Statistical Analysis Plan

Protocol Number: CD-ON-MEDI4736-1108

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

Table of Contents

List of In-Text Tables

List of Abbreviations

Abbreviation or Specialized Term	Definition
ADA	Anti-drug antibody
AE	Adverse event
AESI	AEs of special interest
CI	Confidence interval
CR	Complete response
CRC	Colorectal cancer
CRF / eCRF	Case Report Form (electronic)
DC	Disease control
DCR	Disease control rate
DLT	Dose-limiting toxicity
DoR	Duration of response
DMPK	Drug Metabolism and Pharmacokinetics
ECG	Electrocardiography
ECOG	Eastern Cooperative Oncology Group
FTIH	First time in human
IC	Immune-cell
IM	Immunogenicity
imAE	Immune-mediated Adverse Event
[redacted]	[redacted]
IV	Intravenous
MedDRA	Medical Dictionary for Regulatory Activities
MTD	Maximum tolerated dose
NCI CTCAE	Common Terminology Criteria for Adverse Events (National Cancer Institute, Washington, DC)
NSCLC	Non-small cell lung cancer
OBD	Optimal biological dose
ORR	Overall response rate
OS	Overall survival
PD	Progressive disease

Abbreviation or Specialized Term	Definition
PFS	Progression-free survival
PK-PD	Pharmacokinetics-Pharmacodynamics
PR	Partial response
PK	Pharmacokinetic(s)
Q2W	Every two weeks (Q = *quoque*, Latin)
Q3W	Every three weeks (Q = *quoque*, Latin)
Q4W	Every four weeks (Q = *quoque*, Latin)
RCC	Renal cell carcinoma
SAE	Serious adverse event
SAS	Statistical Analysis System (Cary, NC, USA)
SD	Stable disease
SPP	Statistical programming plan
TC	Tumor-cell
TEAE	Treatment-emergent adverse event
TSH	Thyroid-stimulating hormone
UC	Urothelial carcinoma

1 Introduction

This document describes the statistical methodology and summaries for Study CD-ON-MEDI4736-1108, and investigation of MEDI4736 in adult subjects with advanced solid tumors. As background information, an overview of the study design is provided. The main portion of this document details the statistical summaries relating to each study objective and describes the general conventions and definitions that will be used.

In addition, a set of table templates and specifications are planned to be created in a statistical programming plan (SPP) to complement this document.

2 Study Overview

2.1 Study Objectives

2.1.1 Primary Study Objective(s)

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 CRC refractory to standard therapy or for which no standard therapy exists.

Dose-expansion Phase

The primary objectives of the dose-expansion phase are:

- 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 version 1.1 guidelines.
- To evaluate the antitumor activity of MEDI4736 in subjects with PD-L1-high urothelial carcinoma (UC) as assessed by RECIST v1.1.
- 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 carcinoma, glioblastoma multiforme (GBM), ovarian cancer, soft tissue sarcoma, small-cell lung cancer (SCLC), microsatellite instability (MSI) high cancers, human papilloma virus (HPV) positive cancers, or nasopharyngeal carcinoma.

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.

2.1.2 Secondary Objectives

- To describe the PK of MEDI4736
- To determine the immunogenicity of MEDI4736
- To evaluate the antitumor activity of MEDI4736 (except for subgroups of UC and NSCLC subjects where this is considered a primary objective) as assessed by RECIST v1.1.
- To evaluate the antitumor activity of MEDI4736 in subjects with UC, regardless of PD-L1 status as assessed by RECIST v1.1.
- To evaluate the antitumor activity of MEDI4736 in subjects with PD-L1-low/neg UC as assessed by RECIST v1.1.

  To evaluate the antitumor activity of MEDI4736 as assessed by RECIST v1.1 in subjects with PD-L1-high UC as compared to PD-L1-low/neg UC.

2.1.3 Exploratory Objectives

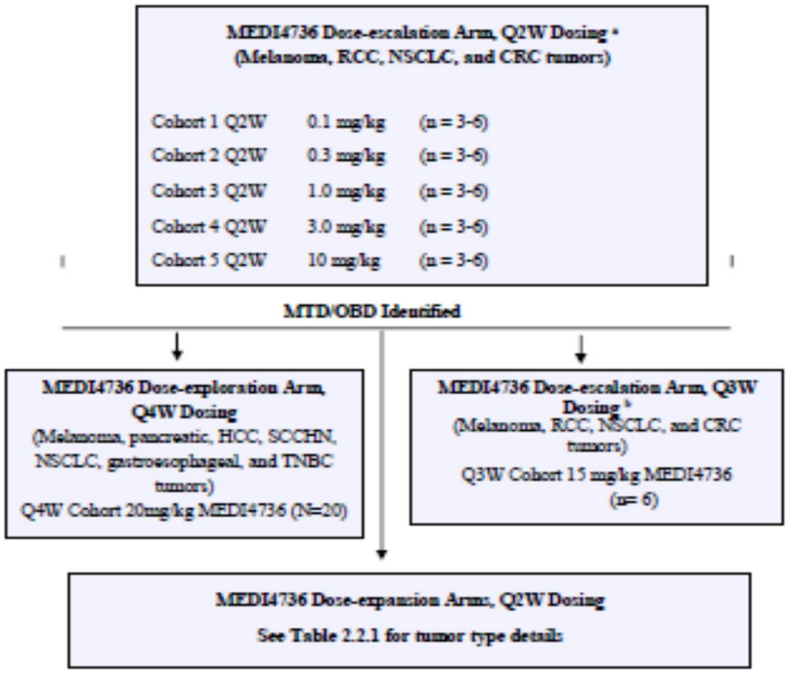
[redacted]

2.2 Study Design

Study CD-ON-MEDI4736-1108 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 according to a standard 3+3 design at

doses from 0.1 to 10 mg/kg MEDI4736 Q2W and 15 mg/kg Q3W in subjects with advanced melanoma, renal cell carcinoma (RCC), NSCLC, or colorectal cancer (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, urothelial carcinoma, GBM, ovarian cancer, soft tissue sarcoma, SCLC, MSI high cancers, human papilloma virus (HPV) positive cancers, or nasopharyngeal carcinoma; In addition, a dose exploration cohort will examine MEDI4736 at an alternative dosing schedule (20 mg/kg MEDI4736 Q4W) in subjects with advanced cutaneous melanoma, uveal melanoma, pancreatic adenocarcinoma, NSCLC, HCC, SCCHN, gastroesophageal cancer, TNBC or pancreatic adenocarcinoma. A study flow diagram of the study design is shown in Figure 2.2.1.

Figure 2.2.1 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.

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

Table 2.2-1 Number of Subjects Enrolled by Tumor Type in Dose Expansion Cohorts

Tumor Type	Total Planned Enrollment
Advanced cutaneous melanoma	20
Uveal melanoma	20-60
HCC	20-60
SCCHN	20-60
Squamous NSCLC (Total) 1L 2L ≥ 3L	170-190 10-30 80 80
Non-squamous NSCLC (Total) 1L 2L ≥ 3L	110-140 10-30 20-30 80
Gastroesophageal	20-60
TNBC	20- 60
Pancreatic adenocarcinoma	10-60
UC (Total) Initial UC subjects Amendment 8 and beyond PD-L1 high PD-L1 low/neg Non-evaluable for PD-L1	20-192 20-60 132 ≥ 70 50 12
GBM (Total) MGMT negative	20-60 ≥ 10
Ovarian cancer (Total) Platinum sensitive	20-60 ≥ 10
Soft tissue sarcoma	20-60
SCLC	20-60
MSI-high cancers	20-60
HPV + tumors (Total) Cervical cancer	20-60 ≤ 10 [a]
Nasopharyngeal carcinoma	10-60
Total	**692-1,322**

In the Dose-expansion cohorts, an evaluation of a possible correlation between clinical activity of MEDI4736 and potential biomarkers (eg, PD-L1 expression on tumor or sPD-L1) for different disease types will be ongoing throughout the study. Initially, tumoral PD-L1 expression will be assessed on screening samples after enrollment on an ongoing basis. After a cut-off determination for this assay, a minimum numbers of subjects with tumoral PD-L1 expression above a pre-specified cut-off level (referred to hereafter as PD-L1 high) in the

applicable disease cohorts may be required by prospective testing prior to enrollment. After the first 20-40 subjects in each of HCC, gastroesophageal cancer, TNBC, UC, 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.

For UC cohort, an initial cohort of 63 subjects were enrolled prior to Amendment 8. Amongst these, the first 20 subjects were enrolled regardless of PD-L1 expression, and the remaining 43 subjects were enrolled with a requirement of ≥ 5% tumor cells for PD-L1 expression regardless of immune cell for PD-L1 expression in a pre-treatment tumor biopsy specimen. Under Amendment 8 and beyond of this protocol, the UC cohort will be expanded to evaluate the antitumor activity of MEDI4736 in subjects with PD-L1-high UC and validate the potential of PD-L1 expression (determined by IHC) to predict response to MEDI4736 treatment. Approximately 132 additional UC subjects (regardless of PD-L1 status) will be enrolled in this cohort in order to include a minimum of 70 PD-L1-high subjects and 50 subjects with PD-L1-low/no expression, and approximately 12 subjects with non-evaluable PD-L1 status. [redacted]

2.3 Randomization and Blinding

This is an open-label and single-arm study. Randomization and blinding are not applicable to this study. However, for UC subjects enrolled under Amendment 8 or above, Investigators/ site staff, subjects and CRO/Sponsor personnel involved in reviewing the clinical data will be blinded to individual PD-L1 status. Investigators/site staff may be notified that a subject has an evaluable tumor sample or not, but the specific PD-L1 status (ie, PD-L1-high vs. PD-L1-low/neg) will be blinded. Unblinding to individual PD-L1 status for those who were enrolled under Amendment 8 or above and included in the planned interim and primary/final analyses will occur after database lock for the respective analyses.

In order to monitor the enrollment with respect to number of subjects with PD-L1-high and PD-L1-low/neg enrolled into the study, the aggregate PD-L1 status will be provided by a designated person who is not a member of the study team. Detailed procedure to ensure the blinding was specified under a separate study document.

Personnel at Ventana involved in testing PD-L1 status will be blinded to clinical data (except for information provided in the requisition form).

2.4 Sample Size Considerations

[redacted]

2.4.1 MEDI4736 Dose-escalation

The number of subjects 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 2.4.1-1 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 2.4.1-1 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.

2.4.2 MEDI4736 Dose-exploration

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]

[redacted]

2.4.3 MEDI4736 Dose-expansion

A minimum of approximately 560 subjects will be enrolled in the dose-expansion. Additional subjects, described in each cohort below, may be enrolled if promising clinical activity is observed in any of these cohorts.

2.4.3.1 NSCLC Cohorts

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]

NSCLC Cohorts with Tumoral PD-L1 Expression Requirement

In order to have the estimation with reasonable precision for ORR in the NSCLC subpopulation including subjects who have tumoral PD-L1 expression, all remaining subjects as of protocol Amendment 7 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 will be required to have tumoral PD-L1 expression as determined by prospective testing prior to enrollment. Table 2.4.3-1 provides the detailed requirement of tumoral PD-L1 expression in NSCLC cohorts. [redacted]

Table 2.4.3-1 NSCLC Dose-expansion Cohort PD-L1 Expression Requirements

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

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

Table 2.4.3-2 [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]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[redacted]

2.4.3.2 UC cohort

Of 192 UC subjects enrolled in the study, it is expected that there will be approximately 100 PD-L1-high 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 2.4.3-3 [redacted]

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

[redacted]

The prevalence of PD-L1 status for UC 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-high subjects may continue to ensure a minimum total of 70 PD-L1-high subjects are enrolled.

With 70 PD-L1-high and 50 PD-L1-low/no expression UC 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-low/neg group is assumed to be similar to that observed with chemotherapy in a second-line UC population (Bellmunt et al, 2009).

2.4.3.3 Cohorts Requiring a Minimum of 20 Subjects

Advanced cutaneous melanoma, uveal melanoma, HCC, SCCHN, gastroesophageal cancer, TNBC, 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 Disease Control Rate (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, enrolment may be prioritized to tumor sub-type(s) that showed promising clinical activity, at the sponsor's discretion.

Table 2.4.3-4 [redacted]

[redacted]							
[redacted]							
[redacted]							

2.4.3.4 Cohorts Requiring a Minimum of 10 Subjects

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 2.4.3-5). 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 2.4.3-5 [redacted]

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

[redacted]

3 Statistical Methods

3.1 General Considerations

This study encompasses a variety of disease types, dose levels and dosing schedules in 3 phases (dose escalation, dose expansion and dose exploration). Therefore, final analyses for the clinical study report may be performed at a different time separately for each disease type. For each disease type, the data cut-off (DCO) for the primary analysis may take place at least 24 weeks after the last subject is enrolled into each disease type, unless otherwise specified. The final analysis for each disease type including all study endpoints may take place when overall survival for that disease type is considered mature or after the end of study. At the time of analysis, subject population data (i.e. demographic/baseline characteristics, disposition and treatment exposure) and safety data will also be summarized across all disease types as appropriate. In general, ccategorical data will be summarized by frequency distribution (number and percentage of subjects falling within each category). Continuous variables will be summarized by descriptive statistics.

Assessments of change from baseline to post-baseline or the ratio of post-baseline to baseline will include only those subjects with both baseline and post-baseline measurements. Unless otherwise specified, the baseline is defined as the last non-missing observation collected on or prior to the date of the first dose of study drug for treated subjects. The missing data for a parameter will not be imputed and the subjects with the missing data will be excluded from the summary of this parameter, unless otherwise specified. In general, all calculations will be performed prior to rounding.

The data analyses will be conducted using the SAS® System (SAS Institute, Inc., Cary, NC, USA) Version 9.3 or above in Unix (Sun OS) environment. All SAS® programs used to generate analytical results will be developed and validated [redacted].

3.1.1 PD-L1 Expression Status

PD-L1 expression status (high and low/neg) will be derived from percent of tumor cells and/or immune cells exhibiting cell surface staining for PD-L1 based on pre-specified threshold, assessed by IHC. In the case of multiple specimens (fresh biopsies and/or archival tissues) a subject's PD-L1 status will be derived based on baseline PD-L1 expression, which is determined from the most recent tumor sample (prior to first dose of study treatment) with a quantifiable result.

- For NSCLC and SCCHN cohorts, PD-L1 high subject is defined as a subject's baseline PD-L1 expression with tumor-cell score [TC] ≥ 25%; PD-L1 low/neg subject is defined as a subject's baseline PD-L1 expression with TC < 25%.
- For the UC cohort, PD-L1 high subject is defined as a subject's baseline PD-L1 expression with TC ≥ 25% or immune-cell score [IC] ≥ 25%; PD-L1 low/neg subject is defined as a subject's baseline PD-L1 expression with TC < 25% and IC< 25%.
    - Note: when immune cell area represent ≤1% of the total tumour area, subjects are defined as:
        - PD-L1 high when baseline PD-L1 expression with TC ≥ 25% or IC is 100%.
        - PD-L1 low/neg when baseline PD-L1 expression with TC < 25% and IC < 100%.
- For UC cohort, additional PD-L1 subgroups of interest based on baseline PD-L1 expression are defined as the followings:
    - TC high (TC ≥ 25%) vs TC low/neg (TC < 25%)
    - IC high (IC ≥ 25%) vs IC low/neg (IC < 25%)
        - Note: when immune cell area represent ≤1% of the total tumour area, subjects are defined as:
            - IC high when baseline PD-L1 expression with IC is 100%.
            - IC low/neg when baseline PD-L1 expression with IC < 100%.

3.2 Analysis Populations

The Analysis Populations to be used for primary/final analyses are described below. The analysis population to be used for interim analyses are described in Section 4.

As-treated Population is defined as all subjects who receive any dose of MEDI4736.

Full analysis set (FAS) Population is defined as all subjects from the As-treated Population who had measurable disease at baseline per blinded central review (BICR) and had an opportunity to be followed for at least 24 weeks by the DCO date (i.e., received the first dose of MEDI4736 at least 24 weeks prior to the DCO date).

- Measurable disease at baseline per BICR will be determined according to the BICR efficacy review (See details in BICR charter). Measurability will be determined by the reviewer selected by the adjudicator (if present). If no adjudication is required, then if either reviewer determines the subject to have measurable disease at baseline, the subject will be considered to be measurable.

DLT Evaluable Population is defined as all subjects enrolled in the dose-escalation phase who receive at least two doses of MEDI4736 and complete the safety follow-up through the DLT evaluation period (defined as the time period until the administration of the third dose of MEDI4736) or experience any DLT.

Re-treated Population is defined as all subjects who have entered follow-up and have been re-treated with MEDI4736 after the initial 12 months treatment period.

The number and percent of subjects in each analysis population for evaluation will be summarized as described in Section 3.1. Unless stated otherwise, outcome variables will be summarized based on analysis populations given in Table 3-1.

Table 3-1 Summary of efficacy and safety variables and analysis populations

Outcome variable	Populations
Efficacy Data	
ORR, DCR, BoR, DoR, DSD (using BICR dara)	FAS (primary population)/ As-treated Population (supportive population)
ORR DCR, BoR, DoR, DSD (using investigator data)	As-treated Population
PFS, OS,	As-treated Population
Safety Data	
DLT	DLT Evaluable Population
Demography and baseline characteristics	As-treated Population/FAS
Subject disposition	As-treated Population/FAS
Prior and Concomitant Medications	As-treated Population
Exposure	As-treated Population
Adverse events	As-treated Population
Laboratory measurements	As-treated Population
Vital Signs	As-treated Population
ECG	As-treated Population

BoR Best objective response; DCR Disease control rate; DoR Duration of response; DSD Duration of stable disease; ORR Objective response rate; OS Overall survival; PFS Progression-free survival

All analyses will be based on the treatment that the subject actually received. Efficacy data and/or safety data will be summarized for the initial treatment period and re-treatment period separately, unless otherwise specified. For safety summary, initial treatment period is defined from the time of first dose to the time of being re-treated or till 90 days (+7 days to allow visit window) after the last dose of the initial treatment period, whichever comes first. Re-treatment period is defined from the time of first dose of being re-treated till 90 days (+7 days to allow visit window) after the last dose of the re-treatment period. Efficacy data and/or safety data during the re-treatment period may be summarized for Re-treatment population if data warranted, in which case a small set of summaries of efficacy and safety data from the

re-treatment period only, and summaries of safety data from the initial treatment period and the re-treatment period aggregated will be produced.

To avoid biasing the central reviewers, the baseline scans prior to re-treatment will not be identified (see further in the BICR charter) thus there is no intention to differentiate between efficacy data from the re-treatment period based upon BICR and those from the initial treatment period.

3.3 Study Subjects

3.3.1 Subject Disposition and Completion Status

The number and percentage of subjects screened, screed failed, reasons for screening failures, treated, completed treatment, and not completed treatment due to any of the following reasons: AE; Death; Lost to follow-up; Investigator discretion; Subject non-compliant with treatment; Initiation of alternative therapy; Withdrawal of consent; Disease progression; Protocol violation; Subject request; and Other will be summarized.

Subject status at the end of study will be summarized in terms of the number and percent of subjects who are classified as the following: completed protocol-defined end of study, lost to follow-up, withdrawal of consent, death, or other.

3.3.2 Demographics and Baseline Characteristics

The following demographics and baseline characteristicswill be listed and/or summarised:

- Demographic: demographic information related to sex, age, race, ethnicity, weight, and height will be presented.
- Disease characteristics at baseline: A summary of disease characteristics at baseline may include, but not be limited to disease stage, time from initial diagnosis to study entry.
- Baseline tumor characteristics will be summarized, including number and sites of both target lesions and non-target lesions.
- Prior cancer treatment: The summary may include, but not be limited to the number of prior systemic regimen for SCCHN or line of prior therapy for NSCLC and UC cohorts, type of treatment (i.e. surgery, radiotherapy, chemotherapy, biologic). Smoking History and other smoking related variables (for cigarette users, extent of use will be expressed as pack years).

- ECOG: ECOG performance status will be summarized using frequency distribution.

Summary of disease specific baseline characteristics will also be included but not limited to:

- NSCLC: histology, exposure to prior TKI therapy, exposure to prior platinum-base therapy, mutation status for non-squamous NSCLC (EGFR, ALK, and KRAS).
- SCCHN: HPV status, anatomical location, previous therapy with platinum-based regimen, previous therapy with cetuximab
- Cutaneous melanoma: BRAF mutation , NRAS mutation
- MSI-high cancer: MSI-H types, Method of determining DNA mismatch repair
- GBM: MGMT status, IDH1/IDH2 mutation
- Nasopharyngeal carcinoma: EBV status
- Ovarian cancer: mutations status, BRCA1 mutation, BRCA2 mutation，platinum sensitive
- HPV positive cancer: HPV positive cancer types
- UC: site of primary tumor, histology, hemoglobin at baseline (<10 g/dL), baseline creatinine clearance (<60 mL/min), previous therapy with platinum-based regimen (cisplatin-based, carboplatin-based, other platinum combination), time from last prior systemic therapy (<=3 months), prior BCG administrated and extent of disease at study entry (liver, lymph node only, and visceral metastasis derived based on baseline tumor scan).
    - Visceral metastasis included liver, lung, bone, or any non-lymph node or soft tissue metastasis.

3.3.3 Study Drug Exposure

Study drug exposure will be derived separately for initial treatment and re-treatment periods. Summary of study treatment exposure for initial treatment period will include descriptive statistics of the following: treatment duration, number of MEDI4736 doses and total MEDI4736 dose received during the study, dose intensity and relative dose intensity of MEDI4736. The treatment duration in 8 weeks interval (<=8 weeks, 8-16 weeks, etc) and relative dose intensity (<=60%, 60%-80%, >80%-90%, >90%-100% and >100%) will also be summarized using frequency distribution.

The dose intensity (mg/kg/dose interval) for MEDI4736 is defined as total actual dose (in mg/kg) that a subject received per dose interval. Relative dose intensity is defined as the dose

intensity divided by the planned dose per dose interval. The details of the dose intensity calculation will be provided in the SPP.

Dosing modification of MEDI4736 will be summarized for the initial treatment and re-treatment periods for the following categories: the number of subjects with dose delays/omissions, the reasons for dose delay/omissions (AEs, scheduling conflict, and other), the number of subjects for whom the entire dose was not administered as scheduled (infusion interruption), and the reasons the entire dose was not administered as scheduled (AEs and other).

3.3.4 Concomitant Medications

Prior and concomitant medications will be summarized by the second highest ATC class and preferred term. Within each level of summarization (ATC class and preferred term), a subject will be counted once if he/she takes one or more medications.

Prior medications are defined as those with a start date prior to the date of first dose of study medication. Concomitant medications include those medications:

- with a start date greater than or equal to the date of first dose of study medication, or
- with a start date prior to the date of first dose of study medication and a stop date either after the date of first dose of study medication or marked as “continuing”, or

3.4 MTD/OBD Analysis

The number of DLTs during the Dose Escalation Phase will be presented by dose levels and overall. The MTD level (which can be different for Q2W and Q3W) may be indicated in the summary.

3.5 Efficacy Analyses

Efficacy analyses will be performed separately for each disease type on subjects who have received MEDI4736 10 mg/kg Q2W in either the dose escalation or expansion phases. Efficacy data from 10 mg/kg Q2W in either the Dose Escalation Phase or Dose Expansion Phase will be combined for analyses.

For NSCLC cohorts (squamous and non-squamous), efficacy analyses will also be performed separately for each cohort by line of therapy (1st line, 2nd line, 3rd line or above, and 2nd line or above) with a further breakdown by PD-L1 status (PD-L1 high and PD-L1 low/no expression). Analyses will be repeated for all NSCLC subjects regardless of histology.

For the SCCHN cohort, efficacy analyses will be performed separately for HPV positive, HPV negative and overall (regardless of HPV status), with a further breakdown by PD-L1 status (PD-L1 high and PD-L1 low/no expression).

For the UC cohort, efficacy analyses will be performed for 2L+ UC subjects regardless of PD-L1 expression, with a further breakdown by the PD-L1 subgroups including TC high vs low/neg, IC high vs low/neg , and PD-L1 high (either TC or IC high) vs PD-L1 low/neg (both TC and IC low/neg). See Section 3.1.1.

PFS/OS analysis will not be presented if there are not a sufficient number of events (at least 10) in each subgroup.

3.5.1 Primary Efficacy Endpoint and Analyses

Primary Efficacy Endpoint

The primary efficacy endpoint for the NSCLC cohort and the UC cohort in this study is objective response, which is defined as a best overall response (BoR) of confirmed CR or PR based on RECIST v1.1 by BICR.

BoR is calculated based on the overall visit responses from each assessment including unscheduled visits. It is the best response a subject has had from the start of treatment until objective documentation of PD (per RECIST v1.1 as assessed by BICR), or subject withdrawn from the study, or subject started new anticancer therapy, whichever occurs first. Categorization of BoR will be based on RECIST v1.1 using the following response categories/orders: CR , PR, SD, PD, and NE. Overall visit responses along with the date of response will be provided by the BICR (i.e. the reviewers will provide the overall visit response according to RECIST 1.1 and no programmatic derivation of visit response is necessary).

A BoR of CR or PR must be confirmed. A CR/PR requires confirmation no less than 4 weeks (28 days) after the first response criterion was met and with no evidence of progression between the initial and CR/PR confirmation visit. A confirmed CR is defined as two CRs that were separated by at least 28 days with no evidence of progression in-between. A confirmed PR is defined as two PRs or an un-confirmed PR and an un-confirmed CR that were separated by at least 28 days with no evidence of progression in-between.

For determination of a BoR of SD, the SD should be recorded at least 6 weeks +/- 7 days, i.e. at least 35 days (to allow for the assessment window), after the date of the first dose. For a subject without measurable lesions at baseline, overall visit response "Non-CR/non-PD which is preferred over "stable disease" will be provided by the ICR (See further details in the ICR charter). For the determination of BoR, an overall visit response with "Non-CR/non-PD" is considered as SD.

Subjects who responded with an unconfirmed CR/PR at the time of data cutoff will be reported as unconfirmed CR/PR under the SD category provided the minimum criteria for SD duration (35 days) are met, otherwise this will be reported under the NE category.

Analysis of Primary Endpoint

Objective response rate is defined as the proportion of subjects with OR. The primary endpoint of OR based on RECIST v1.1 by BICR will be analyzed by estimating the ORR and its 2-sided 95% CI with the exact probability method.

An objective response will be considered as an ongoing response if the subject who had documented OR is still alive and progression-free (per RECIST v1.1 as assessed by BICR) at the time of data cutoff. The number and percentage of subjects with ongoing response will be provided. The percentage is calculated based on number of subjects with OR. Additional details related to analysis of ORR for UC cohort are described below.

Analysis of ORR for UC cohort

The primary analysis of ORR based on RECIST v1.1 by BICR will be performed for all 2L+ PD-L1 high UC subjects in the FAS enrolled in the entire study. The primary endpoint for UC cohort in PD-L1-high 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% (Bellmunt et al, 2009). An analysis of ORR for all 2L+ PD-L1 high UC subjects in the FAS enrolled under Amendment 8 and beyond will be conducted as a supportive analysis. The primary analysis for UC cohort will occur at least 24 weeks after the last PD-L1-high UC subject's first dose of study treatment.

If the primary endpoint for the PD-L1-high subgroup of the UC cohort is met, the ORR based on RECIST v1.1 by BICR along with its 95% CI will be also provided for all 2L+ UC subjects in the FAS (regardless of PD-L1 status) enrolled in the entire study. The primary

endpoint for UC 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% (Bellmunt et al, 2009).

Additional analysis of ORR as determined by the investigator according to RECIST v1.1 will be conducted for As-treated Population with opportunity to be followed for at least 24 weeks, 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.

Concordance/Discordance of BoR programmatically derived per RECIST 1.1 based on investigator disease responses and the disease response per BICR will be summarized in a frequency table. The agreement rate for subjects with objective responses and with objective responses will be also provided.

3.5.2 Secondary Efficacy Endpoints and Analyses

The secondary efficacy endpoints include objective response (except for subgroups of NSCLC and UC cohorts where OR is considered the primary endpoint), duration of response (DoR), disease control (DC), time to response (TTR), duration of stable disease (DSD), progression-free survival (PFS), overall survival (OS), and change in target lesion size. All endpoints except Overall Survival (OS) are based on RECIST 1.1 as assessed by the BICR (if available) and investigator. The site investigator disease response assessment will be a programmatically-derived from the investigator's recorded measurements and assessments for target, non-target, and new lesions according to RECIST v1.1.

Duration of Response

Duration of Response (DoR) is defined as the time from the date of first documented response (CR or PR) until the first date of documented PD (per RECIST v1.1), or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of data cut-off for analysis, DoR will be censored at the PFS censoring time. The PFS censoring rule specified in Table 3.5-1 will be applied.

The DoR will only be evaluated for subjects who have a documented confirmed response (CR or PR) based on RECIST v1.1 and is calculated as following:

DoR (months) = (Date of PD/Death or censoring – Date of first response + 1) / (365.25 / 12)

If the visit when the initial CR or PR is observed spans multiple dates, the latest date will be used for calculation of response duration.

The median DoR and its 95% CI will be estimated using the Kaplan-Meier method.

Disease Control

The Disease Control (DC) is defined as a best overall response of confirmed CR, confirmed PR or SD (per RECIST v1.1). Disease control at 12 and 24 weeks is defined as a best overall response of confirmed CR, confirmed PR or having SD with duration of SD for a minimum duration of 12 weeks (-7 days, i.e., 77 days), and 24 weeks (-7 days, i.e., 161 days), following the start of study treatment, respectively. A window of 1 week is applied since not all subjects adhere to the scheduled tumor measurement date.

The secondary endpoint of DC will be analyzed by estimating the Disease Control Rate (DCR), defined as the proportion of subjects with DC and its 2-sided 95% CIs using an exact probability method.

Progression-free survival

Progression-free survival (PFS) is defined as the time from the date of the first dose of study treatment(s) until the first date of documented PD (per RECIST v1.1) or death due to any cause, whichever occurs first, regardless of whether the subject withdraws from treatment or receives another anti-cancer therapy prior to progression.

For subjects who are alive and progression-free at the time of data cutoff for analysis, PFS will be censored at the time of the date of last evaluable disease assessment. If the subject progresses or dies after ≥ 2 consecutively missed disease assessments, PFS will be censored at the time of the latest evaluable disease assessment prior to the missed assessments.

PFS (months) = (Date of PD/Death or censoring – Date of first dose + 1) / (365.25 / 12).

The details of censoring rule are listed in Table 3.5-1:

Table 3.5-1 Censoring Rule for Analysis of PFS

Situation	Date of PD / Death or Censoring	Primary Outcome
No disease assessment at baseline or post-baseline visits	Date of first dose	Censored
Alive and progression-free	Date of last evaluable disease assessment	Censored

Situation	Date of PD / Death or Censoring	Primary Outcome
Documented Progressive Disease (PD)	Date of earliest sign of PD	Progressed
Death before first progressive disease assessment	Date of death	Progressed
Death between adequate assessment visits	Date of death	Progressed
PD or death immediately after ≥ 2 consecutively missed or NE disease assessments	Date of last evaluable progression-free disease assessment prior to missed or NE assessments	Censored

In this study, progression or death after ≥2 consecutive missed disease assessment visits is defined (according to disease assessment schedules specified in the protocol) as below:

- ≥ 126 days (two disease assessment visits [16 weeks] plus 2 weeks window to allow for a late assessment) since the last post-baseline evaluable disease assessment, if progression or death occurs prior to end of treatment.
- ≥ 136 days (two disease assessment visits [4 months] plus 2 weeks visit window to allow for a late assessment) since the last post-baseline evaluable disease assessment, if progression or death occurs after end of treatment but within 12 months since last dose of study treatment.
- ≥ 211 days (two disease assessment visits [6 months] plus 4 weeks visit window to allow for a late assessment) since the last post-baseline evaluable disease assessment, if progression or death occurs after 12 months since last dose of study treatment.

The date of PD (per RECIST v1.1) for DoR, DSD and PFS endpoints will be derived as the date of one of the following criteria in case of multiple radiographic assessments performed at different times for the same visit assessment. The earliest date will be chosen:

- Earliest assessment date for target lesions (in the same visit) if the sum of longest diameters (SLD) meets the criteria for PD;
- Earliest assessment date for any non-target lesion with a status of unequivocal progression (in the same visit) if PD is documented based on the non-target lesion response;
- Earliest of new tumor lesion dates (in the same visit).

The date of PD (per RECIST v1.1) for DoR, Duration of stable disease and PFS endpoints based on the BICR will be derived as the following:

- For adjudicated subjects, the date of PD is obtained from the date of PD assessed by the reviewer that the adjudicator agreed with.
- For non-adjudicated subjects, the date of PD is derived as the earliest of the PD dates from reviewers.

Median PFS with its 95% CI and the proportion of subject with progression free at time points of interest, such as 6 months (PFS-6m), 9 months (PFS-9m) and 12 months (PFS-12m) with its 95% CI, will be evaluated using the Kaplan-Meier method.

Duration of Stable Disease

Duration of stable disease (DSD) is defined as the time from the first dose of study treatment(s) until the first date of documented PD (per RECIST v1.1), or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of data cut-off for analysis, duration of SD will be censored at the PFS censoring time. The PFS censoring rule specified in Table 3.5-1 will be applied. The DSD will only be evaluated for subjects with a BoR of SD based on RECIST v1.1. Duration of SD is defined as follows:

DSD (months) = (Date of PD/Death or censoring – Date of first dose + 1) / (365.25 / 12)

The median DSD and its 95% CI will be estimated using the Kaplan-Meier method.

Time to Response

Time to response (TTR) is defined as the time from the first dose of study treatment until the first documentation of disease response and will be evaluated only in subjects who have confirmed CR or PR based on RECIST v1.1. TTR is defined as follows:

TTR (months) = (Date of first CR or PR – Date of the first dose of study treatment + 1) / (365.25/12)

The median TTR and its 95% CI will be assessed using Kaplan-Meier method.

Overall Survival

Overall survival (OS) will be measured from the start of study treatment(s) until death due to any cause. For any subject who is not known to have died at the time of data cutoff for analysis, OS will be censored at the last recorded date on which the subject was known to be

alive. If subjects are confirmed to be alive or if the death date is post the data cutoff date, these subjects will be censored at the date of data cutoff.

Overall survival (months) = (Date of death or censoring – Date of MED4736 start + 1) / (365.25 / 12).

OS will be summarized using Kaplan-Meier estimates (median time, 95%CI for median time and 6-month, 9-months and 1-year OS rates with 95% CIs).

Percent Change in Target Lesion Sizes

Best percentage change from baseline of the sum of the longest diameters (SLD) of target lesions per RECIST 1.1 will be derived as the biggest decrease or the smallest increase from baseline on the SLD among all post-baseline disease assessment including unscheduled assessments. The best percentage change by subject will be presented in a 'Waterfall' plot, to show each subject's best percentage as a separate bar, with the bars ordered from the largest increase to the largest decrease. Additionally, the percent change from baseline of the SLD for the BICR data per RECIST 1.1 at each post-baseline disease assessment will be presented by subject.

For the BICR data, SLD of target lesions (per RECIST v1.1) from the reviewer selected by the adjudicator will be used when adjudication for overall visit response has occurred, but in the case where no adjudication was required the SLDs of target lesions (per RECIST v1.1) from the reviewer who reviewed the baseline scan first will be used for the derivation.

3.5.3 Exploratory Efficacy Endpoints and Analyses

[redacted]

3.5.4 Subgroup Analysis

In order to assess the consistency of treatment benefit, the exploratory analyses of ORR (based on both BICR determination and investigator determination according to RECIST 1.1) will be performed for some applicable cohorts.

For NSCLC cohorts, the analyses of ORR will be performed for all PD-L1 high 2L+ squamous NSCLC subjects and all PD-L1 high 2L+ NSCLC subjects (regardless of histology) by the following subgroups:

- Age (<65, ≥ 65 yrs)
- Sex (Female, Male)
- Race (White, Others)
- Region (North America, Europe, Asia)
- ECOG performance status (0, 1)
- Smoking status (Never, Former, Current)

For SCCHN cohorts, the analyses of ORR will be performed for all SCCHN subjects by the following subgroups, with a further breakdown by PD-L1 status (PD-L1 high vs PD-L1 low/no expression):

- Age (<65, ≥ 65 yrs)
- Sex (Female, Male)
- Race (White, Others)
- Region (North America, Europe, Asia)
- ECOG performance status (0, 1)
- Smoking status (Never, Former, Current)
- HPV status (positive, negative)

For UC cohorts, the analyses of ORR will be performed for all 2L+ UC subjects by the following subgroups, with a further breakdown by the PD-L1 subgroups including TC high vs low/neg, IC high vs low/neg, and PD-L1 high (either TC or IC high) vs PD-L1 low/neg (both TC and IC low/neg).

The subgroup will be (but not limited) as follows.

- Age (<65, ≥ 65 yrs)
- Sex (Female, Male)
- Race (White, other)
- Region (North America, Europe, Asia)
- ECOG performance status (0, 1)
- Smoking status (Never, Former, Current)
- Site of primary tumor
- Liver metastatic at baseline (Yes, No)
- Lymph node only disease at baseline (Yes, No) Visceral metastatic at baseline (Yes, No)
- Baseline creatinine clearance (<60 mL/min, >=60 mL/min)
- Baseline hemoglobin (<10 g/dL, >=10 g/dL)
- Prior therapy with platinum-based regimen (Cisplatin-based, Carboplatin-based)
- Time from last prior systemic therapy (<=3 months, >3 months)
- Prior BCG (Yes, No)
- Bellmunt risk factor including hemoglobin < 10 g/dL, ECOG ≥ 1, and the presence of liver metastasis (0, 1, 2, 3)

3.5.5 Handling of Dropouts and Missing Data

For a description of the handling of censored data for efficacy endpoints such as PFS, DoR, DSD and OS, see Sections 3.5.2.

Missing Target lesion measurement data

For the disease response derivation in target lesion (TL) data, if a lesion size is missing due to the lesion being too small to be measured, the missing value is defaulted to 5 mm. If a lesion size is missing due to technical difficulty of the measurement (i.e., poor quality of scan, blurring lesion etc.), the measurement for that lesion will not be imputed and the target lesion visit response is not evaluable (NE). Overall visit response will also be NE. However, a visit response of PD should still be assigned if any of the following occurred:

- A new lesion is recorded
- A non-target lesion (NTL) visit response of PD is recorded
- The sum of TLs is sufficiently increased to result in a 20% increase, and an absolute increase of ≥ 5mm, from nadir even assuming the non-recorded TLs have disappeared

3.6 Safety Analyses

Safety data including AEs, SAEs, laboratory parameters, ECGs, vital signs and ECOG performance status, will be summarized by disease type and overall across disease type on subjects who have received MEDI4736 10 mg/kg Q2W unless otherwise specified. Safety data from subjects receiving 10 mg/kg Q2W in the dose escalation phase and dose expansion phase will be combined for analyses. Selected AE/SAE summaries by dose levels across all disease types will be provided to assess dose response.

For NSCLC cohorts (squamous and non-squamous), the SCCHN cohort and UC cohort, safety analyses will be performed by PD-L1 status (PD-L1 high and PD-L1 low/neg) and overall for all subjects in respective cohorts who received MEDI4736 at doses of 10 mg/kg Q2W. For NSCLC, safety summaries will be provided for all NSCLC subjects regardless of histology. For the UC cohort, safety summaries will be provided for all UC subjects regardless of line of therapy.

Repeated or unscheduled tests will not be summarized for each scheduled visit, but will be included for summaries of "Worst-case" on treatment values and shift-table analyses. "Worst-case" on treatment (i.e. maximum or minimum on-treatment value depending on the direction

of an adverse effect) is defined as the nadir and/or zenith including any scheduled and unscheduled post-baseline assessments that occur through the final safety follow up visit. The final safety follow up visit (last record on study) is defined as the last visit with non-missing data that occurred up till 30 days (+7 days to allow visit window) following the last dose of MEDI4736 for ECGs, vital signs, ECOG, laboratory parameters except hematology; up till 90 days (+7 days to allow visit window) following last dose of MEDI4736 or till the initiation of the subsequent anticancer therapy (excluding palliative radiotherapy given as monotherapy), whichever occurs first for hematology laboratory parameter.

If the number of subjects with available data is less than 1/3 of the total number of subjects in the As-treated Population for overall summary (across disease types) or for one disease type at one scheduled time of evaluation, no summary statistics will be presented at that time point for overall summary or for that disease type, unless otherwise indicated.

3.6.1 Adverse Events

Adverse events will be coded using Medical Dictionary for Regulatory Activities and assigned grades based on NCI CTCAE v4.03.

Summaries of adverse events will include only "treatment-emergent" events. Treatment-emergent adverse event (TEAE) will be defined for the initial treatment period and the re-treatment period separately. TEAEs are defined as any adverse events that first occur on or after the date of initial receipt of MEDI4736 and with an onset date no more than 90 days after the last dose of MEDI4736 at each treatment period. Any AEs that are considered as non-treatment emergent will be presented in the listings only.

The AE reporting period for this study is the period through 90 days after the last dose of MEDI4736 or until the initiation of alternative anticancer therapy per protocol, therefore, the primary set of AE summaries will be based on the TEAEs observed up until 90 days after the last dose of MEDI4736 or until the initiation of the subsequent anticancer therapy (excluding palliative radiotherapy given as monotherapy) following discontinuation of MEDI4736 will be used for the AE summary tables. Selected AE summaries (i.e. SAE, AESI, and AE resulting in death) will also be produced containing AEs observed up until 90 days after the last dose of MEDI4736 (without taking subsequent therapy into account) as the secondary set of AE summaries. Any adverse events in the period that occur after a subject has received subsequent anticancer therapy (following discontinuation of MEDI4736) will be flagged in the data listings.

Subjects will be counted only once for each preferred term, once for each system organ class, and by the worst CTCAE grade, regardless of how many events the subject experienced. The TEAE summaries for the primary set (i.e. AEs until 90 days following discontinuation of study treatment or until the initiation of the first subsequent therapy excluding palliative radiotherapy given as monotherapy, whichever occurs first) to be provided are listed below.

- All TEAE
- TEAE with CTCAE grade 3 or higher
- TEAE by Highest Severity
- Treatment related TEAE
- Treatment related TEAE with CTCAE grade 3 or higher
- Treatment related TEAE by Highest Severity
- Serious TEAE
- Serious TEAE by Highest Severity
- Serious TEAE by Serious AE Criteria
- Treatment related Serious TEAE
- TEAE Resulting in Permanent Discontinuation of MEDI4736
- Treatment related TEAE Resulting in Permanent Discontinuation of MEDI4736
- TEAE Resulting in Dose Delay
- Treatment related TEAE Resulting in Dose Delay
- TEAE and Treatment related Resulting in Death

An overall summary of the number and percentage of subjects in each category as described above will be provided. Another overview of TEAE in each category with excluding disease progression of specific cancer types will also be provided.

In addition, the TEAE summaries listed below will be produced for the secondary set (i.e. AEs until 90 days following discontinuation of study treatment).

- Serious TEAE
- Treatment related Serious TEAE
- TEAE and Treatment related Resulting in Death

3.6.1.1 Adverse Events of Special Interest (AESI)

Some clinical concepts (including some selected individual preferred terms) have been considered "AEs of special interest" (AESI) to the MEDI4736 program. Some AESI's have been described in protocol section 5.3. These AESIs will be identified based on sponsor-defined ad-hoc queries (AHQ). A listing of the preferred terms in each grouping will be provided prior to data base lock. The AESI grouping have been identified as the following: Adrenal insufficiency, Diarrhoea, Colitis, Select hepatic events, Infusion related/ Hypersensitivity/Anaphylactic reactions, Pneumonitis, Hyperthyroidism, Hypophysitis, Hypothyroidism, Dermatitis, Rash, Select pancreatic events, Select renal events, Other rare events of a potential immune-mediated nature.

AESI summaries by grouped term and preferred term for the primary set (i.e. AESIs until 90 days following discontinuation of study treatment or until the initiation of the first subsequent therapy excluding palliative radiotherapy given as monotherapy, whichever occurs first) to be provided are listed below.

- All AESI (Any Grade and CTCAE grade 3 or higher)
- AESI by Highest Severity
- Treatment related AESI (Any Grade and CTCAE grade 3 or higher)
- Treatment related AESI by Highest Severity
- Serious AESI
- AESI Resulting in Permanent Discontinuation of MEDI4736
- AESI Resulting in Dose Delay
- AESI and Treatment related AESI Resulting in Death

- AESI ongoing at death
- AESI ongoing at DCO
- AESI by outcome

In addition, the AESI summaries listed below will be produced for the secondary set (i.e. AESIs until 90 days following discontinuation of study treatment).

- All AESI
- AESI by Highest Severity
- Treatment related AESI
- Treatment related AESI by Highest Severity

3.6.1.2 AESIs During Which Systemic Steroids, Endocrine Therapy, or Other Immunosuppressants Were Administered

AESIs during which systemic steroids, endocrine therapy, or other immunosuppressants were administered will be programmatically identified by searching for dates of initiation of these agents and comparing to the onset dates and resolution dates of AESIs for individual subjects. Specifically, an AESI during which systemic steroids, or other immunosuppressants were administered is defined as AESI for which there was concomitant administration of systemic steroids, or other immunosuppressants, within 30 days of onset of the AESI, but prior to its resolution. Similarly, an AESI (hyperthyroidism, hypophysitis, or hypothyroidism) during which endocrine therapy were administered is defined as AESI for which there was concomitant administration of endocrine therapy within 30 days of onset of the AESI, but prior to its resolution.

The concomitant medications administered to subjects will be identified by searching the clinical database for select ATC codes to identify systemic steroids, endocrine therapy and other immunosuppressants. See a list of select ATC codes in the imAE Charter.

Summaries of AESIs during which systemic steroids, endocrine therapy, or other immunosuppressants were administered for the primary set (i.e. AESIs until 90 days following discontinuation of study treatment or until the initiation of the first subsequent

therapy excluding palliative radiotherapy given as monotherapy, whichever occurs first) to be provided are listed below.

- AESI and treatment related AESI during which systemic steroid were administered (Any grade, >=Grade 3 and by Highest Severity)
- AESI and treatment related AESI during which high-dose systemic steroid were administered (Any grade, >=Grade 3 and by Highest Severity)
    - High-dose systemic steroid is defined as dose greater than or equal to 40 mg prednisone or equivalent per day
- AESI and treatment related AESI during which other immunosuppressives were administered (Any grade, >=Grade 3 and by Highest Severity)
- AESI and treatment related AESI during which systemic steroid or other immunosuppressives were administered (Any grade, >=Grade 3 and by Highest Severity)
- AESI and treatment related AESI (Hyperthyroidism, Hypophysitis, and Hypothyroidism only) during which endocrine therapy were administered (Any grade, >=Grade 3 and by Highest Severity)

3.6.1.3 Immune-mediated Adverse Events (imAE)

To fully characterize the AESI (excluding AESI group Infusion related/ Hypersensitivity/ Anaphylactic reactions) during which systemic steroids, endocrine therapy, or other immunosuppressants were administered (See Section 3.6.1.2), the Sponsor will perform medical review of those AESIs and classify them as immune- mediated AEs (imAEs) or not imAEs. See further details in the imAE Charter.

Immune-mediated AEs will be defined as any AESIs that (1) required the use of systemic steroids, endocrine therapy, or other immunosuppressants within 30 days of onset of the AESI and prior to resolution, (2) is consistent with an immune mediated mechanism of action, and (3) for which, there is no clear alternate etiology.

Since the clinical database for this study does not specifically link the start of medication with an adverse event, imAEs will therefore be derived by first programmatically identifying AESIs, for which there was concomitant administration of systemic steroids, endocrine

therapy, or other immunosuppressants, within 30 days of onset of the AESI, but prior to its resolution. A further clinical evaluation of all such events will be made to ensure there was no clear alternate etiology before classifying them as imAEs for the purpose of analysis and reporting. Note that for this study, adverse event that changes grade is reported as a new adverse event record with new onset date in the clinical database.

The imAEs will be summarized in the same manner as for the summaries for AESI described above in Section 3.6.1.1 and Section 3.6.1.2 for the primary set (i.e. imAEs until 90 days following discontinuation of study treatment or until the initiation of the first subsequent therapy excluding palliative radiotherapy given as monotherapy, whichever occurs first).

In addition, the following analyses of imAE will be provided by imAE group. See further details in the imAE Charter with respect to derivation rules associated with time to first onset and resolution of imAE.

- Time to first onset of imAE (Descriptive statistics with median and range for time to first onset of AE, and frequency for number of subjects with time to first onset of AE within 1-28 days, 29-56 days, 57-84 days, 85-112 days, >112 days will be provided.)
- Time to first onset of CTCAE grade 3 or higher imAE
- Time to resolution of imAE (Time to resolution will be calculated from first onset to complete resolution, and will be summarized using the Kaplan-Meier method. Median and range will be presented.)
- Time to resolution of Grade >=3 imAE (Time to resolution will be calculated from first onset of Grade >=3 event to complete resolution, and will be summarized using the Kaplan-Meier method. Median and range will be presented.)
- Time to resolution of Grade >=2 imAE (Time to resolution will be calculated from first onset of Grade >=2 event to complete resolution, and will be summarized using the Kaplan-Meier method. Median and range will be presented.)
- Time to resolution/improvement of Grade >=3 imAE (Time to resolution/ improvement will be calculated from first onset of Grade >=3 event to resolution or the event improved to Grade 2 or lower, and will be summarized using the Kaplan-Meier method. Median and range will be presented.)

In addition, the following analyses regarding systemic steroid use for imAE will be provided by imAE group. See further details in the imAE Charter with respect to derivation rules

associated with duration and time to systemic steroid use for imAE. The following analysis except for duration of steroid use will be produced by imAE group for both all systemic steroids and high dose systemic steroids.

- Starting steroid dose
- Time to first steroid dose
- Highest dose steroid given
- Time to highest steroid dose
- Duration of initial steroid use (first use of steroid per subject per imAE group, regardless of initial dose)
- Duration of initial high dose steroid use (first use of a steroid where the starting dose meets high dose definition per subject per imAE group)

3.6.1.4 Mortality

Deaths occurring while subjects were on study treatment, in the safety follow-up period, or after completion of the safety follow-up period will be summarized as below:

- Total number of deaths (including deaths ≤ 90 days after last dose of study medication and deaths occurring ≥90 days after the last dose of study drug)
- Total number of deaths related only to disease under investigation, as determined by investigator (including deaths ≤ 90 days after last dose of study medication and deaths occurring ≥90 days after the last dose of study drug)
- Number of deaths ≤90 days after last dose of study medication
- Total number of deaths related only to TEAE and onset date prior to initiation of subsequent anti-cancer therapy (excluding palliative radiotherapy given as monotherapy)
- Total number of deaths related only TEAE and onset date post initiation of subsequent anti-cancer therapy (excluding palliative radiotherapy given as monotherapy) but ≤90 days after last dose of study medication
- Total number of subjects where death was reported to be related to the disease under investigation (as determined by the investigator) and TEAE (onset date prior to initiation of subsequent anti-cancer therapy excluding palliative radiotherapy given as monotherapy)

- Total number of subjects where death was reported to be related to the disease under investigation (as determined by the investigator) and TEAE (onset date after initiation of subsequent anti-cancer therapy excluding palliative radiotherapy given as monotherapy)

- Subjects with unknown reason for death and other deaths (not falling in the above categories)

Note that if a Grade 5 AE considered as "disease progression" is the only AE/SAE with outcome of death reported, and the investigator assessed causality as not related to study drug for a subject, then this subject will be listed under the "Death related to disease under investigation ONLY", instead of under the corresponding AE/TEAE categories.

3.6.1.5 Subgroup Analyses

The following safety endpoints are selected for subgroup analyses across all disease types.

- All TEAE
- TEAE with CTCAE grade 3 or higher
- Serious TEAE
- TEAE Resulting in Permanent Discontinuation of MEDI4736
- TEAE Resulting in Death
- All AESI

The subgroup will be (but not limited) as follows.

- Age (<65, ≥ 65 yrs)
- Sex (Female, Male)
- Race (White, Black/African-American, Asian, other)
- Region (North America, Europe, Asia)
- ECOG performance status (0, 1)
- Smoking status (Never, Former, Current)
- Baseline creatinine clearance (<60 mL/min, >=60 mL/min)

- Baseline hemoglobin (<10 g/dL, >=10 g/dL)

3.6.2 ECG

Electrocardiogram (ECG) parameters (PR, RR, QRS, QT, QTcB, and QTcF) from central read (if available) and local read will be summarized separately using descriptive statistics for actual values and changes from baseline by scheduled time of evaluation including end of treatment visit and 30 days safety follow-up visit as well as for the maximum post-baseline values. A single value will be used for the measurement of an interval from triplicate ECGs. This value is the average of the three measurements from the individual ECGs. If triplicate ECGs are not performed, the value from a single ECG will be used for summary. The QTcF will be considered as the primary correction method to assess subject cardiac safety. Since RR from local read is not captured on the eCRFs, no QTcB or QTcFs for local read will be derived, and QTcB or QTcF captured on the eCRFs from local read will be used for summary.

The number and percentage of subjects having the following notable ECG interval values on treatment will be summarized.

- Maximum QTcF and QTcB intervals > 450 milliseconds, > 480 milliseconds, > 500 milliseconds
- Maximum uncorrected QT intervals > 500 milliseconds
- Maximum changes from baseline in QTcF and QTcB > 30, >60 and > 90 milliseconds

For the outlier analysis on the ECG intervals, only the subject with “new” cases (as compared to baseline) will be included for summary. “New” means the category of the QTc abnormality was not present at baseline and became present for at least one post-baseline ECG assessment. For example, a subject is classified as new QTc > 450 msec if that subject had a baseline QTc <=450 msec and had a maximum post-baseline QTc interval > 450 msec. Percentages are calculated based on the number of subjects who had a baseline and at least one post-baseline assessment.

3.6.3 Clinical Laboratory Parameters

Laboratory tests will be grouped according to hematology, serum chemistry, urinalysis, coagulation, and thyroid function tests (TSH, free T3, and free T4).

For all continuous laboratory assessments, absolute value and change from baseline will be summarized for each scheduled assessment, and "worst-case" on treatment using descriptive statistics.

Analyses of Laboratory Parameters with NCI CTCAE Grade

Laboratory abnormalities with toxicity grades according to the NCI CTCAE 4.03 will be derived according to laboratory values. Shift tables from baseline to worst toxicity grade on treatment will be presented. Separate summaries indicating hyper- and hypo- directionality of change will be produced, where appropriate. In addition, the number and percentage of subjects experiencing at least 1-Grade shift, at least 2-Grade shift, and any shift to a worst post-baseline toxicity Grade of 3 to 4 from baseline will be summarized. For each lab test condition, percentages are calculated based on the number of treated subjects who have a baseline and at least one post-baseline assessment. In the shift table analysis, for a given subject, if the CTCAE grade is missing for all post baseline assessments for one laboratory test, the subject will be counted only once for that laboratory test under the "Missing" CTCAE grade category. If a subject has both missing and non-missing CTCAE grades for one laboratory test, the missing CTCAE grade of that laboratory test will be treated as the lowest grade.

Laboratory abnormalities with toxicity grades according to the NCI CTCAE 4.03 will be derived for the following parameters:

- Hematology: Anemia (Hemoglobin hypo), White Blood Cell, Neutrophils, Platelets, Lymphocytes
- Serum chemistry: Alanine Amino Transferase (ALT), Aspartate Amino Transferase (AST), Alkaline Phosphatase (ALP), Total bilirubin, Creatinine (without taking baseline into account when deriving CTCTAE grade), Albumin, Cholesterol, Magnesium hypo and hyper, Sodium hypo and hyper, Potassium hypo and hyper, Corrected calcium hypo and hyper, Glucose hypo and hyper, Bicarbonate

Analyses of Laboratory Parameters without NCI CTCAE Grade

For selected parameters including thyroid function tests (TSH, free T3, and free T4) with no CTCAE grading shift tables from baseline to "Worst-case" on treatment value will be provided. "Worst-case" on treatment value will be categorized as low (L), normal (N), or high (H) using laboratory reference range (on both directions).

Additional summaries will include a shift table for urinalysis (Bilirubin, Blood, Glucose, Ketones, Protein) comparing the baseline value to the maximum on-treatment value.

Liver Function Parameters

Subjects with elevated post-baseline ALT, AST or Total Bilirubin that fall into the following categories will be identified. Number and percentage of these subjects will be tabulated.

Liver Function Parameters	Category
ALT	• >=3 × – <=5 × ULN • >5 × – <=8 × ULN • >8 × – <=10 × ULN • >10 × – <=20 × ULN • >20 × ULN
AST	• >=3 × – <=5 × ULN • >5 × – <=8 × ULN • >8 × – <=10 × ULN, • >10 × – <=20 × ULN • >20 × ULN
Total bilirubin	• >=2 × – <=3 × ULN • >3 × – <=5 × ULN • >5 × ULN
ALT or AST	• >=3 × – <=5 × ULN • >5 × – <=8 × ULN • >8 × – <=10 × ULN, • >10 × – <=20 × ULN • >20 × ULN
Potential Hy's law	• (AST >= 3 × ULN or ALT >= 3 × ULN) and[a] Total Bilirubin >= 2×ULN

ULN: upper limit of normal range.

a: Total Bilirubin >= 2×ULN is defined as at least one case of post-dose TBL >= 2 x ULN occurred after the first incidence date of ALT >= 3 x ULN or AST>= 3 x ULN post treatment

Individual subject data where elevated ALT or AST plus total bilirubin fall into the "Potential Hy's law" will be listed.

Assessment of Nephrotoxicity

Creatinine clearance rate (C_{Cr}) will be calculated using serum creatinine and the Cockcroft-Gault formula (Cockcroft and Gault 1976) to estimate glomerular filtration rate (GFR). Shift tables from baseline to "Worst-case" on treatment C_{Cr} value will be provided. Baseline and "Worst-case" on treatment C_{Cr} value will be categorized for the following categories:

- Normal: ≥ 90 mL/min
- Mild Impairment: ≥ 60 − < 90 mL/min
- Moderate Impairment: ≥ 30 − < 60 mL/min
- Severe Impairment: ≥ 15 − < 30 mL/min
- Kidney Failure: < 15 mL/min

3.6.4 Vital Signs

Descriptive statistics of baseline value, post-baseline value and change from baseline value for heart rate, blood pressure, temperature, and respiratory rate will be provided for each scheduled time point including end of treatment visit and 30 days safety follow-up visit as well as for the maximum and minimum post-baseline on treatment values.

3.7 Pharmacokinetics of MEDI4736

Only subjects who receive at least 1 dose of MEDI4736, and provide at least 1 post-treatment sample, will be evaluated.

Individual MEDI4736 concentrations will be tabulated with descriptive statistics. The PK of MEDI4736 will be assessed using parameters including C_{max}, trough concentration (C_{min}), time to C_{max} and AUC after the first dose. MEDI4736 steady-state PK parameters including peak concentration at steady state ($C_{max,ss}$), trough concentration at steady state ($C_{min,ss}$), and time to C_{max} will be estimated. Accumulation to steady state will be assessed as the ratio of

$C_{max,ss}$:C_{max} and $C_{min,ss}$:C_{min}. All PK parameters will be estimated by non-compartmental analysis. Descriptive statistics of non-compartmental PK parameters will be provided.

Pharmacokinetic data analyses will be performed by the MedImmune MedImmune Clinical Pharmacology, Pharmacometrics, and DMPK group or designee.

3.7.1 [redacted]

[redacted]

3.8 [redacted]

[redacted]

3.9 Assessment of Immunogenicity of MEDI4736

Only subjects who receive at least one dose of MEDI4736 and provide the baseline and at least 1 post-treatment sample, will be evaluated.

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-MEDI4736 antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-MEDI4736 antibodies. The impact of ADAs on PK will also be assessed if data allow. Samples confirmed positive for ADAs may also be evaluated for neutralizing antibody activity.

Analyses to assess the immunogenic potential of MEDI4736 will be performed by the MedImmune Clinical Pharmacology, Pharmacometrics, and DMPK group or designee.

3.10 [redacted]

[redacted]

4 Interim Analysis

Interim analyses for disease types other than NSCLC and UC cohorts including efficacy (based on the site investigator-assessed tumor data) and key safety analyses may be performed prior to the final analysis for the clinical study report [redacted]

4.1 Interim Analyses for NSCLC Cohort

For the NSCLC cohorts, the PD-L1 expression status cutoff determination analysis based on percent of tumor cells exhibiting cell surface staining assessed by immumohistochemistry (IHC) was made from a subset of NSCLC subjects with clinical outcome data and PD-L1 status available as of 29 April 2014. [redacted] No efficacy analysis using BICR data was performed and no data were available from BICR for those interim analyses.

4.2 Interim Analyses for UC cohort

4.2.1 Interim Analysis for PD-L1 Cutoff in UC

Following review of PD-L1 expression and response data (assessed by investigator per RECIST v1.1) in the initial 20 UC subjects enrolled and followed for a minimum of 12 weeks, a cutoff of 25% for either IC or TC in a baseline sample was chosen for response analysis because the presence of PD-L1 in >=25% of immune cells or >= 25% of tumor cells both appeared to enrich for response. [redacted]

4.2.2 Planned Interim Analysis for Efficacy

An interim analysis of efficacy will be conducted after approximately 103 UC subjects treated with MEDI4736 had an opportunity to be followed for at least 13 weeks (at least two RECIST follow-up scans plus 1 week visit window).

The primary analysis of ORR (exact 95% confidence interval) at the time of the interim analysis will be based on RECIST v1.1 by BICR for all treated UC subjects with an opportunity to be followed for at least 13 weeks (as primary efficacy population). Supportive analysis using BICR-assessed ORR will be performed for all treated UC subjects with an opportunity to be followed for at least 24 weeks (as supportive efficacy population). Similar analyses using BICR-assessed ORR will be also performed for all treated 2L+ post-platinum UC subjects, which is defined as subjects with locally advanced or metastatic UC who either have disease progression during or following platinum-containing chemotherapy, or have disease progression within 12 months of neoadjuvant or adjuvant treatment with platinum-containing chemotherapy.

In order to assess the potential effect of the patterns of PD-L1 expression on antitumor activity of MEDI4736 in UC subjects, efficacy data will also be analyzed by pre-specified subgroups based on PD-L1 expression (See Section 3.1.1). Analysis of secondary endpoints as outlined in Section 3.5.2 will also be performed. For endpoints dependent on disease assessments, the analysis of those endpoints will also be repeated based on the investigator assessments of tumor data.

The Analysis Populations to be used for the interim analyses are described below.

- As-treated Population is defined as all subjects who received any dose of MEDI4736. To avoid the underestimation of the safety due to an insufficient follow-up period, the As-treated Population will be restricted to subjects dosed at least 30 days prior to the DCO date for interim analysis. This is the analysis population for the interim analysis of all safety data.

- Primary Efficacy Population is defined as all UC subjects in the As-treated Population who had an opportunity to be followed for at least 13 weeks by the DCO date for interim analysis (i.e., received the first dose of MEDI4736 at least 13 weeks prior to the DCO date).This is the primary analysis population for the interim analysis of all efficacy data.

- Supportive Efficacy Population is defined as all UC subjects in the As-treated Population who had an opportunity to be followed for at least 24 weeks by the DCO date for interim analysis (i.e., received the first dose of MEDI4736 at least 24 weeks prior to the DCO date). This is the supportive analysis population for the interim analysis of all efficacy data.

An updated efficacy analysis will be conducted on the primary efficacy population from the first planned interim analysis (i.e., approximately 103 subjects, as described above). This analysis will be done based on a DCO date, which will be approximately 90 days after the DCO date for the first interim analysis. Key efficacy information, including ORR and duration of response will be updated at this time.

There are no plans to stop the trial based on either of these analyses and no formal statistical adjustments are planned. However, results from these analyses may be shared with the regulatory agencies for discussions on future development and registration opportunities of MEDI4736 in UC subjects.

Safety analyses at the planned interim analyses will be based on all UC subjects who received any dose of MEDI4736 and had opportunity to be followed for at least 30 days (i.e. subjects dosed at least 30 days prior to the DCO date). The safety analyses will be conducted as described in Section 3.6.

4.2.3 Additional Interim Analysis for Efficacy

An additional efficacy analysis will be conducted for UC subjects in the As-treated Population from the first planned interim analysis (i.e., approximately 191 subjects) as described in Section 4.2.2. This additional efficacy analysis will be done in the same manner as described above for the planned interim analysis. The DCO date used for this analysis will be same DCO date used for updated efficacy analysis, as described in Section 4.2.2.

There are no plans to stop the trial based on either of these analyses and no formal statistical adjustments are planned. However, results from these analyses may be shared with the regulatory agencies for discussions on future development and registration opportunities of MEDI4736 in UC subjects.

4.2.4 Other Interim Analysis

An interim analysis for the Breakthrough Therapy Designation (BTD) request was conducted after approximately 30 PD-L1-high UC subjects were enrolled and followed for at least 12 weeks. A total of 61 UC subjects treated as of 20 November 2015 were included for safety analysis. Of the 61 treated UC subjects, 42 were considered response evaluable. The efficacy data (based on investigator RECIST data) and adverse event data was analyzed by PD-L1 status and overall.

[redacted]

Additional interim analyses may take place to support interactions with the regulatory authorities. The enrollment will not be interrupted or terminated for efficacy based on those interim analyses.

5 References

Bellmunt J, Theodore C, Demkov T, Komyakov B, Sengelov L, Daugaard G, et al. Phase III trial of vinflunine plus best supportive care compared with best supportive care alone after platinum-containing regimen in patients with advanced transitional cell carcinoma of the urothelial tract. J Clin Oncol. 2009;27:4454-61.

Common Terminology for Adverse Events, Version 4.03. United States Department of Health & Human Services, National Institutes of Health, National Cancer Institute, Washington, DC, 2009.
http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf. Downloaded May 10, 2012.

Guidance for Industry. Clinical Trial Endpoints for the Approval of Cancer Drugs and Biologics. United States Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). Center for Biologics Evaluation and Research (CBER). Washington, DC. May, 2007.
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ ucm071590.pdf. Downloaded August 9, 2012.

Plimack ER, Bellmunt J, Gupta S, Berger R, Montgomery RB, Health K, et al. Pembrolizumab (MK-3475) for advanced urothelial cancer: updated results and biomarker analysis from KEYNOTE-012. J Clin Oncol. 2015;33(suppl):abstract 4502.

Rosenberg JE, et al. Atezolizumab in patients (pts) with locally-advanced or metastatic urothelial carcinoma (mUC): results from a pivotal multicenter phase II study (IMvigor 210). Ann Oncol. 2015. Abstract 21LBA.

Wolchok JD, Hoos A, O'Day S et al. Guidelines for the evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clinical Cancer Research 2009; 15: 7412-7420.