (Odd-numbered Doses [After Dose 1]): Per FDA request, an IM assessment was added before Dose 3 only. Remaining IM sample times are unchanged.
3. Section 5.2.3 (Pharmacokinetic Evaluation and Methods): The list of samples taken at the time of the second dose was corrected by adding Day 8.
4. Section 15 (Summary of Protocol Amendments and Administrative Changes to the Protocol), Amendment 1, was revised to clearly state that the postinfusion observation period of 3 hours follows the 60-minute vital sign assessment.

Protocol Amendment 3, 12Jun2013

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 3. The protocol was amended to reflect the following:

- The dose-expansion phase was broadened to include MEDI4736 treatment for the following tumor types: advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, NSCLC squamous and non-squamous histology, gastroesophageal cancer, TNBC, and pancreatic adenocarcinoma. Colorectal cancer was removed from the dose-expansion phase. These additional tumor types are included in the dose-expansion phase based on high unmet need and preclinical data suggesting that an anti-PD-L1 antibody may be beneficial in these populations.
- Changed the duration of treatment from 6 months past the observation of DC plus an additional 6 months of maintenance (every 2 months) treatment to a treatment period of up to 12 months. The maintenance treatment period has been removed from this study and will be evaluated in future studies. The Q2W and Q3W treatment periods were extended to allow for continued treatment up to 12 months in the absence of maintenance treatment and to allow for consistent dosing across all subjects enrolled. In addition, language was added to permit continuation of treatment in subjects with confirmed PD but no signs of clinical deterioration if investigators consider that subjects continue to receive benefit from treatment. In the absence of rapid clinical deterioration, these changes may discourage the early discontinuation of MEDI4736 and provide a more complete evaluation of its antitumor activity.
- Clarified that subjects in follow-up may be retreated with MEDI4736 at the highest dose previously received if evidence of PD is during follow-up, and that only one round of retreatment will be allowed.
- Added assessments to evaluate PRO.
- Revised objectives to support the dose-expansion phase and addition of PROs.
- Antitumor activity will be assessed by RECIST guidelines (v1.1; Eisenhauer et al, 2009) with modifications instead of irRC. RECIST guidelines are the standard basis for disease assessments in solid tumors and will be familiar to investigators involved in the broader, revised dose-expansion phase of this study. In addition, clinical data to date with PD-1 and PD-L1 targeting antibodies suggests that the majority of response patterns will be amenable to assessment with RECIST-based measurement.
- B7-H1 was changed to PD-L1 throughout the protocol for consistency.
- In addition, clarifications were added to certain sections to aid in operational implementation and minor copyedits were made.

Major changes to the protocol are summarized below:

Title page: Updated to reflect the change in medical monitor.

List of Abbreviations: Updated to match the contents of this protocol amendment.

Study Abstract: Updated to be consistent with changes made to the body of the protocol amendment.

Section 1.1 (Disease Background): Additional tumor types were mentioned for the dose-expansion phase, the life expectancy for each, and the treatment options.

Section 1.2.2 (Summary of Nonclinical Experience): New nonclinical data were added.

Section 1.2.3 (Summary of Clinical Experience): Available clinical safety, PK, pharmacodynamic, and ADA data from this study were added. Clinical experience from competitor data was added to discuss recent advancements and rationale for additional tumor types being added to the dose-expansion phase.

Section 1.3 (Research Hypothesis): Updated for consistency with change in exploratory objectives.

Section 1.4 (Rationale for Study Conduct): Included tumor types that were added to the dose-expansion phase.

Section 1.5 (Benefit-risk and Ethical Assessment): Updated to include competitor efficacy and safety data to support additional tumor types in the dose-expansion phase.

Section 2.1 (Primary Objective): A primary objective for the dose-expansion phase was added.

Section 2.3 (Exploratory Objectives): An exploratory objective for PROs was added for consistency with exploratory endpoint analysis.

Section 3.1 (Overview of Study Design): Updated to incorporate changes to dose-expansion phase and clarify presentation of study design; Figure 3.1-1 was revised for consistency with information in text and clarity of study design. The enrollment status for the MEDI4736 Q2W dose-escalation arm was added.

Section 3.2 (Estimated Duration of Subject Participation): Changed the duration of treatment from 6 months past the observation of DC plus an additional 6 months of maintenance (every 2 months) treatment to a period of up to 12 months. The maintenance treatment period has been removed from this study and will be evaluated in future studies. The Q2W and Q3W treatment periods were extended to allow for continued treatment up to 12 months in the absence of maintenance treatment and to allow for consistent dosing across all subjects enrolled. In addition, language was added to permit continuation of treatment in subjects with confirmed PD but no signs of clinical deterioration if investigators consider that subjects continue to receive benefit from treatment. In the absence of rapid clinical deterioration, these changes may discourage the early discontinuation of MEDI4736 and provide a more

complete evaluation of its antitumor activity. Also, clarified that only one round of retreatment with MEDI4736 will be allowed.

Section 3.3 (Study-stopping Criteria): Changes were made to the criteria to align with new procedures and other protocols.

Section 3.4 (Rationale for Study Design and Doses): Included rationale to support the additional tumor types in the dose-expansion phase and the use of RECIST v1.1 guidelines with modification for disease assessment.

Section 4.2 (Subject Selection and Withdrawal): Text was added to include all tumor types and therapeutic response criteria for the dose-expansion phase.

Section 4.2.1 (Inclusion Criteria): Incorporated additional inclusion criteria and revised existing criteria to support tumor types in the dose-expansion phase.

Section 4.2.2 (Exclusion Criteria): Incorporated additional exclusion criteria and revised existing criteria to support tumor types in the dose-expansion phase.

Section 4.2.3 (Withdrawal Criteria): Item 5 was added to align with study procedures and other protocols. Item 11 was expanded to require, in addition to confirmation of PD, an investigator determination that the subject is no longer benefiting from treatment with MEDI4736.

Section 4.5.1.1 (Investigational Product Preparation): Added statement that WFI will be supplied by each site, and clarified investigational product preparation to align with study procedures.

Section 4.5.3 (Treatment Regimen): Section was expanded to provide more detailed description of the treatment regimens in the dose-escalation and dose-expansion phases, and include figures for clarity.

Section 4.5.4 (Treatment Administration): Revised text to align with study procedures.

Section 4.5.5 (Monitoring of Dose Administration): Window of ± 15 minutes was added to the postinfusion 3-hour period of observation for clarification of study procedure. Dose rate modification was clarified for subjects experiencing Grade ≤ 2 infusion-related reactions.

Section 4.5.6 (Dose Escalation): Clarified that the Q3W dose-escalation arm will be initiated in parallel with the dose-expansion phase. Criteria for exploring higher doses were also clarified.

Section 4.5.7 (Dose-limiting Toxicity): Deleted hormone levels to be within normal limits as a criterion for managed Grade 3 endocrinopathy.

Section 4.5.8 (Dose Modification for Toxicity Management): Added that dose modification will not be required for laboratory abnormalities that are not deemed to be clinically significant; Table 4.5.8-1 modified to include additional irAE terms and toxicity assessments.

Section 4.6.1 (Permitted Concomitant Medications): Additional details were added for clarification.

Section 4.6.2 (Excluded Concomitant Medications): Additional details were added for clarification.

Section 5.1 (Schedule of Study Procedures), Section 5.1.1 (Screening), Section 5.1.2 (Treatment Period), Section 5.1.3 (End of Treatment), Section 5.1.4 (Post Treatment Follow-up):

- Schedule of study procedures table for the maintenance period and section describing assessments during the maintenance period were removed for consistency with changes in treatment schedule;
- Treatment periods were clarified;
- PRO assessments were added for the dose-expansion phase;
- Hepatitis B and C viral titers were added for HCC subjects with hepatitis B or C;
- Every 8-week ECG assessments were deleted and scheduled to coincide with MEDI4736 administration;
- Assessment schedules were modified for alignment with changes to the dose-expansion cohorts and to accommodate subjects in retreatment.
- Table 5.1-2 was revised to only present a schedule of study procedures in follow-up for subjects who have completed the MEDI4736 12-month treatment and achieved DC and subjects who have discontinued MEDI4736 due to toxicity in the absence of PD.
- A new appendix was created (Appendix 9) to present a separate schedule of study procedures in follow-up for subjects who have discontinued MEDI4736 treatment due to confirmed PD.

Section 5.2.2 (Clinical Laboratory Tests): Added hepatitis B and C viral titers as an additional safety test for HCC subjects with hepatitis B or C.

Section 5.2.3 (Pharmacokinetic Evaluation and Methods): Assessment schedule modified for alignment with changes to treatment schedule; assessment schedule for subjects being retreated with MEDI4736 after evidence of PD in follow-up was clarified.

Section 5.2.5 (Biomarker Evaluation and Methods): Added collection of CTC from TNBC subjects in the dose-expansion phase. Clarified that whole blood for RNA and/or miRNA/mRNA sample preparation will be collected from all subjects and tumor samples will be collected from dose-expansion subjects.

Section 5.2.6 (Disease Evaluation and Methods): Revised tumor assessments to be based on RECIST guidelines (v1.1; Eisenhauer et al, 2009) with modifications. The modification included is to require a repeat confirmatory scan upon documentation of disease progression, and is similar to the irRC.

Section 5.2.7.1 (Archival Tumor Samples): Clarified that archival tumor samples must be deemed available during the screening period, to permit assessment of tumoral PD-L1 expression at screening if necessary to meet minimum requirement that 10 subjects with NSCLC and 10 subjects with TNBC have tumoral PD-L1 expression.

Section 5.2.7.2 (Tumor Biopsies): Clarification was added for the number of subjects required to have tumor biopsies in the dose-expansion phase. Biopsies using fine-needle aspirations were removed. Core biopsies are considered to be more valuable than fine-needle aspirations for the analyses included in this study.

Section 5.2.8 (Patient-reported Outcomes Assessments): New section was added to support addition of PRO endpoint.

Section 5.2.9 (Estimate of Volume of Blood to be Collected): Updated volume of blood to be collected to be consistent with study procedures.

Section 6.4.3.2 (Hepatic Function Abnormality): Included “(or equivalent)” after SMC since it may change in name.

Section 6.5 (Safety Management During the Study): The MedImmune safety management description was updated to reflect current practices.

Section 7.2 (Analysis Populations): Removed Efficacy Evaluable Population and changed title of Safety Population to As-treated Population. With the exception of MTD evaluation, all analyses, including safety and efficacy, will be conducted with the As-treated Population.

Section 7.3.1 (Primary Endpoints): Identified the tumor types to be assessed under the primary objective for the dose-escalation phase and added a primary objective for the dose-expansion phase.

Section 7.3.2.3 (Antitumor Activity): Revised to align with change to RECIST guidelines with modification for tumor assessment instead of irRC. Modified the definition of duration of response to extend to death due to any cause, so that duration of response is now defined as the duration from the first documentation of objective response to the first documented disease progression or death due to any cause, whichever occurs first.

Section 7.3.3 (Exploratory Endpoints): Items 8 and 9, revised the assessments to be conducted on archived and fresh tumor samples. A PRO endpoint was added to support the exploratory objective.

Section 7.4 (Subgroup Analysis): New section added to describe the subgroup analysis for the dose-expansion cohorts.

Section 7.6 (Sample Size and Power Calculations): The sample size description for the dose-expansion was updated to reflect the changes in the number and size of cohorts.

Appendix 1: Updated to reflect changes in signatories.

Appendices 2 through 8: New appendices providing sample PRO questionnaires.

Appendix 9: New appendix presenting a schedule of study procedures in follow-up and a description of each visit for subjects who have discontinued MEDI4736 treatment due to confirmed PD. Assessments separated from follow-up assessments for subjects who completed MEDI4736 treatment and achieved DC and subjects who have discontinued MEDI4736 due to toxicity in the absence of PD for greater clarity.

Protocol Amendment 4, 04Nov2013

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. The protocol was amended to reflect the following:

- The number of subjects to be enrolled in the NSCLC cohorts was increased.
- The dose-expansion procedures were clarified and a number of sample timepoints were reduced.
- A schedule of procedures for retreatment was added as an appendix for clarity.

Major changes to the protocol are summarized below:

List of Abbreviations: Updated to be consistent with the body of the protocol.

Study Abstract: Updated to reflect changes in the body of the protocol amendment.

Section 1.2.3 (Summary of Clinical Experience): Safety, efficacy, and PK data were updated.

Section 1.5 (Benefit-risk and Ethical Assessment): Section was updated to reflect current safety and efficacy data for the study.

Section 3 (Study Design): The study flow diagram was updated to reflect the revised number of subjects in each dose-expansion cohort.

Section 3.1.2 (Dose Expansion): A description of the NSCLC squamous and non-squamous cohorts was added to give details on the number of subjects with each line of therapy. A revision of the description of PD-L1 positive sample requirements for each cohort was also added.

Section 3.4 (Rationale for Study Design and Doses): A rationale for use of MEDI4736 in NSCLC was added.

Section 4.2.1 (Inclusion Criteria): Inclusion criterion #3c was added to define NSCLC requirements. Inclusion criterion #4 was modified to discuss the number of subjects and type of cancer that will be required to have PD-L1 tumor positivity in the study. Inclusion criterion #5 was added to define the number of subjects in each NSCLC cohort that is required to be tumoral PD-L1 positive for this study. Inclusion criterion #6 was added to define disease progression and what is required for the NSCLC previous lines of therapy. Inclusion criterion #13 was revised to give more details around archived tumor sample requirements. Inclusion criterion #15 was added and inclusion criterion #16 was revised to give more detail around biopsy requirements.

Section 4.5.5 (Monitoring of Dose Administration): Section was revised to remove the requirement for 3 hour observation period for subjects in dose-expansion since only one infusion-related reactions has been reported in the Q2W dose-escalation cohorts.

Section 5.1 (Schedule of Study Procedures): Tables 5.1-1 and 5.1-2 were modified to describe sampling during the dose-expansion phase and to reduce the number of laborartory evaluation required for subjects.

Section 5.1.1 (Screening), Section 5.1.2 (Treatment Period), Section 5.1.3 (End of Treatment), and Section 5.1.4 (Post-treatment Follow-up): Sections were updated to reflect the changes to the schedule of study procedures.

Section 5.2.6 (Disease Evaluation and Methods): A sentence was added to clarify that scans would be stored for possible future central evaluation.

Section 5.2.7.1 (Archival Tumor Samples): The description of the archival tumor sample requirements was clarified.

Section 5.2.7.2 (Tumor Biopsies): The section was modified to clarify requirements for tumor biopsies and PD-L1 tumor positivity.

Section 5.2.8.2 (EORTC QLQ-C30 and Cancer-specific Modules): Several typographical errors were corrected.

Section 7.3.2.1 (Pharmacokinetics): A description of population analysis was added.

Section 7.6 (Sample Size and Power Calculations): The section was updated to reflect the changes in samples size for the NSCLC cohorts and the requirements for number of subjects per cohort that need to have tumoral PD-L1 positivity.

Appendix 2 (Pain Questionnaire): An example of the pain questionnaire was added for clarity.

Appendix 10 (Schedule of Study Procedures for Subjects in Retreatment of MEDI4736): A schedule of study procedures was added to clarify what procedures are required in retreatment.

Protocol Administrative Change 1, 10Jan2014

The purpose of this administration change is to correct inadvertent errors created during the last protocol amendment.

The following changes were made:

Cover Page – EudraCT number was added.

Section 3.1.2 (Dose Expansion) – Correct a typographical error.

Section 4.5.3.1 (Treatment Regimen) – Correct a typographical error.

Section 4.5.3.2 (Dose Expansion) - Correct a typographical error.

Section 5.1 (Schedule of Study Procedures) – Align anticancer/testis antigen antibodies collection time points for dose-escalation and dose-expansion phases. Clarify that Visits for Dose 1 Days 3 and 5 are for dose-escalation subjects only.

Section 5.1.2.1 (Dose 1, Day 1) – Added note that PBMC collection is for dose-expansion phase only to match Table 5.1-1.

Section 5.1.2.3 (Dose 1, Day 3) – Clarify that miRNA/mRNA collection and AE/SAE assessments are only for subjects in the dose-escalation phase.

Section 5.1.2.4 (Dose 1, Day 5) – Added a note that Circulating soluble factor, hematology, and AE/SAE collections are only for subjects in the dose-escalation phase.

Section 5.1.2.9 (Odd-numbered Doses) – Immunogenicity assessment was clarified and add miRNA collection for dose-expansion subjects was added.

Section 5.1.2.10 (Even-numbered Doses) – Immunogenicity, PK, and sPD-L1 collections were clarified for dose-escalation and dose-expansion subjects to match Table 5.1-1.

Protocol Amendment 4.1, Germany, 08May2014

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. The protocol was amended to reflect the following:

- Add EudraCT number to protocol
- Add the dose-expansion rationale to the protocol.

Major changes to the protocol are summarized below:

Cover page: The EudraCT number was added to the protocol.

Abstract and Section 3.1.2 (Dose Expansion): A statement was added that the 10 mg/kg Q2W is being taken into expansion.

Section 3.4 (Rationale for Study Design and Doses): A rationale for dose-expansion was added.

Table 4.5.8-1 (MEDI4736 Dose Modification Due to Toxicity): The column header was corrected.

Protocol Amendment 5, 21May2014

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 5. The protocol was amended to reflect the following:

- The title of the study was changed to a Phase 1/2 to support the NSCLC and SCCHN expansion cohorts. The dose-escalation phase was considered the Phase 1 part of the study and the dose-expansion phase is considered the Phase 2 portion of the study.
- The number of subjects to be enrolled in the SCCHN expansion cohort is being increased based on preliminary efficacy and safety data in the first 60 subjects. The additional SCCHN subjects will be enrolled according to tumoral PD-L1 expression to allow for a correlation to clinical response. Additional clinical characteristics (prior therapies, HPV status, smoking history, etc.) and potential biomarkers will also be explored in relation to clinical benefit derived from MEDI4736 treatment in subjects with SCCHN.
- The pancreatic adenocarcinoma and uveal melanoma expansion cohorts are being increased based on preliminary efficacy and safety in the first 20-30 subjects to allow for additional signal searching to identify a subset of patients that may benefit from MEDI4736 treatment (including any correlation between PD-L1 expression and clinical response).
- Eight new expansion cohorts were added based on the potential for efficacy of MEDI4736 in a broad range of tumor types. These additional cohorts were chosen based on 1) unmet medical need, 2) PD-L1 tumoral expression, 3) evidence of responsiveness to other immunotherapy treatments, 4) viral etiology and expression of virally-induced tumor associated antigens, 5) association of the cancer with TILs, 6) high levels of tumor antigens due to a high mutation burden or translocations, or 7) preclinical efficacy modeling.
- Digital ECGs at select sites were added to provide robust ECG data for MEDI4736 and to support future pivotal studies.
- Updated MEDI4736 clinical experience was added from monotherapy studies to provide clinical rationale (safety and preliminary efficacy) to support continuation of the study and addition of newly defined expansion cohorts.
- Some study procedures were clarified and a number of sample timepoints were reduced to eliminate subject burden.

Major changes to the protocol are summarized below:

Title Page: Replaced [redacted] as back-up medical monitor. In addition, the EudraCT number was added to the protocol cover page.

List of Abbreviations: Updated to be consistent with the body of the protocol.

Study Abstract: Updated to reflect changes in the body of the protocol amendment.

Section 1.1 (Disease Background): Out-dated data was removed.

Section 1.2.2 (Summary on Nonclinical Experience): Final interim audited data for a 3-month GLP toxicity study were added.

Section 1.2.3 (Summary of Clinical Experience): Safety, efficacy, and PK data were updated for Study CD-ON-MEDI4736-1108 and safety data for Study D4190C00002 were added. In addition, data on other PD-1 and PD-L1 studies were updated.

Section 1.3 (Research Hypothesis): The co-primary objectives were added for completeness.

Section 1.4 (Rationale for Study Conduct): The rationale of the study was updated to reflect the additional expansion cohorts and increased SCCHN expansion cohort.

Section 1.5 (Benefit-risk and Ethical Assessment): Section was updated to reflect current safety and efficacy data for the study.

Section 2.1 (Primary Objective): An additional primary objective for the dose-expansion phase was added for SCCHN.

Section 2.3 (Exploratory Objectives): A new exploratory objective of antitumor activity assessed by irRECIST was added.

Section 3 (Study Design): The study flow diagram was updated to reflect the revised number of subjects in each dose-expansion cohort. The description of dose expansion was revised to include the new tumor cohorts.

Section 3.4 (Rationale for Study Design and Doses): Rationale for use of MEDI4736 in bladder cancer, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI-high cancers, HPV-positive cancers, and nasopharyngeal carcinoma were added. A rationale for dose-expansion dose was added.

Section 4.2.1 (Inclusion Criteria): Inclusion criterion #3 was modified to add the new tumor types. Inclusion criterion #6 was added to further define the SCCHN population. Inclusion criterion #7 was added to define the MSI-high population. Inclusion criterion #8 was added to define the HPV-positive cancer population. Inclusion criterion #9 was added to limit the GBM subject population. Inclusion criterion #10 was added to define the ovarian population. Inclusion criterion #13 was modified to describe the requirement for each tumor type.

Inclusion criterion #19 was revised to add the RANO guidelines for GBM. The biopsy language in inclusion criteria #22 and #23 were modified to exclude GBM.

Section 4.2.2 (Exclusion Criteria): Exclusion criterion #6 was modified to describe the steroid dose and duration for GBM. Exclusion criterion #25 was added to describe edema in subjects with GBM.

Section 4.5.1.1 (Investigational Product Preparation): The language was modified to allow dose preparation up to 30 mg/kg and to allow dosing day weight to be used for dose calculation.

Section 4.5.3.2 (Dose Expansion): The new expansion cohorts were added.

Section 4.5.8 (Dose Modification for Toxicity Management): Pneumonitis was added as potential irAE.

Table 4.5.8-1 (MEDI4736 Dose Modification Due to Toxicity): The column header was corrected.

Section 4.6.2 (Excluded Concomitant Medications): Temporary use of corticosteroids was added and may be permitted upon discussion with the medical monitor for underlying or concurrent illness.

Section 5.1 (Schedule of Study Procedures): Table 5.1-1 was modified to reduce procedures and visits during expansion and to add questionnaires and procedures for the new tumor types. Table 5.1-2 was modified to reduce procedures in follow-up. Footnotes were added to both tables to describe procedures and time requirements for clarification.

Section 5.1.1 (Screening): The detailed descriptions of procedures were removed to reduce redundancy and errors.

Section 5.1.2 (Treatment Period): The detailed descriptions of procedures were removed to reduce redundancy and errors.

Section 5.1.3 (End of Treatment): Section number revised. A definition of end of treatment was added for clarification. The detailed descriptions of procedures were removed to reduce redundancy and errors.

Section 5.1.4 (Post-treatment Follow-up): The detailed descriptions of procedures were removed to reduce redundancy and errors.

Section 5.2.1 (Medical History and Physical Examination, Electrocardiogram, Weight, and Vital Signs): A description of ECG procedures was added and a description of digital ECG procedures was added.

Section 5.2.6 (Disease Evaluation and Methods): The RANO guidelines for GBM were added.

Section 5.2.7.2 (Tumor Biopsies): The number of tumor biopsies by tumor type was revised and the new expansion cohort information was added.

Section 5.2.8.2 (EORTC QLQ-C30 and Cancer-specific Modules): Description of the GBM and ovarian cancer-specific modules were added.

Section 5.2.8.3 (FACT-BL): Section was added to describe the bladder cancer-specific module.

Section 6.1.3 (Other Events of Special Interest): Definition of AESI was added and descriptions of pneumonitis and hypersensitivity reactions were added.

Section 7.3.1 (Primary Endpoints): The description of the endpoint for SCCHN was added for completeness.

Section 7.6 (Sample Size and Power Calculations): Section was revised to reflect the increased sample sizes and the new expansion cohorts.

Section 14 (References): New references were added to support the text in the body of the protocol.

Appendix 10 (Patient-reported Outcome Questionnaire EORTC QLQ-BN20): Sample questionnaire added.

Appendix 11 (Patient-reported Outcome Questionnaire EORTC QLQ-OV28): Sample questionnaire added.

Appendix 12 (Patient-reported Outcome Questionnaire FACT-BL): Sample questionnaire added.

Appendix 13 (Schedule of Study Procedures for Subjects in Retreatment of MEDI4736): Table 13-1 was modified to reduce procedures in retreatment. Footnotes were added for clarification of timing and to add descriptions.

Section 15.1 (Rebaseline) and Section 15.1.1 (Retreatment Period): The detailed descriptions of procedures were removed to reduce redundancy and errors.

Appendix 14 (Schedule of Study Procedures in Follow-up for Subjects Who Have Discontinued MEDI4736 Treatment Due to Confirmed Progressive Disease): Flow cytometry at 2 months was removed from Table 15-2. The collection of the FACT-BL was added to Table 15-2. A description of digital ECGs was added to Table 15-2 as a footnote. The detailed descriptions of procedures were removed to reduce redundancy and errors.

Protocol Amendment 6, 18Jun2014

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 6. The protocol was amended to remove the expanded 2L SCCHN cohort after consultation with the US FDA.

Protocol Administrative Change 2, 21Jul2014

The purpose of this administrative change is to correct inadvertent errors created during the last protocol amendment.

The following changes were made:

- Section 5.1 (Schedule of Study Procedures), Table 5.1-1 – Removed footnote "c" for flow cytometry samples in dose-expansion cohorts and corrected footnote "c" to clarify that the 3-hour post end of infusion sample is for subjects in dose-escalation cohorts only.
- Appendix 13 (Schedule of Study Procedures for Subjects in Retreatment of MEDI4736), Table 15-1 – Row added for ECGs for Q2W dose-expansion. Fixed footnote lettering to start at "a"; changed immunogenicity collection to every 12 weeks starting at Dose 3 to match PK sample; removed post-dose sample collections for sPD-L1from Dose 1 and every 12 weeks starting at Dose 3 for Q2W and every third dose for Q3W; removed post-dose sample collection for PK from every 12 weeks starting at Dose 3 for Q2W and every third dose for Q3W; removed post-Dose 1 collection for flow cytometry; changed flow cytometry collection from odd doses to even doses after Dose 2; and fixed footnote lettering to match list throughout the table. Post-dose samples were removed from circulating soluble factors and the footnote deleted.

Protocol Amendment 6, France, 30Jul2014

The protocol was amended to state that French sites will not enroll subjects in the expanded NSCLC cohorts.

Protocol Amendment 6, United States, 11Sep2014

The purpose of this amendment was to add a 20-subject dose-exploration cohort to examine the safety of 20 mg/kg dosed Q4W.

Major changes to the protocol are summarized below:

Title Page: Added the 2 primary medical monitors from the CRO and removed the back-up medical monitor. Naimish Pandya was replaced with Dominic Lai as the sponsor's medical monitor.

Study Abstract: Updated to reflect changes in the body of the protocol amendment.

Section 2.1 (Primary Objective): A primary objective for the dose-exploration cohort was added.

Section 3.1 (Overview of Study Design): The dose-exploration cohort was added and the sample size was revised to reflect the additional 20 subjects. Figure 3.1-1 was revised to add the dose-exploration cohort.

Section 3.1.2 (Dose Exploration): Section was added to describe the dose-exploration cohort.

Section 3.4 (Rationale for Study Design and Doses): The rational for the Q4W dosing schedule for dose-exploration was added.

Section 4.2 (Subject Selection and Withdrawal): The dose-exploration cohort was added.

Section 4.2.1 (Inclusion Criteria): Inclusion criterion 5f was added to define the NSCLC subjects to be enrolled in the dose-exploration cohort. Inclusion criterion #24 was added to define the dose-exploration subjects.

Section 4.2.4 (Replacement of Subjects): Dose-exploration subjects will not be replaced.

Section 4.5.3.2 (Dose Exploration): Section added to describe the Q4W treatment for the dose-exploration subjects.

Section 4.5.5 (Monitoring of Dose Administration): The observation period for subjects in the dose-exploration cohort (Q4W) was added.

Section 5.1 (Schedule of Study Procedures): Table 5.1-2 was added to describe the schedule of study procedures for Q4W dosing. Reference to Table 5.1-2 for Q4W dosing was added.

Section 5.1.3 (End of Treatment): Sentence removed because it was left in error when the procedure descriptions were removed in Amendment 5.

Section 5.2.7.2 (Tumor Biopsies): A description of when tumor biopsies will be collected for dose-exploration was added for clarification.

Section 5.2.8 (Patient-reported Outcomes Assessments): A statement was added the subjects in the dose-exploration cohort will not complete PROs.

Section 5.2.9 (Estimate of Volume of Blood to be Collected): A subsection was added to describe the blood volume for the dose-exploration cohort.

Section 7.3.1 (Primary Endpoints): The primary endpoints for the Q4W dosing schedule were added.

Section 7.6 (Sample Size and Power Calculations): Section updated to add dose-exploration cohort.

Appendix 13 (Schedule of Study Procedures for Subjects in Retreatment of MEDI4736): For Table 15-1, footnote "c" was added to PBMC collection for even numbered doses starting after Dose 2.

Appendix 14 (Schedule of Study Procedures in Follow-up for Subjects Who Have Discontinued MEDI4736 Treatment Due to Confirmed Progressive Disease): For Table 15.1.1-1, Day 14 and Month 2 samples were removed for PK and sPD-L1.

Protocol Administrative Change 3, 06Oct2014

The purpose of this administrative change is to change the medical monitors and to correct inadvertent errors created during the last protocol amendment.

The following changes were made:

Cover Page – The medical monitor section was updated to add the PRA medical monitors, to change the sponsor's medical monitor from Naimish Pandya to Dominic Lai, and to remove the back-up medical monitor.

Section 5.1 (Schedule of Study Procedures) – A sentence was removed that was left in error. A sentence was added to point to the retreatment schedule. The location of the study procedures table for subject with progressive disease was corrected from Appendix 13 to Appendix 14. For Table 5.1-1, footnote "f" was added for PBMC samples in dose-expansion cohorts.

Section 5.1.3 (End of Treatment) – A sentence describing the end of treatment procedures that were removed in the last amendment was removed. The sentence referring to Appendix 14 was moved to Section 5.1 (see above).

Section 5.1.4 (Post-treatment Follow-up) – Section was fixed to correct typographical error.

Section 5.2.1 (Medical History and Physical Examination, Electrocardiogram, Weight, and Vital Signs) – A typographical error in the abbreviation of ECG was corrected.

Appendix 13 (Schedule of Study Procedures for Subjects in Retreatment of MEDI4736), Table 15-1 – Footnote "c" was added for PBMC samples for even numbered doses after Dose 2.

Appendix 14 (Schedule of Study Procedures: Follow-up for Subjects Who Have Discontinued MEDI4736 Treatment Due to Confirmed Progressive Disease), Table 15.1.1-1 – Samples for Day 14 and 2 months post dose were removed or PK and sPD-L1.

Protocol Amendment 7, 17Nov2014

The purpose of this amendment was to change tumoral PD-L1 requirements for future subjects being enrolled. In addition, the toxicity management guidelines were updated to discuss inflammatory reactions attributed to local antitumor response. In addition, wording was removed to allow French sites to enroll in the expanded NSCLC cohorts.

Study Abstract: Updated to reflect changes in the body of the protocol amendment.

Section 1.2.3.1 (MEDI4736): Safety, efficacy, and PK data were updated for Study CD-ON-MEDI4736-1108.

Section 1.5 (Benefit-risk and Ethical Assessment): Safety date for Study CD-ON-MEDI4736-1108 was updated.

Section 3.1.3 (Dose Expansion): Table 3.1-1 was updated with recent data. Tumoral PD-L1 status requirements were modified.

Section 4.2.1 (Inclusion Criteria): Tumoral PD-L1 requirements were changed in inclusion criterion #13.

Section 4.2.2 (Exclusion Criteria): Exclusion criterion #12 was modified to remove untreated CNS metastases.

Section 4.5.8 (Dose Modification for Toxicity Management): Guidelines were added to discuss inflammatory reactions attributed to local antitumor response. Guidelines for infusion related reactions were added for all grades to the table for clarity.

Section 5.2.7.2 (Tumor Biopsies): Tumoral PD-L1 status requirements were changed.

Section 6.4.3.3 (Pregnancy): Reporting requirement for pregnancy in partners of male study subjects was added to align with global safety procedures.

Section 7.3.1 (Primary Endpoint): The analysis for ORR by line of therapy and histology in the NSCLC subpopulations with subjects who have tumoral PD-L1 expression was added.

Section 7.6 (Sample Size and Power Calculations): Sample size justification for the requirements on tumoral PD-L1 expression for NSCLC subjects is provided.

Protocol Amendment 8, 25Nov2015

The purpose of this amendment was to expand the UBC cohort in the dose-expansion phase to evaluate the antitumor activity of MEDI4736 in subjects with PD-L1-positive UBC and validate the potential for PD-L1 expression to predict response to MEDI4736 treatment. In addition, the toxicity management guidelines were updated to reflect the current version (02Oct2015), and they were moved from the body of the protocol (Section 4.5.8) to Appendix 15. Key changes are listed below.

1. Title page: [redacted] as the sponsor's medical monitor.
2. Study Abstract: Updated to reflect changes in the body of the protocol amendment.
3. Section 1.2.3 (Summary of Clinical Experience): Updated to be consistent with the current MEDI4736 Investigator's Brochure (version 8.0). In addition, data on the correlation between MEDI4736 clinical activity and PD-L1 expression were added to support expansion of the UBC cohort.
4. Section 1.4 (Rationale for Study Conduct): Updated to reflect the assessment of a correlation between PD-L1 expression and response to MEDI4736 treatment.
5. Section 1.5 (Benefit-risk and Ethical Assessment): Revised to reflect the updated data presented in Section 1.2.3 (Summary of Clinical Experience) and to be consistent with the updated emerging safety profile in the current MEDI4736 Investigator's Brochure (version 8.0).
6. Section 2.1 (Primary Objective): Added a primary objective for the dose-expansion phase that will assess the antitumor activity of MEDI4736 in subjects with PD-L1-positive UBC.
7. Section 2.2 (Secondary Objectives): Updated this section to include secondary objectives for evaluation of the antitumor activity of MEDI4736 in UBC subjects by PD-L1-negative status, comparing PD-L1-positive and PD-L1-negative status, and regardless of PD-L1 status.
8. Section 3.1 (Overview of Study Design): Updated to reflect expansion of the UBC cohort in the dose-expansion phase. In addition, updated the number of subjects (by tumor type) enrolled into the dose-expansion phase to show the most current enrollment status (based on data cutoff date of 20Nov2015).
9. Section 3.1.3 (Dose Expansion) and Section 3.4 (Rationale for Study Design and Doses): Updated to reflect expansion of the UBC cohort and rationale for the expansion (ie,

evaluation of the antitumor activity of MEDI4736 in subjects with PD-L1-positive UBC and validation of the potential of PD-L1 expression to predict response to treatment).

10. Section 4.2.1 (Inclusion Criteria): Revised the criteria to include the expanded UBC cohort. The following criteria were revised or added:
    - #5 (histology and prior treatment)
    - #13d (tumor PD-L1 expression requirements)
    - #19a, b (measureable lesions)
    - #20 (archival tumor tissue)
    - #22 (lesion amenable to biopsy)
    - #23 (consent for biopsy samples)
11. Section 4.2.2 (Exclusion Criteria): Revised the criteria to include the expanded UBC cohort or other required updates. The following criteria were revised or added:
    - #4 (prior exposure to immunotherapy)
    - #13 (other invasive malignancy)
    - #25 (prior participation in studies that include MEDI4736)
12. Section 4.5.8 (Dose Modification for Toxicity Management): Revised to be consistent with the updated emerging safety profile in the current MEDI4736 Investigator's Brochure (version 8.0). In addition, dose modification and management guidelines for MEDI4736 were updated to be consistent with the 02Oct2015 version, and the guidelines tables were moved from this section to Appendix 15.
13. Section 5.1 (Schedule of Study Procedures): Updated schedule of study procedures tables to reflect expansion of the UBC cohort.
14. Section 5.2.6 (Disease Evaluation and Methods): Updated to indicate that a modified RECIST may be used to discourage early discontinuation of MEDI4736 and provide a more complete evaluation of antitumor activity than would be seen with conventional response criteria. In addition, disease assessment by BICR was added.
15. Section 5.2.7 (Archival Tumor Samples and Tumor Biopsies): Updated to include requirements for expanded UBC cohort.
16. Section 6.1.3 (Other Events of Special Interest): Added new AESI template language.
17. Section 6.5 (Safety Management During the Study): Replaced reference to "MedImmune SMC (or equivalent)" with "internal safety governance bodies".
18. Section 7 (Statistical Considerations): Updated to reflect expansion of the UBC cohort for evaluation of the antitumor activity of MEDI4736 in subjects with PD-L1-positive UBC and validation of the potential correlation between PD-L1-positive expression and response to MEDI4736 treatment.

Protocol Amendment 9, 04Feb2016

The purpose of this amendment was to update eligibility criteria and PD-L1 testing requirements for the UBC cohort. In addition, clarifications were made to the analysis population for the UBC cohort. Key changes are listed below.

1. Study Abstract: Updated to align with changes made to the protocol body.
2. Section 1.5 (Benefit-risk and Ethical Assessment): Updated with rationale to lower the creatinine clearance requirement for UBC subjects to ≥ 30 mL/min.
3. Section 3.1 (Overview of Study Design): Updated subject enrollment numbers.
4. Section 3.1.3 (Dose Expansion): Changed to update the PD-L1 requirements for subjects in the UBC cohort such that subjects with a non-evaluable tumor sample will not be excluded. In addition, it was clarified that tumor samples to be used for PD-L1 testing must be shipped to, and confirmed as received by, the Sponsor or designated central vendor prior to dosing. It is estimated that approximately 10% of subjects will have tumors that are non-evaluable for PD-L1. As such, the sample size of the UBC cohort was increased by 10% from approximately 120 to approximately 132 subjects. Additional archival tumor tissue from beyond 6 months prior to study entry is also required, if available.
5. Section 4.2.1 (Inclusion Criteria): Updated as follows:
    a. Criterion 14.d was updated to reflect tumor tissue (fresh and/or recent within 6 months prior to study entry) for PD-L1 analysis must be shipped to the Sponsor or designated central vendor prior to the first dose of investigational product. However, subjects may be dosed prior to known PD-L1 results. Subjects in the UBC cohort must also provide additional older archival tissue regardless of age, if available.
    b. Criterion 19.f was updated to specify that UBC subjects with a creatinine clearance of ≥ 30 mL/min will be eligible for study entry.
    c. Criterion 21 was updated to indicate the additional tissue requirement for the UBC cohort, with reference to criterion 14d.
    d. Criteria 16 and 17 and Table 4.2.1-1 were modified to align contraceptive requirements with other protocols and with new template language.
6. Section 4.2.2 (Exclusion Criteria): Criterion 13 was updated to clarify incidental histologic findings of prostate cancer would include findings that, in the opinion of the investigator, do not require active therapy (eg, following cystoprostatecomy that is tumor/node/metastasis stage ≤ pT2N0). Subjects with such findings may be enrolled pending discussion and approval with the study physician.
7. Section 4.4 (Blinding): Revised to remove formal blinding of PD-L1 status. However, existing procedures will be maintained to keep PD-L1 status for UBC subjects enrolled under Amendment 8 or above blinded from participating investigators/site staff, subjects, and contract research organization/Sponsor personnel who are involved in reviewing the clinical data. Detailed procedure to ensure the blinding will be specified under a separate study document.
8. Table 5.1-1 (Schedule of Study Procedures: Screening and Treatment Period): Footnote i was modified to indicate that additional older archival tissue is required of UBC subjects if available. Footnote j was added to indicate that disease assessments performed as standard of care prior to signing of informed consent may be used for screening if obtained within 28 days prior to first dose of investigational product.
9. Table 5.1-2 (Q4W Schedule of Study Procedures: Screening and Treatment Period): Footnote f was added to indicate that disease assessments performed as standard of care

prior to signing of informed consent may be used for screening if obtained within 28 days prior to first dose of investigational product.

10. Section 5.1.1 (Screening): Revised to clarify that standard of care disease assessments obtained within 28 days prior to first dose of investigational product may be used for screening, even if obtained prior to subjects signing informed consent. This change was made to avoid unnecessary repeated disease assessments. Footnote i was added to indicate that for subjects in the UBC cohort, additional archival tissue from > 6 months prior to study entry is also required, if available.
11. Section 5.2.7.1 (Archival Tumor Samples): For subjects in the UBC cohort who provide a fresh tumor biopsy or an archived tumor specimen from within 6 months prior to study entry (ie, from subject signing consent to participate in the study) for PD-L1 IHC analysis during screening for PD-L1 IHC testing, additional archival tumor tissue from > 6 months prior to study entry is also required, if available.
12. Section 7.3.1 (Primary Endpoints) and Section 7.5 (Interim Analysis): Updated to reflect the change in PD-L1 requirements and clarify analysis population for the UBC cohort.
13. Section 7.6 (Sample Size and Power Calculations): Updated to increase number of additional enrolled UBC subjects to take into account that PD-L1 status for some enrolled UBC subjects will be not evaluable due to change on PD-L1 requirements. Additional updates were made to be consistent with the updates in Section 7.3.1 (Primary Endpoints).

Appendix 1 Signatures

Sponsor Signatures

A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects With Advanced Solid Tumors

I agree to the terms of this protocol and all amendments/administrative changes.

Signature and date: Electronic signature is appended

[redacted]

Clinical Development Therapeutic Area Head

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: [redacted]

Signature of Principal Investigator

A Phase 1/2 Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of MEDI4736 in Subjects With Advanced Solid Tumors

I, the undersigned, have reviewed this protocol and all amendments, and I agree to conduct this protocol in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with the International Conference on Harmonisation (ICH) guidelines on Good Clinical Practice (GCP), any applicable laws and requirements, and any conditions required by a regulatory authority and/or Institutional Review Board/Independent Ethics Committee (IRB/IEC).

I understand that the protocol may not be modified without written approval of the sponsor. All changes to the protocol must be submitted to the applicable regulatory authority and IRB/IEC, and must be approved by the IRB/IEC prior to implementation except when necessary to eliminate immediate hazards to the subjects or when the change(s), as deemed by the sponsor, involves only logistical or administrative changes. Documentation of IRB/IEC approval must be sent to the sponsor immediately upon receipt.

Signature and date: _____

Name and title: _____

Address including postal code: _____

Telephone number: _____

Site/Center Number (if available)_____

Appendix 2 Pain Questionnaire

Q1. On a scale ranging from 0 to 10, please rate the severity of your pain in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
Absent										Worst imaginable

Appendix 3 Patient-reported Outcome Questionnaire EORTC QLQ-C30

ENGLISH

EORTC QLQ-C30 (version 3)

We are interested in some things about you and your health. Please answer all of the questions yourself by circling the number that best applies to you. There are no "right" or "wrong" answers. The information that you provide will remain strictly confidential.

Please fill in your initials: _ _ _ _

Your birthdate (Day, Month, Year): _ _ _ _ _ _ _ _

Today's date (Day, Month, Year): 31 _ _ _ _ _ _ _ _

	Not at All	A Little	Quite a Bit	Very Much
1. Do you have any trouble doing strenuous activities, like carrying a heavy shopping bag or a suitcase?	1	2	3	4
2. Do you have any trouble taking a long walk?	1	2	3	4
3. Do you have any trouble taking a short walk outside of the house?	1	2	3	4
4. Do you need to stay in bed or a chair during the day?	1	2	3	4
5. Do you need help with eating, dressing, washing yourself or using the toilet?	1	2	3	4

During the past week:	Not at All	A Little	Quite a Bit	Very Much
6. Were you limited in doing either your work or other daily activities?	1	2	3	4
7. Were you limited in pursuing your hobbies or other leisure time activities?	1	2	3	4
8. Were you short of breath?	1	2	3	4
9. Have you had pain?	1	2	3	4
10. Did you need to rest?	1	2	3	4
11. Have you had trouble sleeping?	1	2	3	4
12. Have you felt weak?	1	2	3	4
13. Have you lacked appetite?	1	2	3	4
14. Have you felt nauseated?	1	2	3	4
15. Have you vomited?	1	2	3	4
16. Have you been constipated?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
17. Have you had diarrhea?	1	2	3	4
18. Were you tired?	1	2	3	4
19. Did pain interfere with your daily activities?	1	2	3	4
20. Have you had difficulty in concentrating on things, like reading a newspaper or watching television?	1	2	3	4
21. Did you feel tense?	1	2	3	4
22. Did you worry?	1	2	3	4
23. Did you feel irritable?	1	2	3	4
24. Did you feel depressed?	1	2	3	4
25. Have you had difficulty remembering things?	1	2	3	4
26. Has your physical condition or medical treatment interfered with your family life?	1	2	3	4
27. Has your physical condition or medical treatment interfered with your social activities?	1	2	3	4
28. Has your physical condition or medical treatment caused you financial difficulties?	1	2	3	4

For the following questions please circle the number between 1 and 7 that best applies to you

29. How would you rate your overall health during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

30. How would you rate your overall quality of life during the past week?

1	2	3	4	5	6	7
Very poor						Excellent

Appendix 4 Patient-reported Outcome Questionnaire EORTC QLQ-BR23

ENGLISH

EORTC QLQ - BR23

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have a dry mouth?	1	2	3	4
32. Did food and drink taste different than usual?	1	2	3	4
33. Were your eyes painful, irritated or watery?	1	2	3	4
34. Have you lost any hair?	1	2	3	4
35. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
36. Did you feel ill or unwell?	1	2	3	4
37. Did you have hot flushes?	1	2	3	4
38. Did you have headaches?	1	2	3	4
39. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
40. Have you been feeling less feminine as a result of your disease or treatment?	1	2	3	4
41. Did you find it difficult to look at yourself naked?	1	2	3	4
42. Have you been dissatisfied with your body?	1	2	3	4
43. Were you worried about your health in the future?	1	2	3	4

During the past four weeks:	Not at All	A Little	Quite a Bit	Very Much
44. To what extent were you interested in sex?	1	2	3	4
45. To what extent were you sexually active? (with or without intercourse)	1	2	3	4
46. Answer this question only if you have been sexually active: To what extent was sex enjoyable for you?	1	2	3	4

Please go on to the next page

ENGLISH

During the past week:	Not at All	A Little	Quite a Bit	Very Much
47. Did you have any pain in your arm or shoulder?	1	2	3	4
48. Did you have a swollen arm or hand?	1	2	3	4
49. Was it difficult to raise your arm or to move it sideways?	1	2	3	4
50. Have you had any pain in the area of your affected breast?	1	2	3	4
51. Was the area of your affected breast swollen?	1	2	3	4
52. Was the area of your affected breast oversensitive?	1	2	3	4
53. Have you had skin problems on or in the area of your affected breast (e.g., itchy, dry, flaky)?	1	2	3	4

Appendix 5 Patient-reported Outcome Questionnaire EORTC QLQ-LC13

ENGLISH

EORTC QLQ - LC13

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week :		Not at All	A Little	Quite a Bit	Very Much
31.	How much did you cough?	1	2	3	4
32.	Did you cough up blood?	1	2	3	4
33.	Were you short of breath when you rested?	1	2	3	4
34.	Were you short of breath when you walked?	1	2	3	4
35.	Were you short of breath when you climbed stairs?	1	2	3	4
36.	Have you had a sore mouth or tongue?	1	2	3	4
37.	Have you had trouble swallowing?	1	2	3	4
38.	Have you had tingling hands or feet?	1	2	3	4
39.	Have you had hair loss?	1	2	3	4
40.	Have you had pain in your chest?	1	2	3	4
41.	Have you had pain in your arm or shoulder?	1	2	3	4
42.	Have you had pain in other parts of your body?	1	2	3	4
	If yes, where _____				
43.	Did you take any medicine for pain?				
	1 No 2 Yes				
	If yes, how much did it help?	1	2	3	4

Appendix 6 Patient-reported Outcome Questionnaire EORTC QLQ-STO22

EORTC QLQ – STO22

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Have you had problems eating solid foods?	1	2	3	4
32. Have you had problems eating liquidised or soft foods?	1	2	3	4
33. Have you had problems drinking liquids?	1	2	3	4
34. Have you had discomfort when eating?	1	2	3	4
35. Have you had pain in your stomach area?	1	2	3	4
36. Have you had discomfort in your stomach area?	1	2	3	4
37. Did you have a bloated feeling in your abdomen?	1	2	3	4
38. Have you had trouble with acid or bile coming into your mouth?	1	2	3	4
39. Have you had acid indigestion or heartburn?	1	2	3	4
40. Have you had trouble with belching?	1	2	3	4
41. Have you felt full up too quickly after beginning to eat?	1	2	3	4
42. Have you had trouble enjoying your meals?	1	2	3	4
43. Has it taken you a long time to complete your meals?	1	2	3	4
44. Have you had a dry mouth?	1	2	3	4
45. Did food and drink taste different from usual?	1	2	3	4
46. Have you had trouble with eating in front of other people?	1	2	3	4
47. Have you been thinking about your illness?	1	2	3	4
48. Have you worried about your weight being too low?	1	2	3	4
49. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
50. Have you worried about your health in the future?	1	2	3	4
51. Have you lost any hair?	1	2	3	4
52. Answer this question only if you lost any hair: If so, were you upset by the loss of your hair?	1	2	3	4

Appendix 7 Patient-reported Outcome Questionnaire EORTC QLQ-PAN26

EORTC QLQ - PAN26

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	**Not at all**	**A little**	**Quite a bit**	**Very much**
31. Have you had abdominal discomfort?	1	2	3	4
32. Did you have a bloated feeling in your abdomen?	1	2	3	4
33. Have you had back pain?	1	2	3	4
34. Did you have pain during the night?	1	2	3	4
35. Did you find it uncomfortable in certain positions (e.g. lying down)?	1	2	3	4
36. Were you restricted in the types of food you can eat as a result of your disease or treatment?	1	2	3	4
37. Were you restricted in the amounts of food you could eat as a result of your disease or treatment?	1	2	3	4
38. Did food and drink taste different from usual?	1	2	3	4
39. Have you had indigestion?	1	2	3	4
40. Were you bothered by gas (flatulence)?	1	2	3	4
41. Have you worried about your weight being too low?	1	2	3	4
42. Did you feel weak in your arms and legs?	1	2	3	4
43. Did you have a dry mouth?	1	2	3	4
44. Have you had itching?	1	2	3	4
45. To what extent was your skin yellow?	1	2	3	4
46. Did you have frequent bowel movements?	1	2	3	4
47. Did you feel the urge to move your bowels quickly?	1	2	3	4
48. Have you felt physically less attractive as a result of your disease and treatment?	1	2	3	4

Please go to the next page

During the past week:	Not at all	A little	Quite a bit	Very much
49. Have you been dissatisfied with your body?	1	2	3	4
50. To what extent have you been troubled with side-effects from your treatment?	1	2	3	4
51. Were you worried about your health in the future?	1	2	3	4
52. Were you limited in planning activities, for example meeting friends, in advance?	1	2	3	4
53. Have you received adequate support from your health care professionals?	1	2	3	4
54. Has the information given about your physical condition and treatment been adequate?	1	2	3	4
55. Have you felt less interest in sex?	1	2	3	4
56. Have you felt less sexual enjoyment?	1	2	3	4

Appendix 8 Patient-reported Outcome Questionnaire EORTC QLQ-HCC18

EORTC QLQ – HCC18

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Did you feel thirsty?	1	2	3	4
32. Have you had problems with your sense of taste?	1	2	3	4
33. Have you lost muscle from your arms or legs?	1	2	3	4
34. Have you had abdominal swelling?	1	2	3	4
35. Have you been concerned by the appearance of your abdomen?	1	2	3	4
36. Have you been concerned by your skin or eyes being yellow (jaundiced)?	1	2	3	4
37. Have you had itching?	1	2	3	4
38. Have you had pain in your shoulder?	1	2	3	4
39. Have you had abdominal pain?	1	2	3	4
40. Have you had fevers?	1	2	3	4
41. Have you had chills?	1	2	3	4
42. Have you worried about getting enough nourishment?	1	2	3	4
43. Have you felt full up too quickly after beginning to eat?	1	2	3	4
44. Have you worried about your weight being too low?	1	2	3	4
45. Have you been less active than you would like to be?	1	2	3	4
46. Have you found it difficult to finish things?	1	2	3	4
47. Have you needed to sleep during the day?	1	2	3	4
During the past four weeks:				
48. Has the disease or treatment had any effect on your sex life?	1	2	3	4

Appendix 9 Patient-reported Outcome Questionnaire EORTC QLQ-H&N35

EORTC QLQ - H&N35

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week. Please answer by circling the number that best applies to you.

During the past week:	Not at all	A little	Quite a bit	Very much
31. Have you had pain in your mouth?	1	2	3	4
32. Have you had pain in your jaw?	1	2	3	4
33. Have you had soreness in your mouth?	1	2	3	4
34. Have you had a painful throat?	1	2	3	4
35. Have you had problems swallowing liquids?	1	2	3	4
36. Have you had problems swallowing pureed food?	1	2	3	4
37. Have you had problems swallowing solid food?	1	2	3	4
38. Have you choked when swallowing?	1	2	3	4
39. Have you had problems with your teeth?	1	2	3	4
40. Have you had problems opening your mouth wide?	1	2	3	4
41. Have you had a dry mouth?	1	2	3	4
42. Have you had sticky saliva?	1	2	3	4
43. Have you had problems with your sense of smell?	1	2	3	4
44. Have you had problems with your sense of taste?	1	2	3	4
45. Have you coughed?	1	2	3	4
46. Have you been hoarse?	1	2	3	4
47. Have you felt ill?	1	2	3	4
48. Has your appearance bothered you?	1	2	3	4

Please go on to the next page

During the past week:		Not at all	A little	Quite a bit	Very much
49.	Have you had trouble eating?	1	2	3	4
50.	Have you had trouble eating in front of your family?	1	2	3	4
51.	Have you had trouble eating in front of other people?	1	2	3	4
52.	Have you had trouble enjoying your meals?	1	2	3	4
53.	Have you had trouble talking to other people?	1	2	3	4
54.	Have you had trouble talking on the telephone?	1	2	3	4
55.	Have you had trouble having social contact with your family?	1	2	3	4
56.	Have you had trouble having social contact with friends?	1	2	3	4
57.	Have you had trouble going out in public?	1	2	3	4
58.	Have you had trouble having physical contact with family or friends?	1	2	3	4
59.	Have you felt less interest in sex?	1	2	3	4
60.	Have you felt less sexual enjoyment?	1	2	3	4

During the past week:		No	Yes
61.	Have you used pain-killers?	1	2
62.	Have you taken any nutritional supplements (excluding vitamins)?	1	2
63.	Have you used a feeding tube?	1	2
64.	Have you lost weight?	1	2
65.	Have you gained weight?	1	2

Appendix 10 Patient-reported Outcome Questionnaire EORTC QLQ-BN20

ENGLISH

EORTC QLQ - BN20

Patients sometimes report that they have the following symptoms. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:		Not at All	A Little	Quite a Bit	Very Much
31.	Did you feel uncertain about the future?	1	2	3	4
32.	Did you feel you had setbacks in your condition?	1	2	3	4
33.	Were you concerned about disruption of family life?	1	2	3	4
34.	Did you have headaches?	1	2	3	4
35.	Did your outlook on the future worsen?	1	2	3	4
36.	Did you have double vision?	1	2	3	4
37.	Was your vision blurred?	1	2	3	4
38.	Did you have difficulty reading because of your vision?	1	2	3	4
39.	Did you have seizures?	1	2	3	4
40.	Did you have weakness on one side of your body?	1	2	3	4
41.	Did you have trouble finding the right words to express yourself?	1	2	3	4
42.	Did you have difficulty speaking?	1	2	3	4
43.	Did you have trouble communicating your thoughts?	1	2	3	4
44.	Did you feel drowsy during the daytime?	1	2	3	4
45.	Did you have trouble with your coordination?	1	2	3	4
46.	Did hair loss bother you?	1	2	3	4
47.	Did itching of your skin bother you?	1	2	3	4
48.	Did you have weakness of both legs?	1	2	3	4
49.	Did you feel unsteady on your feet?	1	2	3	4
50.	Did you have trouble controlling your bladder?	1	2	3	4

Appendix 11 Patient-reported Outcome Questionnaire EORTC QLQ-OV28

ENGLISH

EORTC QLQ - OV28

Patients sometimes report that they have the following symptoms or problems. Please indicate the extent to which you have experienced these symptoms or problems during the past week.

During the past week:	Not at All	A Little	Quite a Bit	Very Much
31. Did you have abdominal pain?	1	2	3	4
32. Did you have a bloated feeling in your abdomen / stomach?	1	2	3	4
33. Did you have problems with your clothes feeling too tight?	1	2	3	4
34. Did you experience any change in bowel habit as a result of your disease or treatment?	1	2	3	4
35. Were you troubled by passing wind / gas / flatulence?	1	2	3	4
36. Have you felt full too quickly after beginning to eat?	1	2	3	4
37. Have you had indigestion or heartburn?	1	2	3	4
38. Have you lost any hair?	1	2	3	4
39. Answer this question only if you had any hair loss: Were you upset by the loss of your hair?	1	2	3	4
40. Did food and drink taste different from usual?	1	2	3	4
41. Have you had tingling hands or feet?	1	2	3	4
42. Have you had numbness in your fingers or toes?	1	2	3	4
43. Have you felt weak in your arms or legs?	1	2	3	4
44. Did you have aches or pains in your muscles or joints?	1	2	3	4
45. Did you have problems with hearing?	1	2	3	4
46. Did you urinate frequently?	1	2	3	4
47. Have you had skin problems (e.g. itchy, dry)?	1	2	3	4
48. Did you have hot flushes?	1	2	3	4
49. Did you have night sweats?	1	2	3	4

Please go on to next page

ENGLISH

During the past week:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
50. Have you felt physically less attractive as a result of your disease or treatment?	1	2	3	4
51. Have you been dissatisfied with your body?	1	2	3	4
52. How much has your disease been a burden to you?	1	2	3	4
53. How much has your treatment been a burden to you?	1	2	3	4
54. Were you worried about your future health?	1	2	3	4

During the past 4 weeks:	**Not at All**	**A Little**	**Quite a Bit**	**Very Much**
55. To what extent were you interested in sex?	1	2	3	4
56. To what extent were you sexually active?	1	2	3	4

Answer the following two questions only if you were sexually active:

57. To what extent was sex enjoyable for you?	1	2	3	4
58. Did you have a dry vagina during sexual activity?	1	2	3	4

Appendix 12 Patient-reported Outcome Questionnaire FACT-BL

FACT-Bl (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-Bl (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the <u>past 7 days</u>.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-Bl (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BL1	I have trouble controlling my urine	0	1	2	3	4
C2	I am losing weight	0	1	2	3	4
C3	I have control of my bowels	0	1	2	3	4
BL2	I urinate more frequently than usual	0	1	2	3	4
C5	I have diarrhea (diarrhoea)	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BL3	It burns when I urinate	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BL5	(For men only) I am able to have and maintain an erection	0	1	2	3	4
Q2	Do you have an ostomy appliance? No___ Yes___ If yes, answer the following two items: ↓					
C8	I am embarrassed by my ostomy appliance	0	1	2	3	4
C9	Caring for my ostomy appliance is difficult	0	1	2	3	4

Appendix 13 Schedule of Study Procedures for Subjects in Retreatment of MEDI4736

Table 1 Schedule of Study Procedures: Rebaseline and Retreatment Period

Evaluation	Rebaseline Day -28 to Day -1	Treatment Period (12 Months)							
		Dose 1			Dose 2 (± 3 days)	Odd-numbered Doses (after Dose 1; ± 3 days)	Even-numbered Doses (after Dose 2; ± 3 days)	After 6 Weeks (Day 43 ± 7 days)	After 12 Weeks and 16 Weeks (Days 85 and 113) Then Every 8 Weeks (± 7 days)
		Days			Days				
		1	5 ± 1	10 ± 1	1				
Verify discontinuation criteria not met	X	X							
Medical history	X								
Hepatitis B and C; HIV	X								
Serum βhCG	X								
Urine hCG or serum βhCG		X			X	X	X		
Kit assignment and MEDI4736 administration		X			X	X	X		
Protocol/Safety Evaluations									
Physical examination	X	X			X	X	X		
Vital signs [a]	X	X			X	X	X		
Postinfusion observation		X			X	X	X		
Weight	X	X			X	X	X		
AE/SAE assessment	X	X	X	X	X	X	X		
Concomitant medications	X	X			X	X	X		
ECOG performance status	X	X			X	X	X		
Laboratory Evaluations									
Hepatitis B and C viral titers (only HCC subjects with hepatitis B or C)	X					X			
Serum chemistry	X	X			X	X	X		

Table 1 Schedule of Study Procedures: Rebaseline and Retreatment Period

Evaluation	Rebaseline Day -28 to Day -1	Treatment Period (12 Months)							
		Dose 1			Dose 2 (± 3 days)	Odd-numbered Doses (after Dose 1; ± 3 days)	Even-numbered Doses (after Dose 2; ± 3 days)	After 6 Weeks (Day 43 ± 7 days)	After 12 Weeks and 16 Weeks (Days 85 and 113) Then Every 8 Weeks (± 7 days)
		Days			Days				
		1	5 ± 1	10 ± 1	1				
Thyroid function tests (TSH and free T3 and T4)	X	X			X	X	X		
Hematology	X	X		X	X	X	X		
Urinalysis	X	X			X	X	X		
Coagulation parameters	X				X	X	X		
Flow cytometric analysis - absolute cell counts, immune cell subsets, activation markers	X	X			X		X [b]		
Circulating soluble factors [c]	X	X			X		X [b]		
Disease Evaluations									
Disease assessment	X							X	X
Optional tumor biopsy (dose-expansion phase only) [c]	X							X	

AE = adverse event; βhCG = beta human chorionic gonadotropin; ECOG = Eastern Cooperative Oncology Group; HCC = hepatocellular carcinoma; hCG = human chorionic gonadotropin; HIV = human immunodeficiency virus; SAE = serious adverse event; TSH = thyroid-stimulating hormone; UBC = urothelial bladder cancer.

[a] Vital signs within an hour prior to the start of infusion, every 15 minutes (± 5 minutes) during MEDI4736 administration, at the end of infusion (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) postinfusion, followed by a 3-hour (± 15 minutes) period of observation. For subsequent doses (at dose levels of 10 mg/kg or less), the 3-hour observation period will not be required unless a subject experiences an infusion-related reaction or a higher dose level is being tested.

[b] Sample collected at Dose 4 only.

[c] Not required for subjects in the UBC cohort.

Rebaseline

All rebaselining procedures must be performed within 28 days before the first retreatment dose of investigational product (Day -28 to Day 1), unless otherwise specified. The rebaseline evaluations may be carried out over more than one visit. If the subject has completed any safety laboratory tests or ECOG assessment within 72 hours of Day 1, they will not need to be repeated.

Retreatment Period

If the subject has completed any safety laboratory tests or ECOG assessment within 72 hours of Day 1, they will not need to be repeated.

Appendix 14 Schedule of Study Procedures in Follow-up for Subjects Who Have Discontinued MEDI4736 Treatment Due to Confirmed Progressive Disease

Table 1 Schedule of Study Procedures: Follow-up for Subjects Who Have Discontinued MEDI4736 Treatment Due to Confirmed Progressive Disease

Evaluation	End of Treatment	Time Since Last Dose of MEDI4736								
		Days (± 3)		Months (± 1 week)						12 Months and Every 3 Months (± 2 weeks)
		14	30	2	3	4	6	8	10	
Protocol/Safety Evaluations										
Pain questionnaire (dose-expansion phase only)	X		X							
EORTC QLQ-C30 and cancer-specific modules (dose-expansion phase only)	X		X							
FACT-BL (UBC subjects only)	X		X							
Physical examination	X		X							
Vital signs	X		X							
Weight	X		X							
Electrocardiogram [a,b]	X		X							
AE/SAE assessment	X	X	X	X	X					
Concomitant medications	X	X	X							
ECOG performance status	X		X							
Subsequent anticancer therapy				X	X	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted				X	X	X	X	X	X	X
Laboratory Evaluations										
Hepatitis B and C viral titers (only HCC subjects with hepatitis B or C)	X		X							
Hematology	X		X							
Serum chemistry	X		X							
Thyroid function tests (TSH, and free T3 and T4)	X		X							
Coagulation parameters	X		X							
Urinalysis	X		X							

Table 1 Schedule of Study Procedures: Follow-up for Subjects Who Have Discontinued MEDI4736 Treatment Due to Confirmed Progressive Disease

Evaluation	End of Treatment	Time Since Last Dose of MEDI4736								
		Days (± 3)		Months (± 1 week)						12 Months and Every 3 Months (± 2 weeks)
		14	30	2	3	4	6	8	10	
Pharmacokinetic assessment	X[b]		X[b]		X					
Immunogenicity assessment	X[b]		X[b]		X					
sPD-L1 concentration[b]	X		X							
Flow cytometric analysis - absolute cell counts, immune cell subsets, activation markers[b]	X									
Circulating soluble factors[b]	X		X							
PBMC collection (immunodiversity, flow cytometry, or functional assessment)[b]	X									
Anticancer/testis antigen antibodies[b]	X									
Circulating tumor cells (dose escalation and TNBC for dose expansion)	X		X							
miRNA/mRNA analysis[b]	X		X							
Disease Evaluation										
Disease assessment	X									

AE = adverse event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EORTC QLQ-C30 = European Organisation for Research and Treatment of Cancer quality-of-life questionnaire; FACT-BL = Functional Assessment of Chronic Illness Therapy-bladder; HCC = hepatocellular carcinoma; miRNA = micro ribonucleic acid; mRNA = messenger ribonucleic acid; PBMC = peripheral blood mononuclear cell; SAE = serious adverse event; sPD-L1= soluble programmed death ligand 1; TNBC = triple negative breast cancer; TSH = thyroid-stimulating hormone; UBC = urothelial bladder cancer.

[a] Digital ECGs will be collected at selected sites. All other sites will perform ECGs per their institution's standard.

[b] Not required for subjects in the UBC cohort.

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[1] ASCO Educational Book 2015. Michael Pestow, MD. "Managing Immune Checkpoint Blocking Antibody Side Effects".

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[2] ASCO Educational Book 2015. Michael Pestow, MD. "Managing Immune Checkpoint Blocking Antibody Side Effects".

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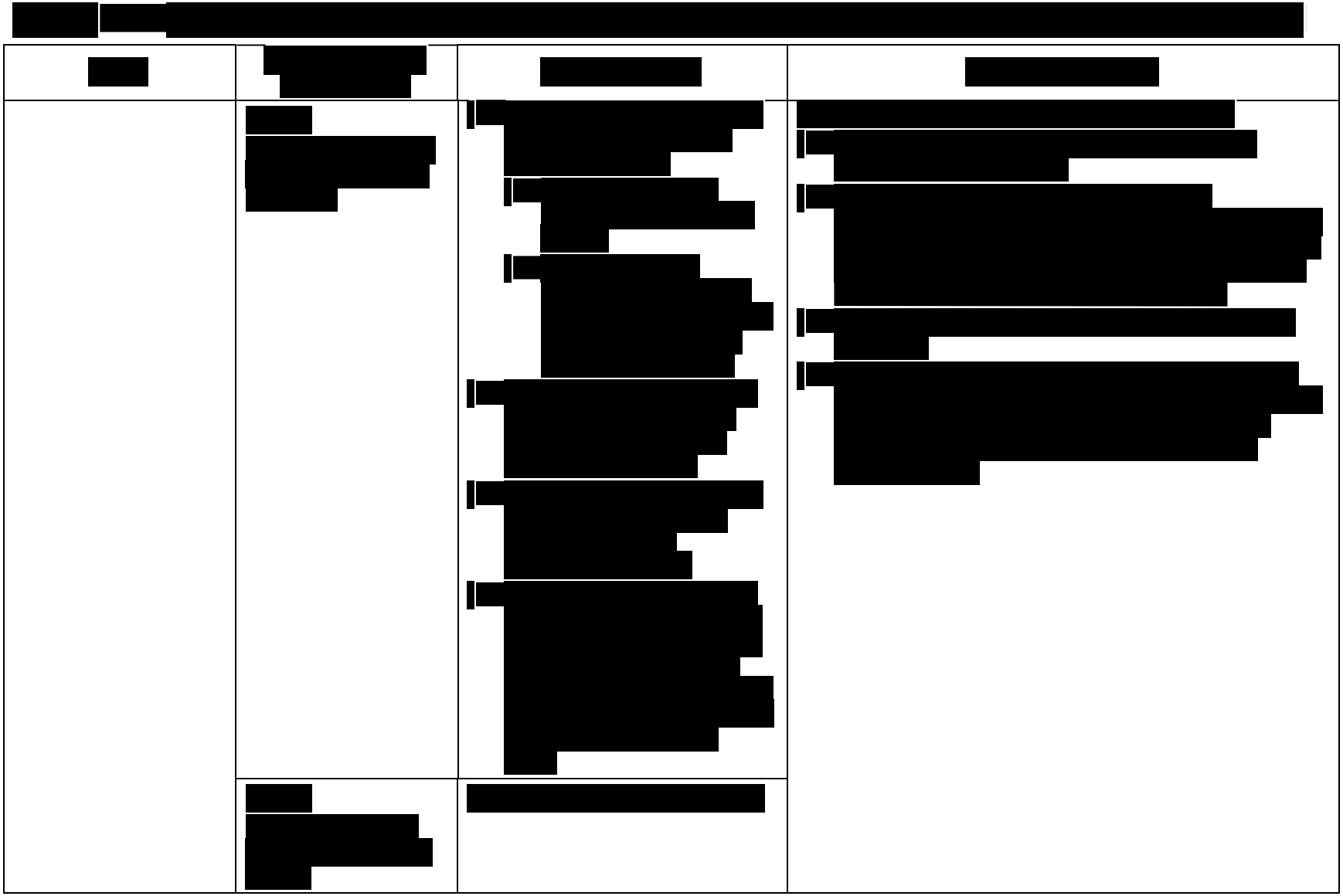

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[4] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

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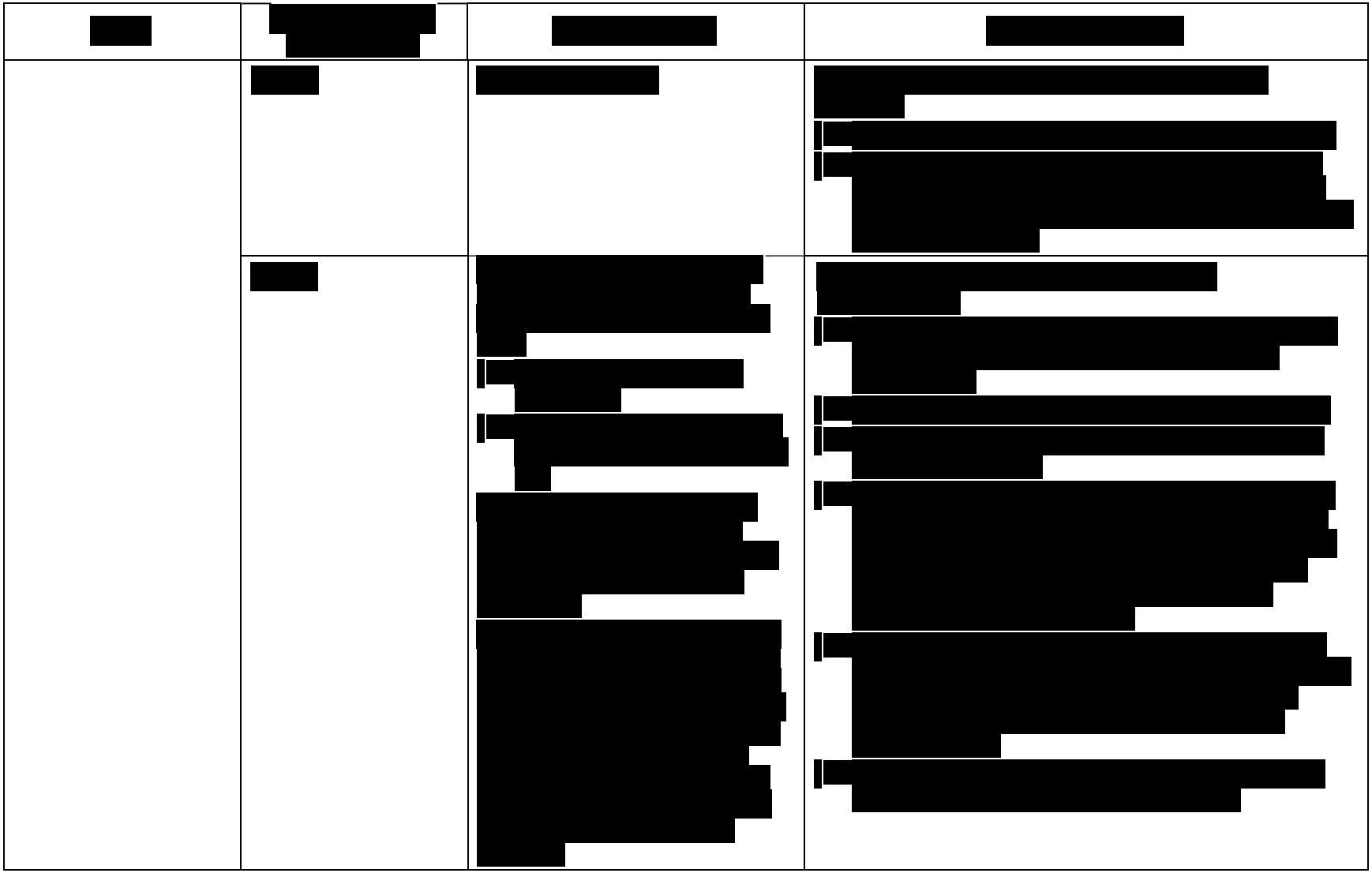

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