A Phase 1b/2 Study of MEDI4736 in Combination with Tremelimumab, MEDI4736 Monotherapy, and Tremelimumab Monotherapy in Subjects with Metastatic or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma

Sponsor Protocol Number: D4190C00021

[redacted]

Investigational Products: MEDI4736, Tremelimumab

Sponsor: MedImmune, LLC, a wholly owned subsidiary of AstraZeneca PLC

[redacted]

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PROTOCOL SYNOPSIS

TITLE

A Phase 1b/2 Study of MEDI4736 in Combination with Tremelimumab, MEDI4736 Monotherapy, and Tremelimumab Monotherapy in Subjects with Metastatic or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma

HYPOTHESIS

MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy will be safe and demonstrate clinical activity in subjects with metastatic or recurrent gastric or gastroesophageal junction (GEJ) adenocarcinoma.

OBJECTIVES

Primary Objectives

1. For Phase 1b: To assess the safety and tolerability, describe any dose-limiting toxicity (DLT), and determine the maximum tolerated dose (MTD) or the highest protocol-defined doses (in the absence of exceeding the MTD) for MEDI4736 in combination with tremelimumab in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.
2. For Phase 2: To determine objective response rate (ORR) and progression-free survival (PFS) at 6 months (PFS-6) based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 as primary measures of clinical activity of MEDI4736 in combination with tremelimumab in second- and third-line subjects whose tumors have a positive interferon-gamma (IFN-γ) gene expression signature and in unselected second- and third-line subjects, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.

Secondary Objectives

1. For Phase 1b: To assess disease control rate (DCR; defined as complete response [CR], partial response [PR], or stable disease [SD]), ORR, and PFS-6 based on RECIST v1.1 as measures of clinical activity of MEDI4736 in combination with tremelimumab in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.
2. For Phase 2: To further describe the safety and tolerability of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.
3. For Phase 2: To assess DCR and duration of response (DoR) based on RECIST v1.1 and overall survival (OS) as additional measures of clinical activity of MEDI4736 in combination with tremelimumab in second- and third-line subjects whose tumors have a positive IFN-γ gene expression signature and in unselected second- and third-line subjects, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.
4. For Phase 2: To define the components of programmed cell death ligand 1 (PD-L1) expression (ie, tumoral vs stromal) that correlate with clinical activity of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.

[redacted]

STUDY ENDPOINTS

Primary Endpoints

1. For Phase 1b: Safety of MEDI4736 in combination with tremelimumab as assessed by the presence of adverse events (AEs), serious adverse events (SAEs), DLTs, laboratory parameters, vital signs, physical examination, and electrocardiogram (ECG) results.
2. For Phase 2: ORR and PFS-6 of MEDI4736 in combination with tremelimumab in second- and third-line subjects whose tumors have a positive IFN-γ gene expression signature and in unselected second- and third-line subjects, MEDI4736 monotherapy, and tremelimumab monotherapy based on RECIST v1.1. Response-based endpoints would be based on blinded independent central review (BICR) if performed, or on investigator assessments.

Secondary Endpoints

1. For Phase 1b: Clinical activity of MEDI4736 in combination with tremelimumab as determined by ORR, DCR at 16 weeks (DCR-16w), DCR at 24 weeks (DCR-24w), and PFS-6.
2. For Phase 2: Safety of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy as assessed by the presence of AEs, SAEs, laboratory parameters, vital signs, physical examination, and ECG results.
3. For Phase 2: Clinical activity of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy as determined by DCR-16w, DCR-24w, DoR, PFS, and PFS at 9 months (PFS-9) based on RECIST v1.1, and OS and 1-year survival.
4. For Phase 2: IFN-γ gene expression signature and how it correlates with clinical activity of MEDI4736 in combination with tremelimumab.
5. For Phase 2: PD-L1 expression and localization (by immunohistochemistry [IHC] or immunofluorescence [IF]) within the tumor microenvironment and how it correlates with clinical activity for MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy.

[redacted]

[redacted]

STUDY DESIGN

This is a randomized, multicenter, open-label, Phase 1b/2 study to evaluate the safety, tolerability, and clinical activity of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma who meet the following criteria:

Second-line (Phase 1b):

- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease, or

Second-line (Phase 2 Arms A, B, and C):

- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease, or
- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months of therapy, or

Third-line (Phase 2 Arm D):

- Must have received and have progressed, or are refractory to two systemic regimens (one standard platinum- or fluoropyrimidine-based chemotherapy regimen and one approved regimen for metastatic or recurrent disease)
- Subjects who have received and have progressed, or are refractory to one systemic platinum or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months will count as a line of therapy in the metastatic/recurrent setting.

Second- and Third-line (Phase 2 Arm E; as of Amendment 6):

- [redacted]
- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease, or
- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months of therapy, or
- Must have received and have progressed, or are refractory to two systemic regimens (one standard platinum- or fluoropyrimidine-based chemotherapy regimen and one approved regimen for metastatic or recurrent disease), and
- Third-line subjects who have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months will count as a line of therapy in the metastatic/recurrent setting.

Up to approximately 135 subjects for Phase 1b/2 will be enrolled at approximately 40 study centers globally.

Phase 1b

The dose and schedule of MEDI4736 in combination with tremelimumab for Phase 1b of the current study is based on emerging safety, clinical, and PK/pharmacodynamic data from the ongoing Study D4190C00006, which is evaluating the combination of MEDI4736 and tremelimumab in subjects with non-small-cell lung cancer (NSCLC). It is anticipated that a dose determined as safe in NSCLC will also be safe in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.

[redacted]

[redacted]. Subjects will be monitored for DLT prior to initiation of enrollment in Phase 2. If unacceptable toxicity is encountered or ≥ 3 out of 9 of subjects experience a DLT during this safety run-in, a lower dose level may be evaluated prior to initiation of Phase 2.

A total of 6 subjects were enrolled in Phase 1b and treated with the dose and schedule described above; there were no DLTs in these 6 subjects. The Phase 1b portion of the study is now complete.

Phase 2

Once the MTD or highest protocol-defined dose (in the absence of exceeding the MTD) has been defined in Phase 1b, enrollment in Phase 2 will begin. In Phase 2, subjects will be enrolled in 1 of 5 treatment arms, as listed below. Second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma will be randomized in a 2:2:1 ratio to Arms A, B, or C. In parallel, third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma will be enrolled in Arm D. Upon closure of Arms A, B, and C and completion of Arm D, second- and third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma and a positive IFN-γ gene expression signature will be enrolled in Arm E.

- Arm A: MEDI4736 in combination with tremelimumab in second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma [redacted]
- Arm B: MEDI4736 monotherapy in second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma [redacted]
- Arm C: Tremelimumab monotherapy in second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma [redacted]
- Arm D: MEDI4736 in combination with tremelimumab in third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma [redacted]
- Arm E (as of Amendment 6): MEDI4736 in combination with tremelimumab in second- and third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma and a positive IFN-γ gene expression signature [redacted]

During Phase 2, subjects will be monitored continuously for safety according to the same criteria employed during Phase 1b. If during the treatment period, ≥ 33% of subjects experience safety events meeting DLT criteria, even if outside of the DLT evaluation period, enrollment may be paused and study data will be reviewed to determine whether additional monitoring or alternate dose levels or treatment schedules should be evaluated prior to further enrollment. In addition, after the first 20 subjects have been dosed with MEDI4736 in combination with tremelimumab for a minimum of 6 weeks (in both second- and third-line settings), safety data will be reviewed by the sponsor.

All subjects will be evaluated for clinical activity, on a regular basis as specified in the protocol, and their disease status primarily analyzed according to RECIST v1.1. Clinical decision making in subjects undergoing treatment will be based on RECIST v1.1 with modifications. Enrollment into any arm in Phase 2 may be discontinued at the discretion of the sponsor should emerging clinical or nonclinical data suggest that continued treatment may not be beneficial to a given arm.

[redacted] Pre-specified interim analyses performed on Arms A and B showed that the criteria for expansion were met; however, enrollment into Arms A, B, and C was stopped at the sponsor's discretion. Based on evolving science suggesting that the IFN-γ gene expression signature will better predict responders of immunotherapy (Ulloa-Montoya et al, 2013; Peng et al, 2015) as well as data from the initial portion of the study, it was decided to proceed with MEDI4736 in combination with tremelimumab in both second- and third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma who had a positive IFN-γ gene expression signature. The discontinuation of Arms A, B, and C was not due to safety concerns. Arm D has completed.

Dose-Expansion in a Biomarker Selected Population

As of Amendment 6, a new arm (Arm E) of MEDI4736 in combination with tremelimumab has been added to evaluate efficacy and safety in subjects with second- and third-line gastric or GEJ adenocarcinoma with a positive tumor IFN-γ gene expression signature. Numerous clinical trials have demonstrated the predictive nature of a Type 1 helper T-cell (Th1) gene signature and the subsequent response to immunotherapy for solid

tumors. [redacted] All subjects will be followed for survival until the end of study (5 years after the last subject is enrolled or the date the study is closed by the sponsor, whichever occurs first). Evaluation of a possible correlation between clinical activity of MEDI4736 and tremelimumab in combination and IFN-γ gene expression as well as other potential biomarkers (eg, tumoral and stromal PD-L1 expression) will be ongoing throughout the study.

TARGET SUBJECT POPULATION

Adult male or female subjects, ≥ 18 years of age at screening, with histologically- or cytologically-confirmed metastatic or recurrent gastric or GEJ adenocarcinomas AND the following:

Second-line (Phase 1b):

- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease, or

Second-line (Phase 2 Arms A, B, and C):

- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease, or
- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months of therapy, or

Third-line (Phase 2 Arm D):

- Must have received and have progressed, or are refractory to two systemic regimens (one standard platinum- or fluoropyrimidine-based chemotherapy regimen and one approved regimen for metastatic or recurrent disease)
- Subjects who have received and have progressed, or are refractory to one systemic platinum or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months will count as a line of therapy in the metastatic/recurrent setting.

Second- and Third-line (Phase 2 Arm E; as of Amendment 6):

- Must have a positive IFN-γ gene expression signature [redacted].
- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease, or
- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months of therapy, or
- Must have received and have progressed, or are refractory to two systemic regimens (one standard platinum- or fluoropyrimidine-based chemotherapy regimen and one approved regimen for metastatic or recurrent disease), and
- Third-line subjects who have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months will count as a line of therapy in the metastatic/recurrent setting.

Subjects who will be enrolled in Arm E must have measurable disease at baseline. Key exclusion criteria are human epidermal growth factor receptor (HER)2-overexpressing metastatic or recurrent GEJ adenocarcinomas and prior exposure to immunotherapy.

TREATMENT AND REGIMENS

Subjects will be treated in either Phase 1b or Phase 2 of the study. [redacted]

Subjects who are treated with MEDI4736 monotherapy (Arm B) or tremelimumab monotherapy (Arm C) may crossover to be treated with MEDI4736 in combination with tremelimumab upon confirmed progressive disease (PD) under restricted circumstances (as outlined in the protocol). Subjects who are treated with the combination of MEDI4736 and tremelimumab may continue their study treatment or have reinduction of the study treatment upon a confirmed PD under restricted circumstances (as outlined in the protocol). Subjects in both Phase 1b and Phase 2 who derived clinical benefit from study treatment during the initial 12-month treatment period and who subsequently developed PD during the 12-month follow-up period, will be treated for up to 12 months with the same regimen that the subject was given upon initial study entry. Dose delays and discontinuations to manage clinically significant treatment-related toxicity will be allowed.

STATISTICAL METHODS

Sample Size and Power Calculations

Up to approximately 135 subjects for Phase 1b/2 will be enrolled in this study.

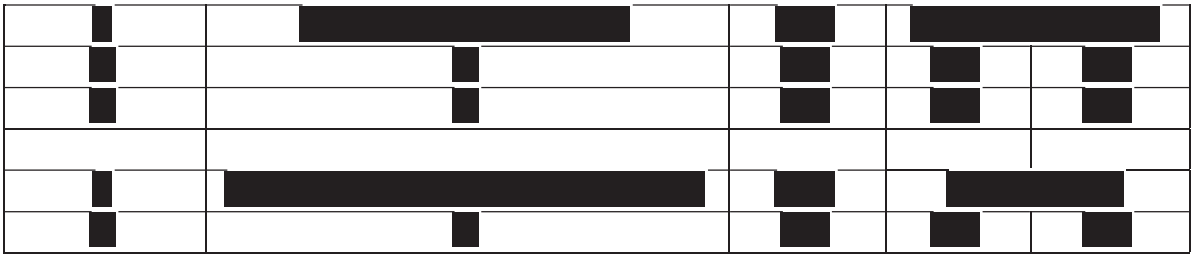
Phase 1b

The sample size for Phase 1b is not based on formal statistical power considerations. The number of subjects in this phase of the study is based on a safety run-in schema investigating the safety and tolerability of a dose and schedule selected for dose expansion in Study D4190C00006.

Phase 2

[redacted]

[redacted]



Efficacy

Efficacy analysis will be based on the As-treated Population, which includes all subjects who receive any investigational product. Response-related endpoints and corresponding time-to-event endpoints for primary and secondary efficacy endpoints programmatically-derived from the investigator's assessments or BICR, as well as OS will be analyzed. More details will be provided in the statistical analysis plan.

OR is defined as best overall response of confirmed CR or confirmed PR according to RECIST v1.1.

DoR is defined as the duration from the first documentation of OR to the first documented disease progression according to RECIST v1.1 or death due to any cause, whichever occurs first.

DC is defined as confirmed CR, confirmed PR, or SD based on RECIST v1.1. DC at 16 and 24 weeks is defined as a best overall response of confirmed CR, confirmed PR or having SD with duration of SD lasting 16 and 24 weeks, respectively.

PFS will be measured from the date of randomization or start of treatment until the documentation of disease progression according to 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 (DCO) for analysis, PFS will be censored at the last tumor assessment date. The PFS-6 [redacted] are the proportion of subjects with PFS at 6 months [redacted]

OS will be measured as the time from date of randomization or the start of treatment until death due to any cause. For subjects who are alive at the time of DCO, OS will be censored on the last date when subjects are known to be alive.

The 2 co-primary efficacy endpoints for Phase 2 are OR and PFS-6 using RECIST v1.1. The ORR is defined as the proportion of subjects with OR. The 2-sided 90% and 95% confidence intervals (CIs) for ORR will be estimated using the exact binomial distribution. Kaplan-Meier curves will be generated for PFS and used to

estimate the PFS-6 along with its 2-sided 90% and 95% CIs.

Secondary efficacy endpoints include DC, DoR, PFS, [redacted], OS, and 1-year survival for Phase 2, and OR, DC and PFS-6 for Phase 1b. The DCR is defined as the proportion of subjects with DC. The 2-sided 90% and 95% CIs of DCR will be provided using an exact probability method. DCR at 16 and at 24 weeks will be estimated along with their 2-sided 90% and 95% CIs. Kaplan-Meier method will be used to estimate the median DoR/PFS/OS and landmark PFS/OS rate along with their CIs.

Only subjects whose archival tumor tissue sample showed a positive IFN-γ gene expression signature will be eligible for enrollment to Arm E. This will allow identification of a unique population of gastric or GEJ adenocarcinoma subjects who may benefit from treatment with immune checkpoint inhibitors and will allow correlations between IFN-γ gene expression and clinical activity of MEDI4736 in combination with tremelimumab to be explored.

During the course of the study, subjects' tumor samples (archival and/or from fresh biopsies) will be analyzed for PD-L1 expression (ie, tumoral vs stromal) that may predict increased frequency of response or longer disease stabilization. The analyses will be performed to see whether there is association between PD-L1 expression levels at baseline and clinical activity. If such association exists, secondary analyses for primary and secondary efficacy endpoints will be conducted in "biomarker positive" and "biomarker negative" subpopulations determined by the cut-off point of PD-L1 expression. The impact of baseline prognostic factors will be explored as appropriate when treatment arms in the subpopulations are compared.

Safety

The safety analysis will be based on the As-treated Population, and will include AEs, SAEs, laboratory evaluations, vital signs, ECGs, and physical examinations from both Phase 1b and Phase 2.
In Phase 1b, the number of DLTs that are identified in the DLT Evaluable Population (defined as subjects enrolled in Phase 1b who receive the protocol-assigned treatment and complete safety follow-up through the DLT evaluation period or experience a DLT during the DLT evaluation period) will be summarized or listed. For both Phase 1b and Phase 2, the number and percentage of subjects reporting treatment-emergent AEs will be summarized overall and by the worst National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 grade, system organ class, and preferred term, with a breakdown by treatment arm/dose cohort. Similarly, the number and percentage of subjects reporting treatment-emergent AEs considered related to investigational product will be summarized. Laboratory abnormalities will be graded according to the NCI CTCAE v4.03, if applicable. Frequencies of worst observed grade will be presented for each laboratory parameter as well as the rates of subjects with Grade 3-4 toxicities. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-baseline grade, will be provided for clinical laboratory tests.

[redacted]

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LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
5-FU	5-fluorouracil
ADA	antidrug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cell
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BICR	blinded independent central review
BP	blood pressure
BSC	best supportive care
CD	cluster of differentiation
CI	confidence interval
CNS	central nervous system
CR	complete response
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
DC	disease control
DCO	Data cut-off
DCR	disease control rate
DCR-12w	disease control rate at 12 weeks
DCR-16w	disease control rate at 16 weeks
DCR-24w	disease control rate at 24 weeks
DEHP	bis (2-ethylhexyl) phthalate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
[redacted]	[redacted]
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
[redacted]	[redacted]
EU	European Union
FAAN	Food Allergy and Anaphylaxis Network
Fc	fragment crystallizable
FDA	Food and Drug Administration

Abbreviation or Specialized Term	Definition
[redacted]	[redacted]
GCP	Good Clinical Practice
GEJ	gastroesophageal junction
GI	gastrointestinal
GLP	Good Laboratory Practice
HER	human epidermal growth factor receptor
HIV	human immunodeficiency virus
HR	hazard ratio
ICF	informed consent form
ICH	International Council for Harmonisation
ICOS	inducible T-cell costimulator
IEC	Independent Ethics Committee
IF	immunofluorescence
IFN	interferon
IFN-γ	interferon-gamma
IGF	insulin-like growth factor
IgG	immunoglobulin G
IgM	immunoglobulin M
IHC	immunohistochemistry
IL	interleukin
ILD	interstitial lung disease
irAE	immune-related adverse event
IRB	Institutional Review Board
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
IV	intravenous(ly)
IXRS	interactive response system
mAb	monoclonal antibody
[redacted]	[redacted]
MRI	magnetic resonance imaging
[redacted]	[redacted]
MTD	maximum tolerated dose
M(x)/T(y)	MEDI4736 (x) mg/kg and tremelimumab (y) mg/kg
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NIAID	National Institute of Allergy and Infectious Diseases
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small-cell lung cancer
OR	objective response

Abbreviation or Specialized Term	Definition
ORR	objective response rate
OS	overall survival
[redacted]	[redacted]
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L1+	programmed cell death ligand 1 positive
PD-L2	programmed cell death ligand 2
PEF	peak expiratory flow
PFS	progression-free survival
PFS-6	PFS at 6 months
[redacted]	[redacted]
PK	pharmacokinetic(s)
PR	partial response
PVC	polyvinyl chloride
Q2W	every 2 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
Q90D	every 90 days
[redacted]	[redacted]
[redacted]	[redacted]
QTcF	QT corrected using Fridericia's formula
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SID	subject identification
SMC	safety monitoring committee
sPD-L1	soluble programmed cell death ligand 1
TCGA	The Cancer Genome Atlas Research Network
TCR	T-cell receptor
Th1	Type 1 helper T-cell
TIL	tumor-infiltrating lymphocyte
TNF-α	tumor necrosis factor alpha
ULN	upper limit of normal
US	United States
w/v	weight per volume

1 INTRODUCTION

1.1 Disease Background

1.1.1 Cancer and Immune Function

The importance of the immune system in cancer development and progression has been recognized during the past decade (Hanahan and Weinberg, 2000). Failure of immune surveillance of pre-neoplastic lesions and micro-metastases is a key step in cancer development. Chronically immunosuppressed individuals show higher rates of cancer. This observation led to the hypothesis that sporadic cancers among immune-competent individuals are likely to be minimally immunogenic, allowing for passive escape from immune surveillance. Recent data suggests that this may be an oversimplification. Some sporadic tumors are highly immunogenic, but actively suppress the local immune environment through production of immunosuppressive cytokines (Shields et al, 2010). As such, the local tumor environment is likely a highly dynamic environment where most tumors grow and metastasize through adaptive responses that modulate antitumor immunity.

The complexity and redundancy of the immune system offers multiple targets that may be manipulated to maximize the body's inherent immune response to a tumor. Immune response may be augmented by directly stimulating effector cells, indirectly stimulating effectors by augmenting antigen presentation activity or costimulation, or by suppressing immunosuppressive factors, cells, or messages (Monti et al, 2005).

1.1.2 Immune-checkpoint Inhibition

Tumor-infiltrating lymphocytes (TILs) have the capacity to control the growth of many types of cancers (Gooden et al, 2011). Most tumors show infiltration by TILs, but tumors modulate the local microenvironment through expression of inhibitory molecules. Engagement of TIL cell-surface receptors with these inhibitory ligands leads to a dysfunctional immune response, causes T-cell exhaustion, and facilitates tumor progression (Baitsch et al, 2012; Crespo et al 2013). Novel monoclonal antibodies (mAbs) that block these inhibitory receptors have shown significant clinical activity across a number of tumor types (Wolchok et al, 2009; Hodi et al, 2010; Robert et al, 2011; Brahmer et al, 2010; Topalian et al, 2012). Specifically, blockade of immune-checkpoint inhibitors such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), programmed cell death 1 (PD-1), and programmed cell death ligand 1 (PD-L1) have shown clinical activity not only in conventionally immune-responsive tumors such as melanoma and renal cell carcinoma but also in non-small-cell lung cancer (NSCLC; Brahmer et al, 2010; Brahmer et al, 2012; Topalian et al, 2012; Gordon et al, 2013), prostate cancer (Harzstark and Small, 2010;

Slovin et al, 2013), pancreatic cancer (Royal et al, 2010), mesothelioma (Calabrò et al, 2013), and other solid tumors (Brahmer et al, 2010; Brahmer et al, 2012; Gordon et al, 2013).

1.2 MEDI4736 and Tremelimumab Background

MEDI4736 and tremelimumab are briefly described below. Refer to the current Investigator's Brochures for details.

1.2.1 MEDI4736 Background

MEDI4736 is a human immunoglobulin G (IgG)-1 kappa monoclonal antibody (mAb) directed against human PD-L1. MEDI4736 is expressed in Chinese hamster ovary cells and has an overall molecular weight of approximately 149 kDa. MEDI4736 selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and cluster of differentiation (CD)80. The fragment crystallizable (Fc) domain of MEDI4736 contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fc gamma receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (ADCC; Oganesyan et al, 2008).

1.2.2 Tremelimumab Background

Tremelimumab (formerly CP-675,206) is a human IgG2 mAb being investigated as a cancer immunotherapeutic agent. Tremelimumab is expressed in NS0 (murine myeloma) cells and has an overall molecular weight of approximately 149 kDa. Tremelimumab is specific for human CTLA-4, with no cross-reactivity to related human proteins. Tremelimumab blocks the inhibitory effect of CTLA-4, and therefore enhances T-cell activation. Tremelimumab shows minimal specific binding to Fc receptors, does not induce natural killer (NK) ADCC activity, and does not deliver inhibitory signals following plate-bound aggregation.

[redacted]

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1.5 Rationale for Conducting the Study

Unmet Need in Advanced Gastric Cancer

Despite recent advances, the prognosis of patients with advanced gastric cancer remains poor (Kang et al, 2012). At present, regimens that combine a platinum and fluorouracil agent either alone or in combination with a third drug such as epirubicin or taxane constitute the most effective treatment option in the first-line metastatic setting, resulting in a median OS of approximately 10 months (Cunningham et al, 2008). In the second-line setting, ramucirumab (a vascular endothelial growth factor receptor 2 antagonist) was recently approved by the United States (US) Food and Drug Administration (FDA), and has demonstrated modest activity in patients with advanced gastric or GEJ adenocarcinoma who progressed after first-line platinum- or fluoropyrimidine-containing chemotherapy (Fuchs et al, 2014). Median OS was 5.2 months in the ramucirumab group versus 3.8 months in the placebo group. Additionally, ramucirumab in combination with paclitaxel was evaluated in the second-line setting in the RAINBOW study, in which more than 600 subjects with metastatic gastric or GEJ adenocarcinoma that progressed on or within 4 months after first-line platinum- and fluoropyrimidine-based combination therapy were randomized to paclitaxel plus ramucirumab or paclitaxel alone (Wilke et al, 2014). Median OS was 9.63 months and 7.36 months, respectively. AEs that occurred in ≥ 20% of subjects (n = 327) treated with ramucirumab plus paclitaxel were fatigue (56.9%), neutropenia (54.4%), neuropathy (45.9%), anorexia (40.1%), abdominal pain (36.1%), leukopenia (33.9%), diarrhea (32.4%),

epistaxis (30.6%), vomiting (26.9%), hypertension (25.1%), and peripheral edema (25.1%; Wilke et al, 2014).

An unmet medical need remains for new second- and third-line treatment options that are safe and effective in subjects with advanced gastric cancer. Immunotherapies hold much promise in treating this patient population by providing a more favorable safety profile and early signs of clinical activity.

[redacted]

Rationale for MEDI4736 and Tremelimumab Combination Therapy

The rationale for evaluating MEDI4736 in combination with tremelimumab in advanced gastric cancer is supported by both nonclinical and clinical data in several other solid tumors.

Mouse models of transplantable solid tumors show superior antitumor activity of combination therapy as compared to monotherapy. Furthermore, the CTLA-4 and PD-1/PD-L1 pathways are non-redundant, suggesting that targeting both may have additive or synergistic activity. The combination of CTLA-4 and PD-1 blockade in melanoma has been shown to result in higher ORRs and 1-year survival than either agent alone (Wolchok et al, 2013).

Profile of Adverse Events with Immunotherapy

MEDI4736 monotherapy, tremelimumab monotherapy, and MEDI4736 in combination with tremelimumab are currently being evaluated in other studies (see Section 1.4). Overall, the AE profile is manageable and supports continued clinical development.

Immune-related adverse events (irAEs) such as diarrhea and colitis have been reported with immunotherapies. With the approval of 2 immune checkpoint inhibitors for melanoma (ipilimumab [Hodi et al, 2010] and pembrolizumab [Hamid et al, 2013]), there is greater recognition of irAEs and management algorithms, including early, aggressive use of steroids, and continued improvement in outcome.

Preliminary Efficacy of Immunotherapy in Advanced Gastric Cancer

Immune checkpoint inhibitors such as MEDI4736 and tremelimumab have provided early evidence of clinical activity in advanced gastric cancer. Study CD-ON-MEDI4736-1108 includes a cohort that is evaluating MEDI4736 monotherapy in subjects with gastroesophageal cancer (Segal et al, 2014). As of 07May2015, out of 40 evaluable subjects with gastroesophageal cancer, there are 2 responses (1 CR and 1 PR). The DCR-24w was 15%. A Phase 2 study of tremelimumab monotherapy in second-line gastroesophageal subjects [redacted] demonstrated clinical activity (4 SD, 1 PR; Ralph et al, 2010).

Rationale for Patient Selection Based on Tumoral IFN-γ Gene Expression Signature

Another key objective of the current study is the understanding of potential biomarkers that are determinants of response and non-response to MEDI4736 and tremelimumab. Clinical trials and preclinical studies have demonstrated the predictive nature of an elevated Type 1 helper T-cell (Th1) gene signature within the tumor and the subsequent response to immunotherapy for solid tumors (Ulloa-Montoya et al, 2013; Peng et al, 2015). IFN-γ is one of the hallmark cytokines, both initiating and propagating the Th1 response. Its expression is closely tied to other proteins and cytokines within the tumor microenvironment. Based on internal investigations, an IFN-γ gene expression panel was identified consisting of 4 genes that will be utilized to try and identify a unique population of gastric or GEJ adenocarcinoma subjects who may benefit from treatment with immune checkpoint inhibitors and spare those who may experience toxicity.

Benefit-risk Evaluation

The emerging data described above demonstrate encouraging clinical activity with MEDI4736 and tremelimumab in gastric or GEJ adenocarcinoma. These data combined with nonclinical data suggesting improved anticancer activity with the MEDI4736 and tremelimumab combination, as compared to either agent alone, make a compelling case for evaluation of this combination in gastric or GEJ adenocarcinoma.

Possible risks are associated with agents such as MEDI4736 and tremelimumab that activate the immune system. The occurrence of irAEs, which is either overlapping or greater for each of these drugs when used as monotherapy, is possible. Potential irAEs may be similar to those seen with the use of ipilimumab, nivolumab, or the combination thereof, 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). Several strategies have been incorporated in the study protocol to mitigate these risks (Section 3.1.5).

Summary and Conclusion

The preliminary clinical activity of immune checkpoint inhibitors as monotherapy or combination therapy may provide alternative options for subjects with metastatic gastric cancer. Many of the AEs associated with immune checkpoint inhibitors are potentially reversible and can be managed (eg, IV steroids for diarrhea [Weber et al, 2012]).

[redacted]

In conclusion, immune checkpoint inhibitors may offer patients with advanced gastric cancer in the second-line and third-line setting potential clinical benefit. In addition, further PD-L1 expression (tumoral vs stromal) may identify a subset of patients who could benefit. Early evaluation of MEDI4736 and tremelimumab combination therapy appears to offer a balance between safety and clinical activity.

1.6 Research Hypothesis

MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy will be safe and demonstrate clinical activity in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.

2 OBJECTIVES AND ENDPOINTS

2.1 Objectives

2.1.1 Primary Objectives

1. For Phase 1b: To assess the safety and tolerability, describe any DLTs, and determine the MTD or the highest protocol-defined doses (in the absence of exceeding the MTD) for MEDI4736 in combination with tremelimumab in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.
2. For Phase 2: To determine ORR and PFS at 6 months (PFS-6) based on RECIST v1.1 (Eisenhauer et al, 2009) as primary measures of clinical activity of MEDI4736 in combination with tremelimumab in second- and third-line subjects whose tumors have a positive IFN-γ gene expression signature and in unselected second- and third-line subjects, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.

2.1.2 Secondary Objectives

1. For Phase 1b: To assess DCR (defined as CR, PR, or SD), ORR, and PFS-6 based on RECIST v1.1 as measures of clinical activity of MEDI4736 in combination with tremelimumab in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.
2. For Phase 2: To further describe the safety and tolerability of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.
3. For Phase 2: To assess DCR and DoR based on RECIST v1.1, and OS as additional measures of clinical activity of MEDI4736 in combination with tremelimumab in second- and third-line subjects whose tumors have a positive IFN-γ gene expression signature and in unselected second- and third-line subjects, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.
4. For Phase 2: To define the components of PD-L1 expression (ie, tumoral vs stromal) that correlate with clinical activity of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma.

2.2 Study Endpoints

2.2.1 Primary Endpoints

1. For Phase 1b: Safety of MEDI4736 in combination with tremelimumab as assessed by the presence of AEs, SAEs, DLTs, laboratory parameters, vital signs, physical examination, and electrocardiogram (ECG) results.
2. For Phase 2: ORR and PFS-6 of MEDI4736 in combination with tremelimumab in second- and third-line subjects whose tumors have a positive IFN-γ gene expression signature and in unselected second- and third- line subjects, MEDI4736 monotherapy, and tremelimumab monotherapy based on RECIST v1.1. Response-based endpoints would be based on BICR if performed, or on investigator assessments.

2.2.2 Secondary Endpoints

1. For Phase 1b: Clinical activity of MEDI4736 in combination with tremelimumab as determined by ORR, DCR at 16 weeks (DCR-16w), DCR-24w, and PFS-6.
2. For Phase 2: Safety of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy as assessed by the presence of AEs, SAEs, laboratory parameters, vital signs, physical examination, and ECG results.
3. For Phase 2: Clinical activity of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy as determined by DCR-16w, DCR-24w, DoR, PFS, [redacted] based on RECIST v1.1, and OS and 1-year survival.

4. For Phase 2: IFN-γ gene expression signature and how it correlates with clinical activity of MEDI4736 in combination with tremelimumab.
5. For Phase 2: PD-L1 expression and localization (by immunohistochemistry [IHC] or immunofluorescence [IF]) within the tumor microenvironment and how it correlates with clinical activity of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy.

[redacted]

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a randomized, multicenter, open-label, Phase 1b/2 study to evaluate the safety, tolerability, and clinical activity of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy in subjects with metastatic or recurrent gastric or GEJ adenocarcinoma who meet the following criteria:

Second-line (Phase 1b):

- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease, or

Second-line (Phase 2 Arms A, B, and C):

- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease, or
- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months of therapy, or

Third-line (Phase 2 Arm D)

- Must have received and have progressed, or are refractory to two systemic regimens (one standard platinum- or fluoropyrimidine-based chemotherapy regimen and one approved regimen for metastatic or recurrent disease)
- Subjects who have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months will count as a line of therapy in the metastatic/recurrent setting.

Second- and Third-line (Phase 2 Arm E; as of Amendment 6):

- Must have a positive IFN-γ gene expression signature [redacted]
- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease, or
- Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months of therapy, or
- Must have received and have progressed, or are refractory to two systemic regimens (one standard platinum- or fluoropyrimidine-based chemotherapy regimen and one approved regimen for metastatic or recurrent disease), and
- Third-line subjects who have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months will count as a line of therapy in the metastatic/recurrent setting.

Up to approximately 135 subjects for Phase 1b/2 will be enrolled at approximately 40 study centers globally (Figure 3.1.1-1).

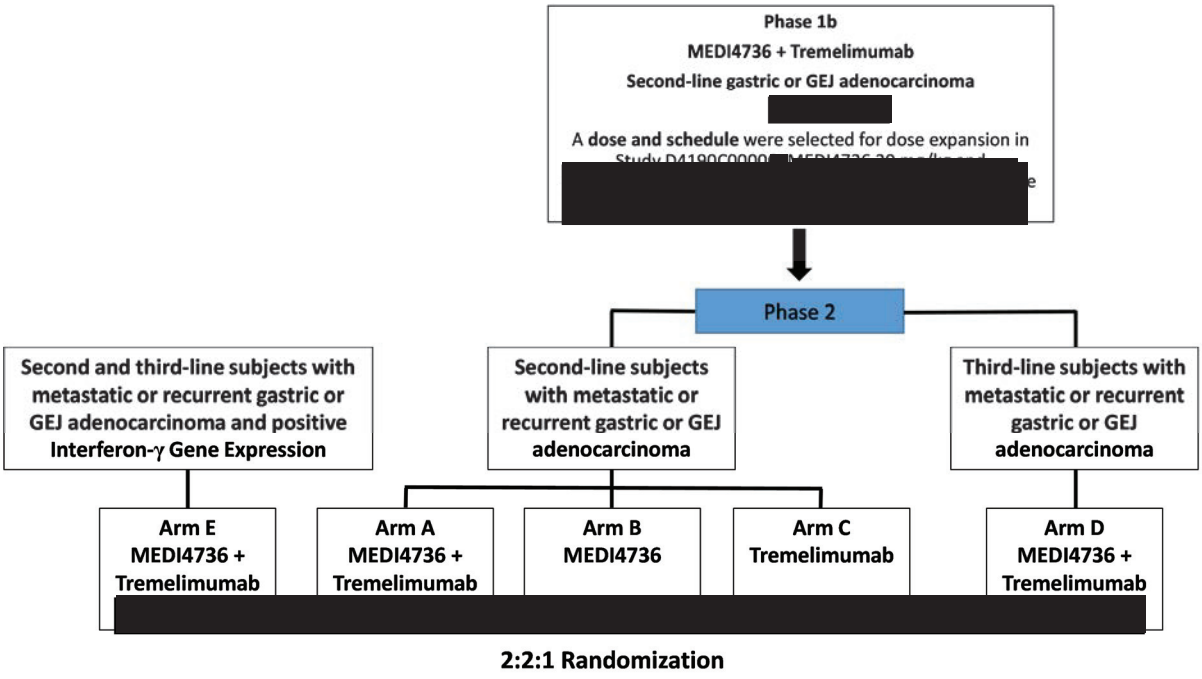

Figure 3.1.1-1 Study Flow Diagram

GEJ = gastroesophageal junction; [redacted]

[redacted]

A safety run-in of up to 9 subjects will be conducted [redacted] Subjects will be monitored for DLT prior to initiation of enrollment in Phase 2. If unacceptable toxicity is encountered or ≥ 3 out of 9 of subjects experience a DLT during this safety run-in, a lower dose level may be evaluated prior to initiation of Phase 2.

Intermediate dose levels may be explored at the discretion of the sponsor based on emerging data. If unacceptable toxicity is encountered at the starting dose level, dose de-escalation will be permitted. [redacted].

A total of 6 subjects were enrolled in Phase 1b and treated [redacted] The Phase 1b portion of the study is now complete.

Phase 2

Once the MTD or highest protocol-defined dose (in the absence of exceeding the MTD) has been defined in Phase 1b, enrollment in Phase 2 will begin. In Phase 2, subjects will be enrolled in 1 of 5 treatment arms, as listed below. Second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma will be randomized in a 2:2:1 ratio to Arms A, B, or C. In parallel, third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma will be enrolled in Arm D. Upon closure of Arms A, B, and C and completion of Arm D, second- and third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma and a positive IFN-γ gene expression signature will be enrolled in Arm E.

- Arm A: MEDI4736 in combination with tremelimumab in second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma [redacted]
- Arm B: MEDI4736 monotherapy in second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma [redacted]
- Arm C: Tremelimumab monotherapy in second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma [redacted]
- Arm D: MEDI4736 in combination with tremelimumab in third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma [redacted]
- Arm E (as of Amendment 6): MEDI4736 in combination with tremelimumab in second- and third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma and a positive IFN-γ gene expression signature [redacted]

In Phase 2 of the study, PD-L1 expression will be monitored throughout the study so as to potentially balance enrollment based on PD-L1 status (as specified in the Laboratory Manual; see Section 4.8.2.2).

Subjects who are treated with MEDI4736 monotherapy (Arm B) or tremelimumab monotherapy (Arm C) may crossover to be treated with MEDI4736 in combination with tremelimumab upon a confirmed progressive disease (PD) under restricted circumstances (see Section 3.1.2.4).

Subjects in both Phase 1b and Phase 2 who derived clinical benefit from study treatment during the initial 12-month treatment period and who subsequently developed PD during the 12 month follow-up period, will be treated for up to 12 months with the same regimen that the subject was given upon initial study entry (see Section 3.1.2.4). Dose delays and discontinuations to manage clinically significant treatment-related toxicity will be allowed.

All subjects will be evaluated for clinical activity, on a regular basis as specified in the protocol (Section 4.2), and their disease status primarily analyzed according to RECIST v1.1. Clinical decision making in subjects undergoing treatment will be based on RECIST v1.1 with modifications. Enrollment into any arm of Phase 2 may be discontinued at the discretion of the sponsor should emerging clinical or nonclinical data suggest that continued treatment may not be beneficial to a given arm.

At the time of this amendment, a total of 89 subjects have been enrolled in Phase 2 in Arms A[redacted] B[redacted] C ([redacted] and D[redacted]. Pre-specified interim analyses performed on Arms A and B showed that the criteria for expansion were met; however, enrollment into Arms A, B, and C was stopped at the sponsor's discretion. Based on evolving science suggesting that the IFN-γ gene expression signature will better predict responders of immunotherapy (Ulloa-Montoya et al, 2013; Peng et al, 2015) as well as data from the initial portion of the study, it was decided to proceed with MEDI4736 in combination with tremelimumab in both second- and third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma who had a positive IFN-γ gene expression signature. The discontinuation of Arms A, B, and C was not due to safety concerns. Arm D has completed.

Dose-Expansion in a Biomarker Selected Population

As of Amendment 6, a new arm (Arm E) of MEDI4736 in combination with tremelimumab has been added to evaluate efficacy and safety in subjects with second- and third-line gastric or GEJ adenocarcinoma with a positive tumor IFN-γ gene expression signature. Numerous clinical trials have demonstrated the predictive nature of a Th1 gene signature and the

subsequent response to immunotherapy for solid tumors [redacted]

[redacted] All subjects will be followed for survival until the end of study (5 years after the last subject is enrolled or the date the study is closed by the sponsor, whichever occurs first). Evaluation of a possible correlation between clinical activity of MEDI4736 and tremelimumab in combination and IFN-γ gene expression as well as other potential biomarkers (eg, tumoral and stromal PD-L1 expression) will be ongoing throughout the study.

The endpoints to be measured in this study are described in Section 2.2.

[redacted]

[redacted]

3.1.2.4 Criteria for Treatment Beyond Progression, Crossover, and Retreatment in the Follow-up Period

Treatment Beyond Progression

For subjects in all arms and treatment periods, if PD (based on RECIST v1.1) occurs before completion of the treatment period, the subject may continue to be treated with the regimen they initially received after study enrollment (unless they have crossed over to the combination regimen at which time the subject would continue the combination regimen) until one of the following criteria is met:

1. Confirmed PD: The assessment of PD by RECIST v1.1 (baseline PD assessment) will be confirmed by a repeat evaluation at the next tumor assessment time point, but no sooner than 4 weeks later. If any subsequent tumor assessment time point shows ≥ 20% increase in the overall tumor burden (the sum of diameters of target lesions and new lesions), when compared to the baseline PD assessment (the sum of diameters of target lesions and new lesions), the subject would be deemed as having confirmed PD.
    a. Note: Subjects in Arm B (MEDI4736 monotherapy) and Arm C (tremelimumab monotherapy) of Phase 2 who experience a confirmed PD (as defined above) will have the option (on a case-by-case basis) to crossover to treatment with MEDI4736 in combination with tremelimumab (using the Phase 2 schedule) for 12 months or until a second confirmed PD. Crossover will be permitted as long as the treatment beyond progression criteria are met and any of the investigational product discontinuation criteria (with the exception of criterion number 10 in Section 4.1.6) are not met. If crossover is not chosen by the investigator, then the study treatment must be discontinued.
    b. Note: Subjects with confirmed PD during 12 months of treatment with MEDI4736 in combination with tremelimumab (Phase 1b, and Arms A and D, and E of Phase 2) may not crossover to either MEDI4736 monotherapy or tremelimumab monotherapy at any time. Subjects enrolled in Phase 1b, and Arms A, D, and E of Phase 2 who exhibit confirmed PD after completing the planned 4 doses of combination treatment, but prior to completing the 12-month dosing period (ie, while receiving MEDI4736 monotherapy) may be eligible for reinduction (on a case-by-case basis) with combination therapy and continued treatment for an additional 12 months (or until the subject meets any of the discontinuation criteria listed below). The subject would be readministered investigational products according to the same treatment guidelines followed during their initial treatment. Subjects who are enrolled in Phase 1b and Arms A, D, and E of Phase 2 and who exhibit disease progression prior to completing the planned 4 doses of combination treatment may be eligible for continued treatment through the end of the planned 12-month treatment period (or until the subject meets any of the discontinuation criteria listed below), but will not be eligible for reinduction.
2. Meets any of the investigational product discontinuation criteria (Section 4.1.6).
3. Clinical symptoms or signs indicating clinically significant PD such as the benefit-risk ratio of continuing therapy is no longer justified.

4. Decline in Eastern Cooperative Oncology Group (ECOG) performance status compared to baseline.
5. Rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention, and/or continuation of study therapy would prevent institution of such intervention.

Retreatment for Subjects Who Enter Follow-up

Subjects enrolled in both Phase 1b and Phase 2 who achieve and maintain DC (ie, CR, PR, or SD) through the end of the initial 12-month treatment period will enter a follow-up period. Only those subjects who progress during the initial 12 months of the follow-up period will be eligible for retreatment for up to 12 months with the same regimen that the subject was given upon initial study entry. As there is preliminary data from other immunotherapy studies that subjects who initially derive clinical benefit from immunotherapy can derive benefit again once the subject has PD while off therapy (Wolchok et al, 2013; Hamid et al, 2013), the protocol will allow retreatment during the follow-up period with the same regimen that the subjects received when initially enrolled in the study if all the following criteria are met:

1. Has not received other anticancer treatments for their disease.
2. Does not meet any of the investigational product discontinuation criteria (Section 4.1.6).
3. Absence of clinical symptoms or signs indicating clinically significant disease progression.
4. No decline in ECOG performance status compared to baseline.
5. Absence of rapid PD or threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention.
6. All AEs while receiving initial therapy must have resolved to ≤ Grade 1 or baseline. Must not have experienced a ≥ Grade 3 AE or neurologic or ocular AE of any grade while receiving initial therapy. Note: Subjects with an endocrine AE of any grade are permitted to be retreated if they are stably maintained on appropriate replacement therapy and are asymptomatic.
7. Must not have used additional immunosuppression other than corticosteroids for the management of an AE, must not have experienced recurrence of an AE if re-challenged, and not currently require maintenance doses > 10 mg prednisone or equivalent per day.

Subjects will be made aware of the potential benefits and risks of continuing the study regimens in the setting of PD by providing separate written informed consent.

3.1.3 Phase 1b

The Phase 1b portion of the study has been described in Section 3.1.1.

A total of 6 subjects were enrolled in Phase 1b; this portion of the study is now complete.

3.1.3.1 Dose-exploration Criteria for Phase 1b

Safety Run-in Rules

1. A minimum of 6 subjects will be enrolled in the safety run-in.
   a. If 2 DLTs occur in the first 6 subjects, an additional 3 subjects will be enrolled.
   b. If ≥ 3 of 9 subjects experience DLTs, lower dose levels will be evaluated.
2. Dose-limiting toxicity will be evaluated during the DLT evaluation period (as defined in Section 3.1.3.2).

3.1.3.2 Dose-limiting Toxicity

Dose-limiting toxicity will be evaluated during the DLT evaluation period in Phase 1b.

[redacted]

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. Dose-limiting toxicity will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03.

A DLT will be defined as any Grade 3 or higher toxicity that occurs during the DLT evaluation period. Toxicity that is clearly and directly related to the primary disease or to another etiology is excluded from this definition. The following will be DLTs:

- Any Grade 4 irAE
- Any ≥ Grade 3 colitis
- Any Grade 3 or 4 noninfectious pneumonitis irrespective of duration
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Any Grade 3 irAE, excluding colitis or pneumonitis, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days
- Liver transaminase elevation > 8 × ULN or total bilirubin > 5 × ULN
- Any ≥ Grade 3 non-irAE, except for the exclusions listed below

The definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days
- Grade 3 endocrine disorder (thyroid, pituitary, and/or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and/or hormone replacement therapy and 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)

- Concurrent vitiligo or alopecia of any AE grade
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least 1 grade within 3 days. Grade 3 or Grade 4 febrile neutropenia will be a DLT regardless of duration or reversibility
- Grade 3 or 4 lymphopenia
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least 1 grade within 3 days
- Isolated Grade 3 elevations in amylase and/or lipase that are not associated with clinical signs or symptoms or radiographic features suggestive of pancreatitis
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days

Immune-related AEs are defined as AEs of an immune nature (ie, inflammatory) in the absence of a clear alternative etiology. In the absence of a clinically significant abnormality, repeat laboratory testing will be conducted to confirm significant laboratory findings prior to designation as a DLT.

While the rules for adjudicating DLTs in the context of dose escalation specified above, an AE not listed above may be defined as a DLT after a consultation with the sponsor and investigators, based on the emerging safety profile.

3.1.3.3 Maximum Tolerated Dose

The MTD is defined as the highest dose within a cohort where no more than 1 of 6 subjects (or less than one-third of subjects if the cohort is larger than 6 subjects) experiences a DLT. This will be determined during Phase 1b based on the assessment of DLT during the DLT evaluation period, as defined in Section 3.1.3.2.

3.1.4 Phase 2

At the time of this amendment, a total of [redacted] subjects have been enrolled in Phase 2 in Arms A [redacted] B [redacted] C [redacted] and D [redacted] Pre-specified interim analyses performed on Arms A and B showed that the criteria for expansion were met; however, enrollment to Arms A, B, and C was stopped at the sponsor's discretion. It was decided to proceed with MEDI4736 in combination with tremelimumab only in second- and third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma who had a positive IFN-γ gene expression signature. The discontinuation of Arms A, B, and C was not due to safety concerns. Arm D has completed.

As described in Section 3.1.1, Phase 2 will include the following 5 treatment arms:

- Arm A: MEDI4736 in combination with tremelimumab in second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma[redacted]
- Arm B: MEDI4736 monotherapy in second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma [redacted]
- Arm C: Tremelimumab monotherapy in second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma[redacted])
- Arm D: MEDI4736 in combination with tremelimumab in third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma[redacted]
- Arm E (as of Amendment 6): MEDI4736 in combination with tremelimumab in second- and third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma and a positive IFN-γ gene expression signature [redacted]

During Phase 2, subjects will be monitored continuously for safety according to the same criteria employed during Phase 1b. If during the treatment period, ≥ 33% of subjects experience safety events meeting DLT criteria, even if outside of the DLT evaluation period (see Section 3.1.3.2), enrollment may be paused and study data will be reviewed to determine whether additional monitoring or alternate dose levels or treatment schedules should be evaluated prior to further enrollment. In addition, after the first 20 subjects have been dosed with MEDI4736 in combination with tremelimumab for a minimum of 6 weeks (in both second- and third-line settings), safety data will be reviewed by the sponsor.

3.1.5 Management of Study Medication Related Toxicities

Based on the mechanism of action of MEDI4736 and tremelimumab 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, nivolumab, and BMS-936559 and may include immune-mediated enterocolitis, dermatitis,

hepatitis, 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 the absence of an alternate etiology (eg, infection or PD), an immune-related etiology should be considered for signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy. In addition to the dose modifications shown in Appendix 5, it is recommended that management of irAEs follow the guidelines outlined for ipilimumab (Weber J et al, 2012).

If the investigator has any question in regards to an AE being an irAE, the investigator should immediately contact the medical monitor. Dose modifications may be required for AEs that are clearly not attributed to MEDI4736 or tremelimumab (such as an accident) or for laboratory abnormalities that are deemed asymptomatic, require no intervention, and are documented in the medical records. Laboratory abnormalities that are felt to meet these criteria must be discussed and agreed on by the medical monitor before treatment can be continued. Dose reductions of MEDI4736 and tremelimumab are not permitted.

Dose interruptions of MEDI4736 and tremelimumab may be required in the event of treatment-related toxicity. General guidelines regarding dose modifications are provided in Appendix 5. In addition, management guidelines for AESIs are detailed in Section 5.3. All toxicities will be graded according to NCI CTCAE v4.03. In case of doubt the investigator should consult with the medical monitor.

[redacted]

[redacted]

3.2.2 Rationale for Study Population

The proposed study population, comprising adult subjects with metastatic or recurrent gastric or GEJ adenocarcinoma that have progressed during or after 1 or 2 prior standard regimens for recurrent or metastatic disease, represents a high unmet medical need. This tumor indication, described below, presents an opportunity for novel treatment approaches that may lead to improved clinical outcomes.

In 2014, it is estimated that 22,220 and 18,170 people will be newly diagnosed with gastric cancer and esophageal cancer, respectively, whereas 26,440 individuals will die due to upper GI tumors (Siegel et al, 2014). Gastroesophageal cancer remains endemic in many parts of the world, with an estimated new cancer incidence of 1,471,000 people or 11.6% of the global cancer burden and an annual death rate of 1,144,000 people or 15.1% of cancer-related deaths worldwide (Ferlay et al, 2010). Globally, gastric cancer is the second leading cause of cancer-related mortality (Luis et al, 2013).

Current therapeutic strategies for advanced gastric or GEJ adenocarcinoma are limited, and survival rarely exceeds 1 year despite aggressive treatment with chemotherapy. A number of different drugs (eg, alkylating agents, platinum compounds, 5-fluorouracil [5-FU], and taxanes) are available for the treatment of gastroesophageal cancer, but no means of selecting therapy based on the tumor biology is currently available. At present, the combination of a

platinum and fluorouracil agent either alone or in combination with a third drug such as epirubicin or taxane constitutes the most effective treatment option in the first-line metastatic setting (Cunningham et al, 2008). Standard first-line options include docetaxel, cisplatin, and 5-FU; epirubicin, cisplatin, and capecitabine/epirubicin, oxaliplatin, and capecitabine; or folinic acid, 5-FU, and oxaliplatin.

The vascular endothelial growth factor receptor 2 antagonist, ramucirumab, as evaluated in the REGARD study and recently approved by the US FDA, has demonstrated modest activity in subjects with advanced gastric or GEJ adenocarcinoma who progressed after first-line platinum- or fluoropyrimidine-containing chemotherapy (Fuchs et al, 2014). Median OS was 5.2 months in the ramucirumab group versus 3.8 months in the placebo group (HR 0.776, 95% confidence interval [CI], 0.603-0.998; p = 0.047). In the RAINBOW study, more than 600 subjects with metastatic gastric or GEJ adenocarcinoma who had disease progression on or within 4 months after first-line platinum- and fluoropyrimidine-based combination therapy were randomized to paclitaxel plus ramucirumab or paclitaxel alone (Wilke et al, 2014). Median OS was 9.63 months and 7.36 months, respectively (HR 0.807; 95% CI, 0.678-0.962; p = 0.017), and median PFS was 4.40 and 2.86 months, respectively (HR 0.635; 95% CI, 0.536-0.752; p < 0.0001). Median time to progression was 5.5 months with ramucirumab plus paclitaxel versus 3.0 months with paclitaxel alone (p < 0.0001), and ORR was 28% versus 16%, respectively (p = 0.0001). Based on these results, the combination of ramucirumab plus paclitaxel is expected to become the standard of care in the second-line setting for metastatic upper GI tumors.

Additional FDA-approved second-line agents include docetaxel and irinotecan. In the COUGAR-02 study, median OS was 5.2 months with docetaxel compared with 3.6 months with best supportive care (BSC; HR 0.67; 95% CI, 0.49–0.92; p = 0.01; Ford et al, 2014). Kang and colleagues evaluated chemotherapy (docetaxel 60 mg/m^2 every 3 weeks or irinotecan 150 mg/m^2 Q2W) plus BSC versus BSC alone in subjects with advanced gastric cancer who received 1 or 2 prior fluoropyrimidine- and platinum-based chemotherapy regimens (Kang et al, 2012). The median OS was 5.3 months with chemotherapy plus BSC (n = 133) versus 3.8 months with BSC alone (n = 69; HR 0.657; 95% CI, 0.485-0.891; p = 0.007). There was no median OS difference between docetaxel and irinotecan (5.2 versus 6.5 months, respectively; p = 0.116). Despite these advances, the toxicity profile of second-line agents is poor and survival is still between 6 to 9 months. Consequently, immunotherapies hold potential promise in this setting.

To date, a number of Asian studies have investigated PD-L1 expression in gastric cancer. Zheng and colleagues evaluated 80 advanced gastric cancer subjects and 40 healthy controls.

They reported significant upregulation of PD-L1 in advanced gastric cancer patients compared with healthy people (p = 0.006; Zheng et al, 2014). The expression of PD-L1 was significantly correlated with differentiation (p = 0.026) and lymph node metastasis (p = 0.041). Wu and colleagues examined PD-L1 expression in cases of human gastric carcinoma (n = 102), adenoma (n = 10), and normal tissues (n = 10; Wu et al, 2006). Programmed cell death ligand 1 was not detected in normal gastric tissues, and very weak immunodetection in gastric adenomas, but PD-L1 was detected in 42.2% of gastric carcinoma tissues. There was no correlation between PD-L1 immunolocalization and patient age, sex, tumor location, or the degree of tumor differentiation in gastric carcinomas. However, PD-L1 immunodetection was significantly correlated with tumor size, invasion, lymph node metastasis, and survival time. Multivariate analysis demonstrated that PD-L1 immunodetection could be used as an independent factor to evaluate the prognosis of gastric carcinoma.

3.2.3 Rationale for Endpoints

Safety

Standard safety parameters (AEs, SAEs, laboratory evaluations, vital signs, ECGs, and physical examinations) will be employed to assess the safety profile of MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, and tremelimumab monotherapy.

Primary and Secondary Efficacy Assessments

OR and DC as assessed by RECIST v1.1 (Eisenhauer et al, 2009) per blinded central review, are standard measures of clinical activity. OS is considered the "gold standard" for quantifying clinical benefit, with PFS being an acceptable surrogate. In the Phase 2 portion of the study, blinded central review will be performed to confirm response data.

Tumoral IFN-γ Gene Expression Signature

Clinical trials and preclinical studies have demonstrated the predictive nature of an elevated Th1 gene signature within the tumor and the subsequent response to immunotherapy for solid tumors (Ulloa-Montoya et al, 2013; Peng et al, 2015). IFN-γ is one of the hallmark cytokines, both initiating and propagating the Th1 response. Its expression is closely tied to other proteins and cytokines within the tumor microenvironment. Based on internal investigations, an IFN-γ gene expression panel was identified consisting of 4 genes that will be utilized to try and identify a unique population of gastric or GEJ adenocarcinoma subjects who may benefit from treatment with immune checkpoint inhibitors and to identify correlations between IFN-γ gene expression and clinical activity of MEDI4736 in combination with

tremelimumab. IFN-γ gene expression testing will be performed for all Phase 2 treatment cohorts; retrospective testing will be performed as necessary.

PD-L1 Expression

In Study CD-ON-MEDI4736-1108, as of 21Aug2014, the DCR at 12 weeks (DCR-12w) was 33% (115/352 subjects) and ORR was 10% (36/352 subjects) in subjects (across 8 tumor types) treated with MEDI4736 10 mg/kg Q2W (Segal et al, 2014). Greater DCR-12w (47% vs 28%) and ORR (22% vs 5%) were observed in PD-L1-positive versus PD-L1-negative subjects, based on a proprietary IHC assay which detects PD-L1 staining on tumor cells.

Of the 41 subjects with gastroesophageal cancer who have been dosed in Study CD-ON-MEDI4736-1108, 28 were evaluable for efficacy analysis (Segal et al, 2014). In these subjects, DCR-12w was 25% (7/28 subjects). [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Collection of Subject Selection Biomarker Data

Candidate biomarkers for subject selection will be assessed to determine whether these markers predict which subjects are most likely to respond to treatment with MEDI4736 in combination with tremelimumab, MEDI4736 monotherapy, or tremelimumab monotherapy.

[redacted]

[redacted]

[redacted]

[redacted]

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

Up to approximately 135 subjects in Phase 1b/2 will be enrolled at up to approximately 40 study centers globally. Additional subjects may be enrolled if dose de-escalation is required or intermediate dose levels are explored.

4.1.2 Inclusion Criteria

Subjects must meet all of the following criteria:

1. Male or female subjects; age ≥ 18 years at the time of screening or age of consent according to local law.
2. Written informed consent and any locally required authorization, Health Insurance and Portability and Accountability Act in the US, European Union (EU) Data Privacy Directive in the EU obtained from the subject/legal representative prior to performing any protocol-related procedures, including screening evaluations.
3. ECOG performance status of 0 or 1.
4. Histologically or cytologically confirmed metastatic or recurrent gastric or GEJ adenocarcinomas. Note: GEJ adenocarcinomas are defined as tumors that have their center within 5 cm proximal and distal of the anatomical cardia, as described in the Siewert classification system (Siewert et al, 2000).
5. Prior lines of therapy:
   a. For Phase 1b: Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease.
   b. For Arms A, B, and C of Phase 2: Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease, or

      Must have received and have progressed, or are refractory to one systemic platinum or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months of therapy.
   c. For Arm D of Phase 2: Must have received and have progressed, or are refractory to two systemic regimens (one standard platinum- or fluoropyrimidine-based chemotherapy regimen and one approved regimen) for metastatic or recurrent disease.

d. For Arm E of Phase 2: Subjects with a positive IFN-γ gene expression signature (as defined in Section 4.3.8.1) must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based chemotherapy regimen for metastatic or recurrent disease, or

   Must have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months of therapy, or

   Must have received and have progressed, or are refractory to two systemic regimens (one standard platinum- or fluoropyrimidine-based chemotherapy regimen and one approved regimen for metastatic or recurrent disease).

e. Subjects who have received and have progressed, or are refractory to one systemic platinum- or fluoropyrimidine-based therapy as part of neoadjuvant or adjuvant regimen with relapse within 6 months will count as a line of therapy in the metastatic/recurrent setting.

6. Screening for IFN-γ expression prior to Arm E enrollment:
   a. Subjects who are being considered for enrollment on Arm E may undergo pre-screening for IFN-γ gene expression either at the time of disease progression or after having completed a minimum of 60 days of the prior line of systemic therapy. In addition, they should meet all other eligibility criteria for enrollment, with the exception of prior lines of therapy if they are being screened during first-or second-line treatment.
   b. Subjects enrolling to Arm E must consent to provide archival tumor tissue for IFN-γ testing. Only subjects with a positive IFN-γ gene expression signature (as defined in Section 4.3.8.1) will be eligible for enrollment to Arm E. IFN-γ testing must be completed to determine enrollment eligibility prior to initiation of therapy. If eligible, subjects must consent to initial and subsequent tumor biopsy samples, if possible.
7. Subjects must have at least one measurable lesion according to RECIST v1.1.
   a. A previously irradiated lesion can be considered a target lesion if the lesion is well defined, measurable and there is objective evidence of interval increase in size.
8. Subjects must have at least one lesion amenable to biopsy and must consent to and provide both pre-treatment and on-treatment tumor biopsies for Phase 2 (optional for Phase 1b). Fresh tumor biopsies should be preferentially obtained from tumor tissues that are safely accessible as determined by the investigator and achieved via non-significant risk procedures (refer to Section 4.3.2.1). Tumor lesions used for biopsy should not be lesions used as RECIST target lesions. Sites are encouraged to confirm adequacy of tumor biopsy material at the time of the procedure.
9. Subjects must consent to provide archival tumor tissue (initial and subsequent tumor biopsy samples, if possible) for correlative biomarker studies (for both Phase 1b and 2), if available. Availability of tissue for transfer to sponsor should be confirmed prior to initiation of study therapy.
10. Adequate organ and marrow function, as defined below. Criteria “a,” “b,” and “c” cannot be met with ongoing or recent blood transfusions (within 14 days of starting first dose) or require growth factor support (within 28 days of starting the first dose)
    a. Hemoglobin ≥ 8 g/dL

b. Absolute neutrophil count ≥ 1,500/μL
c. Platelet count ≥ 100,000/μL
d. Total bilirubin ≤ 1.5 × ULN except subjects with documented Gilbert's syndrome (> 3 × ULN)
e. ALT and AST ≤ 3 × ULN
f. Calculated creatinine clearance ≥ 50 mL/minute as determined by Cockcroft-Gault (using actual body weight) or 24-hour urine creatinine clearance

11. Female patients of child-bearing potential: Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use at least one **highly** effective method of contraception (Table 4.1.2-1) from the time of screening, and must agree to continue using such precautions for 180 days after the last dose of MEDI4736 + tremelimumab combination therapy or 90 days after the last dose of MEDI4736 monotherapy. Non-sterilised male partners of a female subject must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the 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 contraception. Female subjects should refrain from breastfeeding throughout this period.
    a. Females of childbearing potential are defined as those who are not surgically sterile (ie, bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal
    Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:
        i. Women < 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
        ii. Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses > 1 year ago, had chemotherapy-induced menopause with last menses > 1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).
    b. Highly effective methods of contraception, defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly are described in Table 4.1.2-1. 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).

12. Male patients with a female partner of childbearing potential
    a. Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from screening through 180 days after receipt of the final dose of MEDI4736 + tremelimumab combination therapy or 90 days after receipt of the final dose of MEDI4736 monotherapy. 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.
    b. Female partners (of childbearing potential) of a male subject must use a highly effective method of contraception throughout this period (Table 4.1.2-1).

Table 4.1.2-1 Highly Effective[a] Methods of Contraception (< 1% failure rate)

Barrier Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (eg, Mirena®) [a]	• Implants: Etonogestrel implants: eg, Implanon® or Norplan® • Intravaginal device: eg ethinylestradiol / etonogestrel-releasing intravaginal devices: eg, NuvaRing® • Injection: Medroxyprogesterone injection: eg, Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: eg, Ortho Evra® • Minipill: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method.

13. All patients: Patients should not donate blood or blood components while participating in this study and through 180 days after receipt of the final dose of MEDI4736 + tremelimumab combination therapy or 90 days after receipt of the final dose of MEDI4736 or tremelimumab.

4.1.3 Exclusion Criteria

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

1. Subjects with HER2-overexpressing metastatic or recurrent gastric or GEJ adenocarcinomas. Note: Subjects whose tumor HER2-expression status is not known must submit tumor samples for HER2 testing, which can be done locally prior to screening and consent.
2. Subjects with ascites that require active ongoing paracentesis (within 4 weeks prior to the first scheduled dose) to control their disease.
3. Prior exposure to immunotherapy, including, but not limited to, other anti-CTLA-4, anti-PD-1, or anti-PD-L1 mAbs.
4. Known allergy or hypersensitivity to study drug formulations.
5. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [eg, colitis, Crohn's disease], diverticulitis with the exception of a prior episode that has resolved or diverticulosis, celiac disease, irritable bowel disease, or other serious GI chronic conditions associated with diarrhea; systemic lupus erythematosus; Wegener syndrome [granulomatosis with polyangiitis]; myasthenia gravis; Graves' disease; rheumatoid arthritis, hypophysitis, uveitis, etc) within the past 3 years prior to the start of treatment. The following are exceptions to this criterion:
   a. Subjects with vitiligo or alopecia.
   b. Subjects with hypothyroidism (eg, following Hashimoto syndrome) stable on hormone replacement or psoriasis not requiring systemic treatment.
6. Untreated central nervous system (CNS) metastatic disease, leptomeningeal disease, or cord compression. Note: Subjects previously treated for CNS metastases that are radiographically and neurologically stable for at least 4 weeks and do not require corticosteroids (of any dose) for symptomatic management for at least 14 days prior to the first dose of MEDI4736 or tremelimumab are not excluded.
7. Concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or the follow-up period of an interventional study.
8. Receipt of any conventional or investigational anticancer therapy not otherwise specified above within 28 days prior to the first dose of MEDI4736 or tremelimumab.
9. Any concurrent chemotherapy, immunotherapy, or 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. In addition, local treatment (eg, by local surgery or radiotherapy) of isolated lesions for palliative intent is acceptable beyond the DLT evaluation period with prior consultation and in agreement with the medical monitor.
10. Any toxicity from prior therapy that has not been completely resolved to baseline at the time of consent. Subjects with NCI CTCAE v4.03 Grade 1 or 2 toxicities that are deemed stable or irreversible can be enrolled on a case-by-case basis with prior consultation and agreement with the medical monitor.

11. Current or prior use of immunosuppressive medication within 14 days prior to the first dose of MEDI4736 or tremelimumab. The following are exceptions to this criterion:
    a. Intranasal, topical, inhaled corticosteroids or local steroid injections (eg, intra-articular injection).
    b. Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent.
    c. Steroids as premedication for hypersensitivity reactions (eg, computed tomography [CT] scan premedication).
12. History of primary immunodeficiency, solid organ transplantation.
13. Known positive for human immunodeficiency virus (HIV), chronic or active hepatitis B or C or active hepatitis A.
14. Receipt of live, attenuated vaccine within 28 days prior to the first dose of investigational products (Note: Subjects, if enrolled, should not receive live vaccine during the study and 180 days after the last dose of investigational product[s]). Vaccination with a killed vaccine is permitted at any time with consultation with the medical monitor.
15. Females who are pregnant, lactating, or intend to become pregnant during their participation in the study.
16. Major surgery (as defined by the investigator) within 28 days prior to first dose of MEDI4736 or tremelimumab or still recovering from prior surgery. Local procedures (eg, placement of a systemic port, core needle biopsy, and prostate biopsy) are allowed if completed at least 24 hours prior to the administration of the first dose of study treatment.
17. Other invasive malignancy within 2 years except for noninvasive malignancies such as cervical carcinoma in situ, in situ prostate cancer, non-melanomatous carcinoma of the skin, ductal carcinoma in situ of the breast that has been surgically cured.
18. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs from MEDI4736 or tremelimumab, or compromise the ability of the subject to give written informed consent.
19. Any condition that, in the opinion of the investigator or sponsor, would interfere with evaluation of the investigational products or interpretation of subject safety or study results.
20. Subjects who are involuntarily incarcerated or are unable to willingly provide consent or are unable to comply with the protocol procedures.

4.1.4 Subject Enrollment and Randomization

Study participation begins (ie, a subject is “enrolled”) once written informed consent is obtained. Once informed consent is obtained, a subject identification (SID) number will be assigned by a central system (eg, an interactive response system [IXRS]), and the pre-screening/screening evaluations may begin to assess study eligibility

(inclusion/exclusion) criteria. The SID number will be used to identify the subject during the pre-screening/screening process and throughout study participation.

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.

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not receive investigational products. There can be no exceptions to this rule. Subjects who are screening failures should be withdrawn from the study.

4.1.5 Withdrawal from the Study

Subjects are free to withdraw their consent to participate in the study (investigational product and assessments) at any time without prejudice to further treatment. Subjects who withdraw consent will be asked about the reason(s) and the presence of any AEs. If the subject is willing, the subject will be seen and assessed by the investigator. AEs will be followed up. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.6 Discontinuation of Investigational Product

An individual subject will not receive any further investigational product(s) if any of the following occur in the subject in question:

1. Withdrawal of consent from further participation in the study
2. Lost to follow-up
3. An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing
4. Subject experienced an AE that meets the criteria for a DLT during the DLT evaluation period (for Phase 1b and Phase 2; see Section 3.1.3.2 for definition of DLT)
5. Subject experienced an AE that meets the criteria for a DLT, except its occurrence is outside the DLT evaluation period (for Phase 1b and Phase 2; see Section 3.1.3.2 for definition of DLT)
6. Any AE that meets criteria for discontinuation as defined in Section 3.1.5
7. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational product(s) might constitute a safety risk
8. Pregnancy or intent to become pregnant
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. Confirmed PD and all retreatment criteria in the setting of PD are not met (Section 3.1.2)

Subjects who are permanently discontinued from receiving investigational product(s) regardless of the reason (withdrawal of consent from further treatment, due to an AE, other), will be identified as having permanently discontinued treatment and will be followed for protocol-specified assessments including follow-up of any AEs unless consent is withdrawn specifically from further study participation; the subject is lost to follow-up; the subject starts alternative anticancer treatment; or the subject is enrolled in another clinical study. All subjects will be followed for survival until the end of the study. Subjects who decline to return to the site for evaluations should be contacted by phone every 3 months to assess for survival unless consent is withdrawn.

4.1.7 Replacement of Subjects

Phase 1b subjects who are not evaluable for DLT assessment will be replaced. Subjects in Phase 2 will not be replaced.

4.1.8 Withdrawal of Informed Consent for Data and Biological Samples

Biological Samples Obtained for the Main Study

Study data are protected by the use of an SID 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 samples 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 linked to the SID number but will not be labeled with personal identifiers such as the subject's name. If the subject withdraws consent for participating in the genetic research or future research, the sponsor will 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 sample(s) 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 samples 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.

4.2 Schedule of Study Procedures

4.2.1 Enrollment/Screening Period

Table 4.2.1-1 shows all procedures to be conducted at the screening visit. Screening procedures are required for subjects at initial enrollment and prior to re-treatment; repeated screening is not required for subjects who crossover from monotherapy to combination therapy or for subjects who enter reinduction.

Table 4.2.1-1 Schedule of Screening/Baseline Procedures (as of Amendment 6)

Procedure	Screening/Baseline
	Days -28 to -1
Written informed consent/assignment of SID number	X
Verify eligibility criteria	X
Tumor and disease assessments	
History of prior cancer treatment	X
Disease assessment by RECIST v1.1 (CT or MRI)[a]	X
Brain imaging	X
Study procedures and examinations	
Demographics (including age, sex, race, ethnicity)	X

Table 4.2.1-1 Schedule of Screening/Baseline Procedures (as of Amendment 6)

Procedure	Screening/Baseline
	Days -28 to -1
Medical history	X
Physical examination, including height, weight	X
ECOG performance status	X
12-lead ECG [b]	X
Vital signs (temperature, BP, respiratory rate, pulse oximetry)	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Laboratory tests	
Serum chemistry	X
Hematology	X
Thyroid function tests (TSH, free T3, and free T4)	X
Urinalysis	X
Serum pregnancy test	X
Hepatitis B and C [c]; HIV	X
Other laboratory tests and assays	
Archival tumor sample (if available) [d]	X
Fresh tumor biopsy [e]	X
[redacted]	[redacted]
[redacted]	[redacted]

AE = adverse event; BP = blood pressure; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; Ig = immunoglobulin; [redacted] MRI = magnetic resonance imaging; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; [redacted]; SAE = serious adverse event; SID = subject identification; TSH = thyroid-stimulating hormone.

[a] Disease assessment does not need to be repeated if done within 28 days of first dose on the retreatment schedule.

[b] At screening, a single ECG will be obtained.

[c] Includes hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, IgM hepatitis B core antibody, and hepatitis C antibody. If hepatitis B core (total) antibody testing is unavailable then the hepatitis B core IgG and IgM should both be obtained instead.

[d] In Phase 2 for Arm E, only archival tumor (no older than 36 months) tissue will be accepted for biomarker pre-screening.

[e] Fresh tumor biopsies are optional for subjects in Phase 1b. For Arm E, if archival specimens were obtained within 3 months of screening, with no intervening anti-cancer therapy, then these may be submitted in place of a repeat fresh biopsy.

4.2.2 Randomized Treatment Period

Procedures to be conducted during the treatment period are presented in Table 4.2.2-1 for Weeks 1 to 25 and in Table 4.2.2-2 for Week 27 to end of treatment. This schedule of assessments will be followed for the initial Week 1 to 25 treatment period, if subjects enter reinduction, if subjects enter retreatment, or if subjects are allowed to crossover. At study visits when subjects do not receive investigational product, all of the pre-treatment assessments will be performed.

The timing of ECGs and vital sign assessments should be such that it allows the blood draw [redacted] to occur at the exact nominal time. All samples are collected pre-dose unless otherwise indicated.

Table 4.2.2-1 Schedule of Treatment Period (Initial, Retreatment, Reinduction, and Crossover) Study Procedures Weeks 1 to 25 (as of Amendment 6)

Study Period	**Treatment Period: Weeks 1 to 25**														
Week/Day	**W1 D1**	**W1 D2**	**W2 D1 ± 1D**	**W3 D1 ± 3D**	**W5 D1 ± 3D**	**W7 D1 ± 3D**	**W9 D1 ± 3D**	**W11 D1 ± 3D**	**W13 D1 ± 3D**	**W15 D1 ± 3D**	**W17 D1 ± 3D**	**W19 D1 ± 3D**	**W21 D1 ± 3D**	**W23 D1 ± 3D**	**W25 D1 ± 3D**
Procedure/Study Day	**1**	**2**	**8**	**15**	**29**	**43**	**57**	**71**	**85**	**99**	**113**	**127**	**141**	**155**	**169**
Randomization/enrollment	X														
[redacted]	[redacted]						[redacted]				[redacted]				[redacted]
Tumor and disease assessments															
Disease assessment by RECIST v1.1 (CT or MRI) [a]							X				X				X
Brain imaging (if metastasis found at baseline) [a]							X				X				X
Fresh tumor biopsy [l]					X										
Study procedures and examinations															
Physical examination, including weight	X [b]	X			X		X		X		X		X		X
ECOG performance status	X				X		X		X		X		X		X
Vital signs (Q2W dosing) [c]	X	X		X	X	X	X	X	X	X	X	X	X	X	X
Vital signs (Q4W dosing) [c]	X	X			X		X		X		X		X		X
12-lead ECG [d]	X						X								
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests [b]															
Serum chemistry, including LFTs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4.2.2-1 Schedule of Treatment Period (Initial, Retreatment, Reinduction, and Crossover) Study Procedures Weeks 1 to 25 (as of Amendment 6)

Study Period	Treatment Period: Weeks 1 to 25														
Week/Day	W1 D1	W1 D2	W2 D1 ± 1D	W3 D1 ± 3D	W5 D1 ± 3D	W7 D1 ± 3D	W9 D1 ± 3D	W11 D1 ± 3D	W13 D1 ± 3D	W15 D1 ± 3D	W17 D1 ± 3D	W19 D1 ± 3D	W21 D1 ± 3D	W23 D1 ± 3D	W25 D1 ± 3D
Procedure/Study Day	1	2	8	15	29	43	57	71	85	99	113	127	141	155	169
Hematology	X				X		X		X		X		X		X
Thyroid function tests (TSH, free T3, free T4)	X				X		X		X		X		X		X
Urinalysis	X				X		X		X		X		X		X
Urine or serum pregnancy test	X				X		X		X		X		X		X
[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]

Table 4.2.2-1 Schedule of Treatment Period (Initial, Retreatment, Reinduction, and Crossover) Study Procedures Weeks 1 to 25 (as of Amendment 6)

Study Period	Treatment Period: Weeks 1 to 25														
Week/Day	W1 D1	W1 D2	W2 D1 ± 1D	W3 D1 ± 3D	W5 D1 ± 3D	W7 D1 ± 3D	W9 D1 ± 3D	W11 D1 ± 3D	W13 D1 ± 3D	W15 D1 ± 3D	W17 D1 ± 3D	W19 D1 ± 3D	W21 D1 ± 3D	W23 D1 ± 3D	W25 D1 ± 3D
Procedure/Study Day	1	2	8	15	29	43	57	71	85	99	113	127	141	155	169
[redacted]	■				■		■		■						
[redacted]	■			■	■	■	■	■	■	■	■	■	■	■	■
[redacted]	■				■		■		■		■		■		■

AE = adverse event; BP = blood pressure; CT = computed tomography; D = day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; [redacted] LFT = liver function test; [redacted] MRI = magnetic resonance imaging; [redacted] tic; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; [redacted]; RECIST = Response Evaluation Criteria in Solid Tumors; [redacted] SAE = serious adverse event;TSH = thyroid-stimulating hormone; W = week.

Note: On treatment days, evaluations and sample collections should be conducted prior to administration of MEDI4736/tremelimumab unless otherwise indicated. On nontreatment days, all of the pre-treatment assessments will be performed.

[a] Disease assessments should occur within 7 days prior to dosing.

[b] If physical examination or safety laboratory tests are performed within 3 days prior to Dose 1, they do not need to be repeated.

[c] For all treatment arms: Vital signs (temperature, BP, pulse rate, and respiratory rate) will be measured on MEDI4736 and/or tremelimumab treatment days. Vital signs will be measured within 30 minutes prior to the start of tremelimumab and/or MEDI4736 infusion, every 15 minutes (± 5 minutes) during tremelimumab and/or MEDI4736 infusion, at EOI of tremelimumab and/or MEDI4736 infusion (± 5 minutes), and at 30 and 60 minutes (± 5 minutes) post EOI of tremelimumab and/or MEDI4736 infusion. To clarify for subjects receiving combination therapy, vital signs will be measured within 30 minutes prior to start of tremelimumab and MEDI4736 infusion, every 15 minutes (± 5 minutes) during tremelimumab and MEDI4736 infusion, at EOI of tremelimumab and MEDI4736 infusion (+ 5 minutes), and at 30 and 60 minutes (± 5 minutes) post EOI of MEDI4736 infusion. For the first day of administration of investigational product, an additional 2-hour (± 15 minutes) post EOI period of observation will be required following the 60 minutes (± 5 minutes) post EOI assessment of vital signs. For subsequent doses, the additional 2-hour observation period will not be required unless clinically indicated (eg subject experiences an infusion reaction).

[d] For all treatment arms: On Day 1 of Week 1, a single ECG will be obtained within 30 minutes prior to start of infusion, within 30 minutes post EOI, and between 2 and 6 hours post EOI of tremelimumab and/or MEDI4736 infusion. To clarify for subjects receiving combination therapy: On Day 1 of Week 1, a

Table 4.2.2-1 Schedule of Treatment Period (Initial, Retreatment, Reinduction, and Crossover) Study Procedures Weeks 1 to 25 (as of Amendment 6)

Study Period	Treatment Period: Weeks 1 to 25														
Week/Day	W1 D1	W1 D2	W2 D1 ± 1D	W3 D1 ± 3D	W5 D1 ± 3D	W7 D1 ± 3D	W9 D1 ± 3D	W11 D1 ± 3D	W13 D1 ± 3D	W15 D1 ± 3D	W17 D1 ± 3D	W19 D1 ± 3D	W21 D1 ± 3D	W23 D1 ± 3D	W25 D1 ± 3D
Procedure/Study Day	1	2	8	15	29	43	57	71	85	99	113	127	141	155	169

single ECG will be obtained within 30 minutes prior to start of tremelimumab infusion, within 30 minutes post EOI of MEDI4736, and between 2 and 6 hours post EOI of MEDI4736 infusion. At all other timepoints, a single ECG will be obtained prior to investigational product(s) administration and as clinically indicated.

[redacted]

h As previously specified in Section 4.3.2, fresh tumor biopsies will be obtained on Week 5 Day 1 (± 7 days).

Table 4.2.2-2 Schedule of Treatment Period (Initial, Retreatment, Reinduction, and Crossover) Study Procedures Weeks 27 to End of Treatment (as of Amendment 6)

Study Period	Treatment Period: Week 27 to End of Treatment												
Week/Day	W27 D1 ± 1D	W29 D1 ± 3D	W31 D1 ± 3D	W33 D1 ± 3D	W35 D1 ± 3D	W37 D1 ± 3D	W39 D1 ± 3D	W41 D1 ± 3D	W43 D1 ± 3D	W45 D1 ± 3D	W47 D1 ± 3D	W49 D1 ± 3D	W51 D1 ± 3D
Procedure / Study Day	183	197	211	225	239	253	267	281	295	309	323	337	351
[redacted]													

Table 4.2.2-2 Schedule of Treatment Period (Initial, Retreatment, Reinduction, and Crossover) Study Procedures Weeks 27 to End of Treatment (as of Amendment 6)

Study Period	Treatment Period: Week 27 to End of Treatment												
Week/Day	**W27 D1 ± 1D**	**W29 D1 ± 3D**	**W31 D1 ± 3D**	**W33 D1 ± 3D**	**W35 D1 ± 3D**	**W37 D1 ± 3D**	**W39 D1 ± 3D**	**W41 D1 ± 3D**	**W43 D1 ± 3D**	**W45 D1 ± 3D**	**W47 D1 ± 3D**	**W49 D1 ± 3D**	**W51 D1 ± 3D**
Procedure / Study Day	**183**	**197**	**211**	**225**	**239**	**253**	**267**	**281**	**295**	**309**	**323**	**337**	**351**
Tumor and disease assessments													
Disease assessment by RECIST v1.1 (CT or MRI) [a]				X				X				X	
Brain imaging (if metastasis found at baseline) [a]				X				X				X	
Study procedures and examinations													
Physical examination, including weight		X		X		X		X		X		X	
ECOG performance status		X		X		X		X		X		X	
Vital signs [redacted]	X	X	X	X	X	X	X	X	X	X	X	X	X
Vital signs [redacted]		X		X		X		X		X		X	
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X
Concomitant medications	X	X	X	X	X	X	X	X	X	X	X	X	X
Laboratory tests													
Serum chemistry, including LFTs	X	X	X	X	X	X	X	X	X	X	X	X	X
Hematology		X		X		X		X		X		X	
Thyroid function tests (TSH, free T3, free T4)		X		X		X		X		X		X	
Urinalysis		X		X		X		X		X		X	
Urine or serum pregnancy test		X		X		X		X		X		X	

Table 4.2.2-2 Schedule of Treatment Period (Initial, Retreatment, Reinduction, and Crossover) Study Procedures Weeks 27 to End of Treatment (as of Amendment 6)

Study Period	Treatment Period: Week 27 to End of Treatment												
Week/Day	W27 D1 ± 1D	W29 D1 ± 3D	W31 D1 ± 3D	W33 D1 ± 3D	W35 D1 ± 3D	W37 D1 ± 3D	W39 D1 ± 3D	W41 D1 ± 3D	W43 D1 ± 3D	W45 D1 ± 3D	W47 D1 ± 3D	W49 D1 ± 3D	W51 D1 ± 3D
Procedure / Study Day	183	197	211	225	239	253	267	281	295	309	323	337	351
[redacted]													
[redacted]		■											
[redacted]												■	
[redacted]													
[redacted]		■											
[redacted]												■	
[redacted]													
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■
[redacted]	■	■	■	■	■	■	■	■	■	■	■	■	■
[redacted]						■						■	

Table 4.2.2-2 Schedule of Treatment Period (Initial, Retreatment, Reinduction, and Crossover) Study Procedures Weeks 27 to End of Treatment (as of Amendment 6)

Study Period	Treatment Period: Week 27 to End of Treatment												
Week/Day	W27 D1 ± 1D	W29 D1 ± 3D	W31 D1 ± 3D	W33 D1 ± 3D	W35 D1 ± 3D	W37 D1 ± 3D	W39 D1 ± 3D	W41 D1 ± 3D	W43 D1 ± 3D	W45 D1 ± 3D	W47 D1 ± 3D	W49 D1 ± 3D	W51 D1 ± 3D
Procedure / Study Day	183	197	211	225	239	253	267	281	295	309	323	337	351

AE = adverse event; BP = blood pressure; CT = computed tomography; D = day; ECOG = Eastern Cooperative Oncology Group; EOI = end of infusion; [redacted]; LFT = liver function test; MRI = magnetic resonance imaging; PK = pharmacokinetic; Q2W = every 2 weeks; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone; W = week.

Note: On treatment days, evaluations and sample collections should be conducted prior to administration of MEDI4736/tremelimumab unless otherwise indicated.

[a] Disease assessments should occur within 7 days prior to dosing.

[redacted]

4.2.3 Follow-up Period

Table 4.2.3-1 shows all procedures to be conducted during the end of treatment visit and follow-up period. For subjects who complete all 12 months of treatment, the last dosing visit within the 12-month period is considered to be the end of treatment visit. Subjects who discontinue before 12 months will complete the end of treatment visit at the time the decision is made to discontinue treatment.

All subjects are to complete the end of treatment visit, all follow-up visits and be contacted for survival status in accordance with the Schedule of Study Procedures. However, if a subject discontinues from treatment and moves onto alternative anticancer treatment, the follow-up visits will no longer be required; however, survival follow-up assessments would be required as indicated in the Schedule of Study Procedures unless the subject withdraws consent for further survival follow-up. Survival follow-up will continue until the end of study as defined in Section 6.3.

After 90 days, only subjects with investigational product-related SAEs will continue to be followed for safety.

Table 4.2.3-1 Schedule of Follow-up Procedures (as of Amendment 6)

Study Period	Follow-up Period					
Procedure / Study Day or Month	**EOT [a]**	**Day 30 post-EOT ± 3 Days**	**Day 60 post-EOT ± 3 Days**	**Day 90 post-EOT ± 7 Days**	**Q3M After Day 90 post-EOT up to Month 12 post-EOT ± 7 Days**	**Q6M After Month 12 post-EOT ± 14 Days**
[redacted]	[redacted]			[redacted]		
Disease assessments						
Disease assessment by RECIST v1.1 (CT or MRI) [b]	X			X	X	X
Fresh tumor biopsy	X [c]					
Subsequent anticancer therapy		X	X	X	X	X
Survival status		X	X	X	X	X
Study procedures and examinations						
Physical examination	X	X	X	X		
ECOG performance status				X	X	X
Vital signs	X	X	X	X		
12-lead ECG [d]				X		
Assessment of AEs/SAEs	X	X	X	X		
Concomitant medications	X	X	X	X		
Laboratory tests						
Serum chemistry	X	X	X	X		
Hematology	X	X	X	X		
Thyroid function tests (TSH, free T3, free T4)	X	X	X	X		
Urinalysis	X	X	X	X		
Urine or serum pregnancy test	X					

Table 4.2.3-1 Schedule of Follow-up Procedures (as of Amendment 6)

Study Period	Follow-up Period					
Procedure / Study Day or Month	**EOT [a]**	**Day 30 post-EOT ± 3 Days**	**Day 60 post-EOT ± 3 Days**	**Day 90 post-EOT ± 7 Days**	**Q3M After Day 90 post-EOT up to Month 12 post-EOT ± 7 Days**	**Q6M After Month 12 post-EOT ± 14 Days**
[redacted]						
[redacted]				X		
[redacted]				X		
[redacted]	X			X		
[redacted]						
[redacted]				X		
[redacted]				X		
[redacted]	X			X		
[redacted]		X				
[redacted]		X				

AE = adverse event; CT = computed tomography; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; [redacted] EOT = end of treatment; [redacted]; MRI = magnetic resonance imaging; PD = progressive disease; [redacted] RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TSH = thyroid-stimulating hormone.

[a] For subjects who complete the 12-month treatment period, the last dosing visit within that period is considered to be the EOT visit. Subjects who discontinue before 12 months will complete the EOT visit at the time the decision is made to discontinue treatment.

[b] If a subject discontinues treatment due to confirmed PD, only the EOT disease assessment is required if it has been > 28 days since the last disease assessment.

[c] Tumor biopsy collected once upon confirmed PD.

[d] A single ECG will be obtained.

[redacted].

4.3 Description of Study Procedures

4.3.1 Efficacy

Tumor assessments will be based on RECIST v1.1 (Eisenhauer et al, 2009) and will be performed according to the schedule presented in Section 4.2. All subjects will be followed for survival according to the schedule in Table 4.2.3-1 through the end of the study (defined as 5 years after the final subject is enrolled or the sponsor stops the study, whichever occurs first).

Sites will be required to store electronic copies of all scans, and the sponsor will arrange for centralized storage of all imaging data. 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 will occur for independent centralized third-party blinded review of disease assessments. At the discretion of the sponsor, an independent central review of all scans used in the assessment of tumors by RECIST v1.1 for the Phase 2 portion of the study will be conducted. Guidelines for imaging collection and storage will be provided in a separate document. The management of subjects will be based solely upon the results of assessment conducted by the investigator based on RECIST v1.1 per protocol.

Tumor assessments should include the following evaluations: physical examination and CT or magnetic resonance imaging (MRI) scan of the chest, abdomen, and pelvis (pelvic scan is optional unless known pelvic disease is present at baseline). CT or MRI scans of the head and neck will be performed on all subjects at screening; follow-up head and neck scans are optional unless disease is found on the screening examination or clinically indicated. MRI scan of the brain will be performed on all subjects at screening. If the subject has CNS metastases, a brain MRI is also required at each post baseline assessment. If a subject becomes neurologically symptomatic during treatment outside of the setting where the subject has known CNS metastases, a brain MRI is required.

The preferred method of disease assessment is CT with contrast. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. The same method is preferred for all subsequent tumor assessments.

Tumor Evaluations

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 head and neck, 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.
- Pelvis scan is optional unless known pelvic disease is preset at baseline.

MRI scans

- MRI of the head and neck, abdomen and pelvis (pelvic scan is optional unless known pelvic disease is present at baseline) 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 in short axis). Lesions considered truly nonmeasurable include the following: leptomeningeal disease, ascites, pleural/pericardial effusion, and 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 non-target lesions involving the same organ as a single item on the electronic case report form (electronic case report form [eCRF]; eg, "multiple enlarged pelvic lymph nodes" or "multiple liver metastases").

4.3.1.1 Evaluation of Response by Response Evaluation Criteria in Solid Tumors

Tumor response will be assessed by RECIST v1.1.

Evaluation of Target Lesions

- **CR -** 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).
- **PR -** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **PD -** 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 may be considered progression.)
- **SD -** 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

- **CR -** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm in short axis).
- **Non-CR/Non-PD -** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **PD -** 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 nonmeasurable 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 v1.1. 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 study treatment until confirmed PD (see Section 3.1.2.4).

Evaluation of Overall Response

Confirmation of CR, PR, as well as PD is required by a repeat, consecutive assessment no less than 4 weeks from the date of first documentation. If the next protocol scheduled scan is due within 2 weeks after the confirmatory scan was obtained, the protocol-scheduled scan does not need to be done. Treatment of subjects in Phase 1b and Phase 2 will continue between the initial assessment of PD and confirmation for PD (which is not required by RECIST v1.1; see Section 3.1.2.4). These subjects may continue to receive MEDI4736 in combination with tremelimumab beyond confirmed PD in accordance with Section 3.1.2 and if investigators consider that subjects continue to receive benefit from treatment. In the absence of clinical deterioration, such modifications to the RECIST criteria may discourage the early discontinuation of MEDI4736 in combination with tremelimumab and provide a more complete evaluation of MEDI4736 in combination with tremelimumab antitumor activity than would be seen with conventional response criteria.

Table 4.3.1.1-1 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 4.3.1.1-1 Evaluation of Overall Response at a Single Timepoint by RECIST V1.1

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response	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 [b]	No	Partial response
Stable disease	Non-progressive disease and not evaluable [b]	No	Stable disease
Not all evaluated	Non-progressive disease	No	Not evaluable
No target lesion [a]	Not all evaluated	No	Not evaluable

Table 4.3.1.1-1 Evaluation of Overall Response at a Single Timepoint by RECIST V1.1

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 or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease
No target lesion [a]	Unequivocal progressive disease	Yes or No	Progressive disease
No target lesion [a]	Any	Yes	Progressive disease

RECIST = Response Evaluation Criteria in Solid Tumors.

[a] Defined as no target lesions at baseline.

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

[redacted]

4.3.2 Tumor Biopsies

4.3.2.1 Fresh Tumor Biopsies (Phase 2 Only)

Fresh tumor biopsies should be preferentially obtained from tumor tissues that are safely accessible as determined by the investigator and are not obtained from sites that require significant risk procedures, which include, but are not limited to, biopsies of the brain, lung, mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach or bowel wall [refer to the definition of a significant risk device under §812.3(m) in the Investigational Device Exemptions regulation (21 CFR 812)].

At baseline, fresh tumor biopsies will be obtained prior to administration of the first dose of investigational product(s) for all subjects.

In addition, fresh tumor biopsies will be obtained on Week 5 Day 1 (± 7 days) and upon confirmed PD if clinically feasible (ie, repeat biopsy does not pose unacceptable medical risk to a subject as determined by the investigator). Additional biopsies may also be performed if clinically indicated (eg, for mixed responses). For subjects requiring serial image-guided core needle tumor biopsy, those biopsies will be performed according to institutional practice.

For fresh biopsies, the tumor lesion should not be used as a RECIST target lesion. Additional tumor biopsies are permitted as clinically indicated (eg, for mixed responses or upon confirmed PD). If clinically practical, at each fresh biopsy time point, subjects will undergo 4 core biopsies, but a minimum of at least 3 core biopsies are required.

Tumor biopsies will be stored at MedImmune or an appropriate vendor selected by MedImmune.
Additional details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

4.3.2.2 Archival Tumor Samples (Phase 1b and Phase 2)

Initial and subsequent archival tumor tissue should be provided. In Phase 2 Arm E, only archival tumor tissue will be accepted for biomarker pre-screening. Archival tumor samples must be in paraffin blocks for IHC and additional correlative markers For Phase 1b and Arms A, B, C, and D in Phase 2, when an archival tumor block cannot be provided, only freshly cut sections should be provided as described in the Laboratory Manual.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.3.4 Medical History, Physical Examination, Electrocardiogram, and Vital Signs

4.3.4.1 Medical History and Physical Examination

Physical examinations will be performed according to institutional guidelines on study days noted in Section 4.2, and will include assessments of the head, eyes, ears, nose, and throat, respiratory, cardiovascular, GI, urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, and endocrine systems; weight; and height (at screening only).

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.

4.3.4.2 Electrocardiograms

ECGs (12-lead) will be recorded on study days as noted in Section 4.2. At Week 1 Day 1, single ECGs will be obtained within 30 minutes prior to the start of infusion, within 30 minutes post-, and between 2 and 6 hours post-end of infusion of tremelimumab and/or MEDI4736. All other ECGs will be performed once per visit, (prior to investigational product(s) administration if during the treatment period) and as clinically indicated. In case of clinically significant ECG abnormalities, including an ECG that demonstrates a QT corrected using Fridericia's formula (QTcF) value > 500 milliseconds, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) to confirm prolongation.

The same recorder will be used for each subject at each time point, if possible. Date and time settings should be checked at the start of each study day and aligned with an official timekeeper for all machines used in the study.

Skin preparations should be thorough and electrode positions should be according to standard 12-lead ECG placement.

In this study lead V2 will be analyzed and reported as primary. Lead V5 will be analyzed, for all visits, as backup for the individual where analysis in lead V2 is not deemed possible for pre-dose or significant parts of whole visits or whole visits.

The following variables will be reported: heart rate, PR, RR, QRS and QT intervals from the primary lead of the digital 12-lead ECG.

4.3.4.3 Vital Signs

Vital signs (temperature, blood pressure [BP], pulse rate [or pulse oximetry at screening], and respiratory rate) will be measured on study days noted in Section 4.2.

4.3.5 Clinical Laboratory Tests

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. If the subject has completed any safety laboratory tests within 72 hours before Week 1 Day 1, they will not need to be repeated.

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).

The following clinical laboratory tests will be performed according to the schedules of procedures in Section 4.2:

Serum Chemistry

• Calcium	• Lipase
• Chloride	• Gamma glutamyl transferase
• Magnesium	• Lactic dehydrogenase
• Potassium	• Uric acid
• Sodium	• Creatinine
• Bicarbonate	• Blood urea nitrogen
• AST	• Glucose
• ALT	• Albumin
• ALP	• Total protein
• Total bilirubin	• Triglycerides
• Direct bilirubin	• Cholesterol
• Indirect bilirubin	• Amylase
• Thyroid stimulating hormone, free T4, free T3	

Note for serum chemistries: Tests for AST, ALT, ALP, direct bilirubin, indirect bilirubin, and total bilirubin must be conducted concurrently and assessed concurrently. If serum chemistry is unavailable then plasma chemistry may be obtained instead.

Hematology

• White blood cell count with differential • Red blood cell count	• Platelet count
• Hemoglobin • Hematocrit	• Mean corpuscular volume
• Prothrombin time/ International Normalized Ratio	• Mean corpuscular hemoglobin concentration
• Activated partial thromboplastin time	• Fibrinogen

Urinalysis

• Color	• Glucose
• Appearance	• Ketones
• Specific gravity	• Blood
• pH	• Bilirubin
• Protein	

Pregnancy Test (females of childbearing potential only)

• Urine human chorionic gonadotropin
• Serum beta-human chorionic gonadotropin)

Other Safety Tests

• Hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, IgM hepatitis B core antibody, hepatitis C antibody
• HIV antibodies

[redacted]

[redacted]

4.3.8 Biomarker Evaluation and Methods

Blood samples will be collected and analyzed to evaluate [redacted] biomarkers that relate to MEDI4736 treatment according to the schedule presented in Section 4.2.

[redacted]

[redacted]

[redacted]

[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.

4.3.8.1 IFN- γ Gene expression Testing

The Thermo Fisher Interferon Gamma Signature Assay - Gastric Test will be used to identify subjects with a positive IFN-γ gene expression signature for enrollment into Arm E of the Phase 2 portion of the study. [redacted] Utilizing a ratio of the genes of interest compared to the housekeeping genes, a numeric value will be generated for each subject and evaluated against a pre-determined threshold. The result reported will then be reported as either positive (above the pre-determined cut-off) or negative (below the pre-determined cut-off).

4.3.9 Estimate of Volume of Blood to be Collected

A total of approximately 26 mL of blood in total will be collected during the screening period for all screening tests, which may be collected during the 28-day screening period. No more

than approximately 29 mL of blood will be drawn for any one protocol visit during treatment. During the follow-up period, no more than approximately 29 mL of blood will be collected at any one follow-up visit. The total volume to be collected will depend on the length of a subject's participation in the study as well as to which phase of the study they are enrolled (eg, Phase 1b vs Phase 2).

4.4 Study Suspension or Termination

The sponsor reserves the right to temporarily suspend or terminate this study at any time. The reasons for temporarily suspending or terminating the study may include but are not limited to the following:

1. The incidence or severity of AEs in this or other studies indicates a potential health hazard to subjects
2. Subject enrollment is unsatisfactory
3. Noncompliance that might significantly jeopardize the validity or integrity of the study
4. Enrollment into Phase 2 may be discontinued at the discretion of the sponsor should emerging clinical or nonclinical data suggest that continued treatment may not be beneficial to a given treatment

If MedImmune determines that temporary suspension or termination of the study is required, MedImmune will discuss the reasons for taking such action with all participating investigators (or head of the medical institution, where applicable). When feasible, MedImmune will provide advance notice to all participating investigators (or head of the medical institution, where applicable) of the impending action.

If the study is suspended or terminated for safety reasons, MedImmune will promptly inform all investigators, heads of the medical institutions (where applicable), and/or institutions conducting the study. MedImmune will also promptly inform the relevant regulatory authorities of the suspension/termination along with the reasons for such action. Where required by applicable regulations, the investigator or head of the medical institution must inform the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) promptly and provide the reason(s) for the suspension/termination. If the study is suspended for safety reasons and it is deemed appropriate by the sponsor to resume the study, approval from the relevant regulatory authorities (and IRBs/IECs when applicable) will be obtained prior to resuming the study.

4.5 Investigational Products

4.5.1 Identity of Investigational Product(s)

MedImmune will provide the investigator(s) with investigational product (Table 4.5.1-1) using designated distribution centers.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	[redacted]
MEDI4736	MedImmune	[redacted]
Tremelimumab	MedImmune	[redacted]

[redacted]

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Commercially available 0.9% (weight per volume [w/v]) saline will be supplied by each site. Upon completion of the study, copies of investigational product accountability records will be returned to MedImmune. [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted] [redacted]

[redacted]

[redacted].

The corresponding volume of tremelimumab should be rounded to the nearest tenth mL (0.1 mL). If no institutional standard on dose calculations exists, then dose adjustments for each cycle are only needed for a greater than 10% change in weight.

[redacted] [redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

4.5.1.3 Investigational Product Inspection

Investigational products will be supplied to the site in vials in coded kits. Each kit has a unique number that is printed on all labels within the kit (ie, the outer carton label and the label of each vial within the carton). Each vial selected for dose preparation should be inspected. If there are any defects noted with the investigational product(s), the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.6) for further instructions.

[redacted]

If there are any defects noted with the investigational product, the investigator and site monitor should be notified immediately. Refer to the Product Complaint section (Section 4.5.1.6) for further instructions.

[redacted]

4.5.1.5 Monitoring of Dose Administration

Subjects will be monitored prior to, during, and after infusion of MEDI4736 and tremelimumab. Vital signs (temperature, BP, pulse rate, and respiratory rate) will be measured on MEDI4736/tremelimumab treatment days within 30 minutes prior to the start of MEDI4736 and/or tremelimumab administration, every 15 minutes (± 5 minutes) during MEDI4736 and/or tremelimumab administration, at the end of MEDI4736 and/or tremelimumab infusion (± 5 minutes), and at 30 and 60 minutes (± 5 minutes) post end of infusion of MEDI4736. For subjects receiving combination therapy, vital signs will be measured within 30 minutes prior to start of tremelimumab and MEDI4736 infusion, every 15 minutes (± 5 minutes) during tremelimumab and MEDI4736 infusion, at EOI of tremelimumab and MEDI4736 (± 5 minutes), and at 30 and 60 minutes (± 5 minutes) post EOI of MEDI4736 infusion. Pulse oximetry is a required vital sign at screening for baseline comparison. Pulse oximetry is optional on future visits, and should be obtained per clinical investigator if there is clinical concern for respiratory evaluation, including but not limited to immune-related pneumonitis or interstitial lung disease (ILD), as detailed in Appendix 5. For Dose 1, an additional 2-hour (± 15 minutes) observation period will be required after the 60

minutes (± 5 minutes) post end of infusion of MEDI4736 vital sign assessment. The additional 2-hour observation period will not be required for subsequent doses unless clinically indicated (eg, the subject experiences an infusion reaction).

In the event of ≤ Grade 2 infusion-related reaction, the infusion rate of MEDI4736 and tremelimumab may be decreased by 50% or temporarily 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.

Primary prophylaxis against infusion-related reactions is not permitted during this study in order to avoid obscuring a potential safety signal and to enable a future assessment regarding whether premedications should be required for all subjects in future studies. However, at the discretion of the investigator, secondary prophylaxis (ie, prevention of infusion-related reaction following initial episode) is appropriate and will be permitted. Acetaminophen and/or an antihistamine (eg, diphenhydramine) or equivalent medications per institutional standard may be administered per institutional standard at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, treatment with MEDI4736 and tremelimumab will be discontinued.

As with any mAb, allergic reactions to dose administration are possible. Therefore, 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.

All dosing visits are scheduled based on the date of Week 1 Day 1 dosing. Future dosing visits should not be recalibrated based on actual dosing dates unless approved by the sponsor.

[redacted] the subject experiences a related toxicity, the management guidelines provided in Section 3.1.5 should be followed.

4.5.1.6 Reporting Product Complaints

Any defects with the investigational product must be reported *immediately* to the MedImmune Product Complaint Department by the site with further notification to the site monitor. All defects will be communicated to MedImmune and investigated further with the

Product Complaint Department. During the investigation of the product complaint, all investigational product must be stored at labeled conditions unless otherwise instructed.

MedImmune contact information for reporting product complaints:

[redacted]

4.5.2 Additional Study Medications

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

4.5.3 Labeling

Labels for the investigational product will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. Label text will be translated into local languages, as required.

[redacted]

4.5.5 Treatment Compliance

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

4.5.6 Accountability

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.

4.6 Treatment Assignment and Blinding

4.6.1 Methods for Assigning Treatment Groups

In Phase 2, subjects will be enrolled in 1 of 5 treatment arms. Second-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma will be randomized in a 2:2:1 ratio to Arm A (MEDI4736 in combination with tremelimumab), Arm B (MEDI4736 monotherapy), or Arm C (tremelimumab monotherapy). In parallel, third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma will be enrolled in Arm D (MEDI4736 in combination with tremelimumab). Upon closure of Arms A, B, and C and completion of Arm D, second- and third-line subjects with metastatic or recurrent gastric or GEJ adenocarcinoma and a positive IFN-γ gene expression signature will be enrolled in Arm E (MEDI4736 in combination with tremelimumab). [redacted]

The randomization code will be produced by an independent statistician, who is not part of the study team. Randomization/enrollment to treatment groups will be performed using IXRS.

The time between randomization/enrollment and the initiation of treatment should be as short as possible and no more than 1 business day. 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*.

4.6.2 Methods for Ensuring Blinding

This is an open-label study.

4.7 Restrictions During the Study and Concomitant Treatment(s)

The investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (final study visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF.

4.7.1 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 4.7.2. Best

supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control and pain management [including palliative radiotherapy, etc]) should be used when necessary for all subjects.

4.7.2 Prohibited 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. Monoclonal antibodies against CTLA-4, PD-1, or PD-L1 through 90 days post last dose of the study
3. Any concurrent chemotherapy, radiotherapy (except palliative 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
4. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled, topical, intranasal corticosteroids or local steroid injections (eg, intra-articular injection) is permitted. Temporary uses of corticosteroids for concurrent illnesses (eg, food allergies, CT scan contrast hypersensitivity, etc) are acceptable upon discussion with the medical monitor
5. Live attenuated vaccines during the study through 180 days after the last dose of investigational product
6. Herbal and natural remedies should be avoided

4.8 Statistical Evaluation

4.8.1 General Considerations

For the purpose of generating the clinical study report, the primary analysis for this study may occur after all subjects in corresponding arms have either discontinued from the study or been on the study for at least 7 months (Arms, A, B, C, and E) or 5 months (Arm D). Final analyses for this study including selected efficacy/safety endpoints (if primary analysis occurred) will occur after study closure. The study populations are defined as follows:

- DLT Evaluable Population is defined as subjects enrolled in Phase 1b who receive the protocol-assigned treatment and complete safety follow-up through the DLT evaluation period (Section 3.1.3.2) or experience a DLT during the DLT evaluation period.
- As-treated Population is defined as subjects who receive any dose of either investigational product(s).
- Response Evaluable Population is defined as all subjects from the As-treated Population who have a baseline disease assessment with measurable disease and one of the following: (1) at least one post-baseline disease assessment, and/or (2) withdrawn from study treatment prior to post-baseline disease assessment due to clinical progression or death.
- Crossover Population is defined as all subjects who crossover to receive combination therapy (MEDI4736 in combination with tremelimumab) after confirmed progression on the initial treatment assignment of MEDI4736 or tremelimumab monotherapy.
- Re-treated Population is defined as all subjects who have been re-treated with combination therapy (MEDI4736 in combination with tremelimumab) during the first 12 months of follow-up.

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. Analyses may be performed for the crossover and the re-treated populations (if warranted by data). Additional details of statistical analyses will be described in the statistical analysis plan.

4.8.2 Sample Size and Power Calculations

The planned sample size includes up to approximately 135 subjects in Phase 1b/2.

4.8.2.1 Phase 1b

A safety run-in of up to 9 subjects will be required to investigate the safety and tolerability of a dose and schedule selected for dose expansion [redacted]
The sample size for Phase 1b of the study is not based on formal statistical power considerations.

4.8.2.2 Phase 2

Arms A, B and C (Prior to Amendment 6)

Approximately 125 subjects will be randomly assigned in a 2:2:1 ratio to Arms A, B, or C. [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]

Arm D (Prior to Amendment 6)

It is planned to enroll [redacted] subjects in Arm D.

Arm E

Approximately [redacted] additional subjects who are biomarker positive will be assigned to Arm E.

[redacted]

[redacted]

[redacted]

[redacted]

4.8.3 Efficacy

The efficacy analysis will be based on the As-treated Population. Sensitivity analyses for response-related endpoints (OR, DoR, and DC) will be performed based on the Response Evaluable Population.

The following response-related endpoints and corresponding time-to-event endpoints for primary and secondary efficacy endpoints programmatically-derived from the investigator's assessments or BICR, as well as OS, will be analyzed. More details will be provided in the statistical analysis plan.

- OR is defined as best overall response of confirmed CR or confirmed PR according to RECIST v1.1. The best overall response 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 progression, or the last evaluable disease assessment in the absence of PD prior to the 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 1 visit and confirmed by repeat imaging not less than 28 days (4 weeks) after the visit when the response was first observed with no evidence of progression between the initial and CR/PR confirmation visit.
- DoR is defined as the duration from the first documentation of OR to the first documented disease progression according to RECIST v1.1 or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of DCO for analysis, DoR will be censored at the last tumor assessment date. The DoR will be evaluated only for the subjects with an OR.
- DC is defined as confirmed CR, confirmed PR, or SD based on RECIST v1.1. DC at 16 and 24 weeks is defined as a best overall response of confirmed CR, confirmed PR or having SD with duration of SD lasting 16 and 24 weeks, respectively.
- PFS will be measured from the date of randomization or start of treatment until the documentation of disease progression according to RECIST v1.1 or death due to any cause, whichever occurs first. For subjects who are alive and progression-free at the time of DCO for analysis, PFS will be censored at the last tumor assessment date. PFS-6 and [redacted] are the proportion of subjects with PFS at 6 months [redacted], respectively.
- OS will be measured as the time from date of randomization or the start of treatment until death due to any cause. For subjects who are alive at the time of DCO, OS will be censored on the last date when subjects are known to be alive.

4.8.3.1 Primary Efficacy Analysis

Phase 2

- The 2 co-primary efficacy endpoints for Phase 2 are OR and PFS-6 based on RECIST v1.1. The primary analysis of primary efficacy endpoints will be performed as follows.
- The ORR is defined as the proportion of subjects with OR. The 2 sided 90 and 95% CIs for ORR will be estimated using the exact binomial distribution. In addition, to help make a comparison to historical data, the unconfirmed ORR which is defined as the proportion of subjects who achieved a best overall response of confirmed/unconfirmed CR or confirmed/unconfirmed PR will be presented along with its CIs.
- The PFS-6 is the proportion of subjects with PFS at 6 months. Kaplan-Meier curves will be generated for PFS and used to estimate the PFS-6 along with its 2-sided 90% and 95% CIs. The CIs for PFS-6 will be calculated by applying asymptotic normality to the log-log transformation of PFS-6.

4.8.3.2 Secondary Efficacy Analyses

Phase 1b

Secondary efficacy endpoints for Phase 1b include OR and DC according to RECIST v1.1. The analysis of each efficacy endpoint is described below.

- The ORR is defined as the proportion of subjects with OR. The 2-sided 90% and 95% CIs of ORR will be provided based on an exact probability method.
- The DCR is defined as the proportion of subjects with DC. The 2-sided 90% and 95% CIs of DCR will be provided using an exact probability method. DCR-16w and DCR-24w (defined as the proportion of subjects with DC at 16 and 24 weeks, respectively) will be estimated along with their 2-sided 90% and 95% CIs.

Phase 2

Secondary efficacy endpoints for Phase 2 include DoR, DC, PFS, and OS. The analyses of all secondary endpoints will be performed as follows:

- The DoR according to RECIST v1.1 will be analyzed using the Kaplan-Meier method for those subjects with OR in the corresponding analysis populations. The median of DoR with 90% and 95% CIs will be estimated based on the Kaplan-Meier curves.
- The DCR according to RECIST v1.1 is defined as the proportion of subjects with DC. The 2-sided 90% and 95% CIs of DCR will be provided using an exact probability method. DCR at 16 and at 24 weeks (defined as the proportion of subjects with DC at 16 and 24 weeks, respectively) will be estimated along with their 2-sided 90% and 95% CIs.
- The PFS according to RECIST v1.1 will be analyzed using the Kaplan-Meier method. The median PFS with 90% and 95% CIs will be estimated based on the Kaplan-Meier curves. The landmark 9-months PFS rate will be estimated based on the Kaplan-Meier curves along with their 2-sided 90% and 95% CIs.
- The OS will be analyzed using the Kaplan-Meier method. The median OS with 90% and 95% CIs will be estimated based on the Kaplan-Meier curves. The 1-year OS rate will be estimated based on the Kaplan-Meier curves along with their 2-sided 90% and 95% CIs.

Only subjects whose archival tumor tissue sample showed a positive IFN-γ gene expression signature will be eligible for enrollment to Arm E. This will allow identification of a unique population of gastric or GEJ adenocarcinoma subjects who may benefit from treatment with immune checkpoint inhibitors and will allow correlations between IFN-γ gene expression and clinical activity of MEDI4736 in combination with tremelimumab to be explored.

[redacted]

4.8.4 Safety

The safety analysis will be based on the As-treated Population, and will include AEs, SAEs, laboratory evaluations, vital signs, ECGs, and physical examinations from both Phase 1b and Phase 2.

4.8.4.1 Analysis of Adverse Events

In Phase 1b, the number of DLTs that are identified in the DLT Evaluable Population during the DLT evaluation period will be summarized or listed. For both Phase 1b and Phase 2, the number and percentage of subjects reporting treatment-emergent AEs will be summarized overall and by the worst NCI CTCAE v4.03 grade, system organ class, and preferred term, with a breakdown by treatment arm. Similarly, the number and percentage of subjects reporting treatment-emergent AEs considered related to investigational product will be summarized. At each level of subject summarization, a subject will be counted once using the highest grade and level of causality if one or more occurrences of the same system organ class/preferred term is reported. AEs will be graded according to the NCI CTCAE v4.03 and coded using the Medical Dictionary for Regulatory Activities.

4.8.4.2 Analysis of Clinical Laboratory Parameters

Descriptive statistics will be provided for the clinical laboratory results and changes from baseline by scheduled time of evaluation and by treatment arm including end of treatment visit as well as for the maximum and minimum post-baseline values. Laboratory abnormalities will be graded according to the NCI CTCAE v4.03, if applicable. Frequencies of worst observed grade will be presented for each laboratory parameter as well as the rates of subjects with Grade 3-4 toxicities. A shift table, presenting the 2-way frequency tabulation for baseline and the worst post-baseline grade, will be provided for clinical laboratory tests.

4.8.4.3 Analysis of Vital Signs

Descriptive statistics will be provided for the vital signs measurements and changes from baseline by scheduled time of evaluation and by treatment arm including end of treatment visit as well as for the maximum and minimum post-baseline values.

4.8.4.4 Analysis of Electrocardiograms

ECG parameters (PR, RR, QRS, QT, QTcF) will be summarized using descriptive statistics for actual values and for changes from baseline by treatment arm by scheduled time of evaluation including end of treatment visit as well as for the maximum post-baseline values. The QTcF will be considered as the primary correction method to assess subject cardiac safety.

The notable ECG interval values in maximum absolute QTcF intervals (new > 450 milliseconds, new > 480 milliseconds, new > 500 milliseconds) and the maximum absolute uncorrected QT intervals (new > 500 milliseconds) over all post-baseline evaluations, as well as in QTcF maximum changes from baseline (> 30 and

> 60 milliseconds) over all post-baseline evaluations will be summarized by treatment. "New" means the category of the QTc abnormality was not present at baseline and became present at least one post-baseline ECG assessment.

[redacted]

[redacted]

5 ASSESSMENT OF SAFETY

5.1 Definition of Adverse Events

The International Council for 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. The term disease progression should not be reported as an AE or SAE, however, individual events and/or laboratory abnormalities associated with disease progression (see definition of disease progression below) that fulfill the AE or SAE definition should be reported. An abnormal laboratory finding (including ECG finding) that requires medical intervention by the investigator, or a finding judged by the investigator as medically significant should be reported as an AE. If clinical sequelae are associated with a laboratory abnormality, the diagnosis or medical condition should be reported (eg, renal failure, hematuria) not the laboratory abnormality (eg, elevated creatinine, urine red blood cell increased).

AEs 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.

Adverse Events Associated with Disease Progression

Disease progression can be considered as a worsening of a subject's condition attributable to the disease for which the investigational product is being studied. It may be an increase in the severity of the disease under study and/or increases in the symptoms of the disease. The development of a new metastasis or progression of existing metastasis related to the primary cancer under study should not be considered an AE.

New Cancers

The development of a new cancer should be regarded as an SAE. New cancers are those that are not the primary reason for the administration of the investigational product and have been identified after the subject's inclusion in the study.

5.2 Definition of Serious Adverse Events

An SAE is any AE that:

- Results in death
- Is immediately life-threatening
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- 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.

5.3 Definition of Adverse Events of Special Interest

An AESI is one of scientific and medical interest specific to understanding of the investigational product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product.

AESIs for MEDI4736 include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with MEDI4736 monotherapy and combination therapy. An irAE is defined as anAE 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.

AESIs observed with MEDI4736 include:

- Diarrhea / colitis
- Pneumonitis / ILD
- ALT / AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (eg, Guillain-Barré, and myasthenia gravis)
- Endocrinopathies (ie, events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism and Type I diabetes mellitus)
- Rash / dermatitis
- Nephritis / blood creatinine increases
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)
- Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis

- In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological aetiology are also considered AESIs.

Further information on these risks (eg, presenting symptoms) can be found in the current version of the MEDI4736 Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 5). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

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, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting, and unresponsiveness.

5.4 Recording of Adverse Events

AEs will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. AEs 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 5.2 for the definition of SAEs and Appendix 7 for guidelines for assessment of severity and relationship. If an AE evolves into a condition that meets the regulatory definition of "serious," it will be reported on the SAE Report Form.

Infusion of biological products is commonly associated with infusion-related reactions. Anaphylaxis and infusion-related reactions have some common manifestations and may be difficult to distinguish from each other. Infusion-related reactions are commonly observed during or shortly after the first time exposure to therapeutic mAbs delivered through IV infusion. These reactions are less common following subsequent exposures. Unlike infusion-

related reactions, anaphylaxis is a rare event, usually occurring after subsequent exposure to an antigen, and it is most commonly accompanied by severe systemic skin and/or mucosal reactions. The investigator is advised to carefully examine symptoms of adverse reactions observed during or shortly after exposure to MEDI4736 and tremelimumab, and consider the above mentioned facts prior to making a final diagnosis. Reactions occurring at the time of or shortly after subsequent infusions of investigational product are to be judged by the investigator at his/her own discretion. For the investigator's convenience and in order to facilitate consistency in judgments a copy of the National Institute of Allergy and Infectious Diseases (NIAID) and Food Allergy and Anaphylaxis Network (FAAN) guidance for anaphylaxis diagnosis is provided in Appendix 8.

5.4.1 Time Period for Collection of Adverse Events

AEs will be collected from time of signature of informed consent, enrollment, randomization, throughout the treatment period and including the follow-up period of 90 days after the last dose of MEDI4736 and tremelimumab.

SAEs will be recorded from the time of informed consent signature through 90 days after the last dose of MEDI4736 and tremelimumab.

5.4.2 Follow-up of Unresolved Adverse Events

Any AEs that are unresolved at the subject's last AE assessment or other assessment/visit as appropriate in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary. After 90 days, only subjects with investigational product-related SAEs will continue to be followed for safety.

5.4.3 Deaths

All deaths that occur during the study, including the protocol-defined follow-up period must be reported as follows:

- Death clearly the result of disease progression should be reported at the next visit and documented in the eCRF but should not be reported as an SAE.

- Where death is not due (or not clearly due) to disease progression, the AE causing the death must be reported as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of disease progression, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as an SAE. A post-mortem may be helpful in the assessment of the cause of death, and if performed a copy of the post-mortem results should be forwarded to MedImmune Patient Safety or designee within the usual timeframes.

5.5 Reporting 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:

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. 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.

5.6 Other Events Requiring Immediate Reporting

5.6.1 Overdose

An overdose is defined as a subject receiving a dose of investigational product in excess of that specified in the Investigator's Brochures, 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 5.5 for contact information). If the overdose results in an AE, the AE must also be recorded on the AE eCRF (see Section 5.4). 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 5.4 and Section 5.5). MedImmune does not recommend specific treatment for an overdose. The investigator will use clinical judgment to treat any overdose.

5.6.2 Hepatic Function Abnormality

Hepatic function abnormality meeting the definition of Hy's law (ie, any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN) is considered an AESI. 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. Guidelines for management of subjects with hepatic function abnormality are outlined in Section 3.1.5.

Hepatic function abnormality 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 5.5 for contact information), unless a definitive underlying diagnosis for the abnormality (eg, cholelithiasis or 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 Appendix 7), a prompt cumulative review of safety data and the circumstances of the event in question will be conducted and assessed by the MedImmune Safety Monitoring Committee (SMC; or equivalent) 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 SMC (or equivalent) is required for resumption of subject dosing or study entry in the event that the study is interrupted. Where applicable, regulatory authorities IRBs/IECs will be notified of any actions taken with the study.

5.6.3 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 5.5 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. 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 this should be reported ***within 24 hours of knowledge of the event*** to MedImmune Patient Safety using the Safety Fax Notification Form (see Section 5.5 for contact information). The sponsor will endeavor to collect follow-up information on such pregnancies provided the partner of the study subject provides consent.

6 STUDY AND DATA MANAGEMENT

6.1 Training of Study Site Personnel

Before the first subject is entered into the study, a MedImmune representative will review and discuss the requirements of the Clinical Study Protocol and related documents with the investigational staff and also train them in any study-specific procedures and system(s) utilized.

The principal investigator will ensure that appropriate training relevant to the study is given to all of these staff, and that any new information relevant to the performance of this study is forwarded to the staff involved.

The principal investigator will maintain a record of all individuals involved in the study (medical, nursing and other staff).

6.2 Monitoring of the Study

During the study, a MedImmune representative will have regular contacts with the study site, including visits to:

- Provide information and support to the investigator(s).
- Confirm that facilities remain acceptable.
- Confirm that the investigational team is adhering to the protocol, that data are being accurately and timely recorded in the eCRFs, that biological samples are handled in accordance with the Laboratory Manual and that study drug accountability checks are being performed.
- Perform source data verification (a comparison of the data in the eCRFs with the subject's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating subjects. This will require direct access to all original records for each subject (eg, clinic charts).
- Ensure withdrawal of informed consent to the use of the subject's biological samples is reported and biological samples are identified and disposed of/destroyed accordingly, and the action is documented, and reported to the subject.

The MedImmune representative will be available between visits if the investigator(s) or other staff at the center needs information and advice about the study conduct.

6.2.1 Source Data

Refer to the Clinical Study Agreement for location of source data.

6.2.2 Study Agreements

The principal investigator at each/the center should comply with all the terms, conditions, and obligations of the Clinical Study Agreement, or equivalent, for this study. In the event of any inconsistency between this Clinical Study Protocol and the Clinical Study Agreement, the terms of Clinical Study Protocol shall prevail with respect to the conduct of the study and the treatment of subjects and in all other respects, not relating to study conduct or treatment of subjects, the terms of the Clinical Study Agreement shall prevail.

Agreements between MedImmune and the principal investigator must be in place before any study-related procedures can take place, or subjects are enrolled.

6.2.3 Archiving of Study Documents

The investigator follows the principles outlined in the Clinical Study Agreement.

6.3 Study Timetable and End of Study

An individual subject will be considered to have completed the study if the subject was followed through the end of the study (defined below), regardless of the number of doses of investigational product that was received.

The end of the study ("study completion") is 5 years after the final subject is enrolled or the date the study is closed by the sponsor, whichever occurs first.

6.4 Data Management

Data management will be performed according to the Data Management Plan.

A Web Based Data Capture system will be used for data collection and query handling. The investigator will ensure that data are recorded on the eCRFs as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement. The investigator will sign the completed eCRFs. A copy of the completed eCRFs will be archived at the study site.

6.5 Medical Monitor Coverage

Each subject will be provided with contact information for the principal investigator. In addition, each subject will receive a toll-free number intended to provide the subject's

physician access to a medical monitor 24 hours a day, 7 days a week in the event of an emergent situation where the subject's health is deemed to be at risk. In this situation, when a subject presents to a medical facility where the treating physician or health care provider requires access to a physician who has knowledge of the investigational product and the clinical study protocol and the principal investigator is not available, the treating physician or health care provider can contact a medical monitor through this system, which is managed by a third party vendor.

7 ETHICAL AND REGULATORY REQUIREMENTS

7.1 Ethical Conduct of the Study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/GCP, and applicable regulatory requirements.

7.2 Subject Data Protection

The informed consent form (ICF) will incorporate (or, in some cases, be accompanied by a separate document incorporating) wording that complies with relevant data protection and privacy legislation.

MedImmune will not provide individual genotype results to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law**.**

Extra precautions are taken to preserve confidentiality and prevent genetic data being linked to the identity of the subject. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a subject. For example, in the case of a medical emergency, a MedImmune medical monitor or an investigator might know a subject's identity and also have access to his or her genetic data. Also regulatory authorities may require access to the relevant files, though the subject's medical information and the genetic files would remain physically separate.

7.3 Ethics and Regulatory Review

An IRB/IEC should approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the subjects. The investigator will ensure the distribution of these documents to the applicable IRB/IEC, and to the study site staff.

The opinion of the IRB/IEC should be given in writing. The investigator should submit the written approval to MedImmune before enrollment of any subject into the study.

The IRB/IEC should approve all advertising used to recruit subjects for the study.

MedImmune should approve any modifications to the ICF that are needed to meet local requirements.

If required by local regulations, the protocol should be re-approved by the IRB/IEC annually.

Before enrollment of any subject into the study, the final study protocol, including the final version of the ICF, is approved by the national regulatory authority or a notification to the national regulatory authority is done, according to local regulations.

MedImmune will handle the distribution of any of these documents to the national regulatory authorities.

MedImmune will provide regulatory authorities, IRB/IEC, and principal investigators with safety updates/reports according to local requirements, including suspected unexpected serious adverse reactions, where relevant.

Each principal investigator is responsible for providing the IRB/IEC with reports of any serious and unexpected adverse drug reactions from any other study conducted with the investigational product. MedImmune will provide this information to the principal investigator so that he/she can meet these reporting requirements.

7.4 Informed Consent

The principal investigator(s) at each center will:

- Ensure each subject is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study
- Ensure each subject is notified that they are free to discontinue from the study at any time
- Ensure that each subject is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure each subject provides signed and dated informed consent before conducting any procedure specifically for the study
- Ensure the original, signed ICF(s) is/are stored in the investigator’s Study File
- Ensure a copy of the signed ICF is given to the subject

- Ensure that any incentives for subjects who participate in the study as well as any provisions for subjects harmed as a consequence of study participation are described in the ICF that is approved by an IRB/IEC

7.5 Changes to the Protocol and Informed Consent Form

Study procedures will not be changed without the mutual agreement of the coordinating investigator and MedImmune.

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and where required in a new version of the study protocol.

The amendment is to be approved by the relevant IRB/IEC and if applicable, also the national regulatory authority approval, before implementation. Local requirements are to be followed for revised protocols.

MedImmune will distribute any subsequent amendments and new versions of the protocol to each principal investigator(s). For distribution to IRB/IEC, see Section 7.3.

If a protocol amendment requires a change to a site's ICF, MedImmune and the site's IRB/IEC are to approve the revised ICF before the revised form is used.

If local regulations require, any administrative change will be communicated to or approved by each IRB/IEC.

7.6 Audits and Inspections

Authorized representatives of MedImmune, a regulatory authority, or an IRB/IEC may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these activities were conducted, and data were recorded, analyzed, and accurately reported according to the protocol, GCP, guidelines of the ICH, and any applicable regulatory requirements. The investigator will contact MedImmune immediately if contacted by a regulatory agency about an inspection at the site.

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9 SUMMARY OF PROTOCOL AMENDMENT AND ADMINISTRATIVE CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 1, 12Dec2014

The purpose of this amendment was to address comments by the FDA. Key changes were as follows: 1) clarified that MedImmune does not plan to dose escalate beyond the starting doses stated in the protocol; 2) revised the stopping rules for severe late immune-related toxicities; and 3) removed the statement that laboratory abnormalities not deemed to be clinically significant will not be considered DLT. Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 1. Major changes to the protocol are summarized below.

1. Protocol Synopsis: The synopsis was updated to align with the body of the protocol.
2. Section 3.1.1 (Overview): Added text to clarify that dose levels higher than the starting dose levels stated in the protocol will not be explored.
3. Section 3.1.3.1 (Dose-exploration Criteria for Phase 1b): Removed any reference to dose escalation from this section.
4. Section 3.1.3.2 (Dose-limiting Toxicity): Removed the statement, “Laboratory abnormalities that are no deemed to be clinically significant will not be considered a DLT.”
5. Section 3.1.4 (Phase 2): The following changes were made:
   - Replaced “dose expansion” with “Phase 2”, and replaced “dose exploration with “Phase 1b.”
   - Added the following statement: “In addition, after the first 20 subjects have been dosed with MEDI4736 in combination with tremelimumab for a minimum of 6 weeks (in both second- and third-line settings), safety data will be reviewed by the sponsor.”
6. Section 4.1.3 (Exclusion Criteria): Revised criterion 10 to indicate “Any prior therapy that has NOT been…”
7. Section 4.1.6 (Discontinuation of Investigational Product): The following changes were made:
   - Revised criterion 4 as follows (changes underlined): “Subject experienced an AE that meets the criteria for a DLT <u>during the DLT evaluation period</u> (for Phase 1b <u>and Phase 2</u>; see Section 3.1.3.2 for definition of DLT).
   - Added criterion 5: “Subject experienced an AE that meets the criteria for a DLT, except its occurrence is outside the DLT evaluation period (for Phase 1b and Phase 2; see Section 3.1.3.2 for definition of DLT).”
8. Section 4.2.2 (Randomized Treatment Period): Added “Procedures/Study Day” to header of Table 4.2.2-1 (Schedule of Treatment Period Study Procedures Weeks 1 to 25).

9.2 Protocol Amendment 2, 22Jan2015

The purpose of this amendment was to address comments by the FDA. The key change was to state that fresh tumor biopsies should be preferentially obtained from tumor tissues that are safely accessible.

1. Section 4.1.2 (Inclusion Criterion 7): Language was added to indicate that fresh tumor biopsies should be preferentially obtained from tumor tissues that are safely accessible.
2. Table 4.2.1-1 (Schedule of Screening/Baseline Procedures): Electrocardiograms in triplicate were removed from the screening period. A single ECG is required at this time point.
3. Table 4.2.2-1 (Schedule of Treatment Period Study Procedures Weeks 1 to 25): Electrocardiogram on Week 17 Day 1 was changed to Week 9 Day 1 1 to allow recording of ECGs of subjects who progress prior to Week 17.
4. Section 4.3.2.1 (Fresh Tumor Biopsies [Phase 2 Only]): Text was added to indicate that fresh tumor biopsies should be preferentially obtained from tumor tissues that are safely accessible as determined by the investigator and achieved via non-significant risk procedures.
5. Section 4.3.4.2 (Electrocardiograms): Electrocardiograms in triplicate were removed from the screening period. A single ECG is required at this time point. The formula for analysis of ECGs was changed to Fridericia's formula for consistency across other studies.
6. Section 4.8.4.4: The formula for analysis of ECGs was changed from Bazett's to Fridericia's formula for consistency across other studies.

9.3 Protocol Amendment 3, 03Apr2015

The purpose of this amendment was to delete Scenarios 1 and 2; Scenario 2 will be utilized under Amendment 3. Language was modified to indicate the selected dose of [redacted] to be utilized in Phase 1b. Major changes are listed below:

1. The Synopsis was updated to align with changes made to the protocol body.
2. Section 1.4.1 (MEDI4736 Clinical Experience): Clinical experience with combination therapy was moved to section 1.4.3.
3. Section 1.4.2 (Tremelimumab Clinical Experience): Tremelimumab clinical data were updated based on the most recent Investigator's Brochure (12Nov2014 data cut-off date).
4. Section 1.4.3 (Clinical Experience with MEDI4736 and Tremelimumab Combination): This section was added to describe clinical experience with MEDI4736 + tremelimumab combination therapy.
5. Section 1.5 (Rationale for Conducting the Study): A subsection for benefit-risk evaluation was added.

6. Section 3.1.1 (Overview): Text for Scenario 1, which was to be followed if a dose and schedule were not identified in Study D4190C00006, was deleted. Text was added to describe the MEDI4736 + tremelimumab combination dose and schedule that were identified in Study D4190C00006. Language was added to indicate that any Phase 1b cohort not exceeding the MTD may be expanded up to a maximum of [redacted] subjects for further evaluation of exposure versus safety, [redacted] and efficacy. The study flow diagram was updated to reflect the study conduct under Amendment 3.

[redacted]

9. Section 3.1.2.4 (Criteria for Treatment Beyond Progression, Crossover, and Retreatment in the Follow-up Period): Text describing retreatment was added.
10. Section 3.1.3.2 (Dose-limiting Toxicity): Text describing DLT evaluation for [redacted] dosing was deleted.
11. Section 3.1.5 (Management of Study Medication Related Toxicities): Table 3.1.5-1 was deleted and new toxicity management guidelines were inserted in Appendix 5.
12. Section 3.2.1 (Dose Rationale): The dose rationale for combination therapy was updated based on latest available data.
13. Section 4.1.2 (Inclusion Criteria): Inclusion criterion 8 was modified. The following statement was deleted: "For subjects enrolling in Phase 1b, if an archival specimen is not considered suitable for biomarker studies, the subject must provide consent and undergo a fresh tumor biopsy during screening."
14. Section 4.1.3 (Exclusion Criteria): Exclusion criterion 13 was modified to exclude subjects with true positive test results for HIV, hepatitis B, or hepatitis C. Hepatitis A was deleted from the exclusion criterion.
15. Section 4.1.8 (Withdrawal of Informed Consent for Data and Biological Samples): Under the subsection Samples Obtained for Genetic Research or Future Research, the following sentence was deleted: "A file linking this sample identification number with the SID number will be kept in a secure place at the sponsor with restricted access." Modifications were made to describe that the sample identification number is linked to the SID number.
16. Section 4.2.1 (Enrollment/Screening Period): Screening procedures are required for subjects at initial enrollment and prior to re-treatment; screening does not need to be repeated for subjects who crossover from monotherapy to combination therapy. Disease assessment does not need to be repeated if done within 28 days of first dose on the retreatment schedule.
17. Section 4.2.2 (Randomized Treatment Period): Table 4.2.2-1 will be followed for the initial Week 1 to 25 treatment period, if subjects enter reinduction, if subjects enter re-

treatment, or if subjects are allowed to crossover. Evaluation of ECOG performance status was added at Weeks 5, 13, and 21, and at Weeks 29, 37, and 45 in Table 4.2.2-2.

[redacted]

19. Section 4.3.5 (Clinical Laboratory Tests): Red blood cell count and hematocrit were added to hematology tests.
20. Section 4.3.9 (Estimate of Volume of Blood to be Collected): Blood volume during screening was decreased to approximately 43 mL. No more than 63 mL blood will be drawn for any one protocol visit during treatment. Blood volume during follow-up was decreased to approximately 33 mL.
21. Section 4.8.2.1 (Phase 1b): Text was modified to indicate that the number of subjects is based on a safety run-in schema and may be expanded to a maximum of [redacted] subjects for any cohort if the MTD is not exceeded.
22. Appendix 5 (MEDI4736 and Tremelimumab Dose Modifications for Toxicity Management): Toxicity management information was modified to align with current practice and moved to the appendix from Section 3.1.5.

9.4 Protocol Amendment 4, 10Apr2015

The purpose of this amendment is to correct Table 4.2.2-2 (Schedule of Treatment Period [Initial, Retreatment, Reinduction, and Crossover] Study Procedures Weeks 27 to End of Treatment). In Protocol Amendment 3, there was a formatting error in the sequence of the Section 4.2.2 table heading numbering; consequently the Table 4.2.2-2 was truncated. Also the serology exclusion criterion was updated and minor edits were added.

1. Table 4.2.2-2 (Schedule of Treatment Period [Initial, Retreatment, Reinduction, and Crossover] Study Procedures Weeks 27 to End of Treatment) has been restored in full.
2. Section 4.1.3 (Exclusion Criteria): Exclusion Criterion 13 was changed **from** "True positive test results for HIV, hepatitis B, or hepatitis C" **to** "Known positive for HIV, chronic or active hepatitis B or C or active hepatitis A."
3. Synopsis; Section 4.8.8: Futility analysis for Arm A and Arm B in Phase 2 was added.

9.5 Protocol Amendment 5 21Dec2015

The purpose of this amendment was to update the study design and to update the description of study procedures. Additionally, the potential expansion plan for third-line gastric or GEJ adenocarcinoma, Arm D, was updated. Clarifications of eligible prior therapies, study schedules, collection of vitals and ECGs were also made.

1. The EudraCT number was added and the information for the Medical Monitor was updated.
2. The Protocol synopsis text was modified to include updated eligibility and study design. Planned analyses in the summary section were updated.
3. Section 1.4 Summary of Clinical Experience and subheadings were updated based on current information from clinical studies.
4. Section 2.1.1 Primary Objectives the abbreviation for RECIST was used in replacement of the full term.
[redacted]
6. Section 3.1.1 was updated with new criteria to provide clarification regarding subject eligibility
7. Figure 3.1.1-1 The study flow diagram was updated to reflect changes in study design.
8. Section 3.1.2 Treatment Regimen was updated to provide clarification for the duration of infusion.
9. Section 3.1.4 was updated to provide additional details for the Arm D expansion cohort.
10. Section 3.1.5 Management of Study Medication Related Toxicities was updated based on 02Oct2015 Dosing and Toxicity Management Guidelines.
11. Section 3.2.3 Rationale for Endpoints was updated to include information on how data would be reviewed.
12. Section 4.1.2 Inclusion criteria updated to include clarifications of eligible prior therapy, hepatitis history, hemoglobin, transfusion time prior to study enrollment, and number of weeks from last paracentesis prior to study enrollment. [redacted]
13. Table 4.2.2-1 was updated to reflect new highly effective methods of contraception.
14. Section 4.2.1 was updated to specify that subjects who enter reinduction do not need to undergo repeated screening.
15. Table 4.2.1-1 Schedule of Screening/Baseline Procedures was updated to clarify labs for reinduction.
16. Table 4.2.2-1 Schedule of Treatment period was updated to clarify collection of vital signs and ECGs across the treatment arms.
17. Table 4.2.3-1 Schedule of Follow-up Procedures was clarified to allow urine or serum pregnancy tests.
18. Section 4.3.1 Efficacy was updated to clarify written statements.

19. Section 4.5.1.4 Treatment Administration was update to clarify the duration of MEDI4736 infusion.
20. Section 4.5.1.5 Monitoring Dose Administration was updated to clarify collection of vital signs across the treatment arms.
21. Section 4.7.1 was clarified to remove the sentence regarding use of opioids.
22. Section 4.8 was updated with the planned number of subjects, sample size and power calculations for Phase 2.
23. Section 4.8.8 Interim analysis was updated commensurate with the amended study design. Added text to clarify futility cut-off in the initial group of patients prior to proceeding with a potential expansion of Arm D.
24. Section 4.8.2.2 Sample size and power calculations updated to describe a futility cut-off in the initial group of patients prior to proceeding with a potential expansion of Arm D.
25. Section 5.2 Definition of Serious Adverse Events was revised with updated MedImmune patient safety guidelines.
26. Section 5.3 Definition of Adverse Events of Special Interest was revised with updated MedImmune patient safety guidelines.
27. Section 5.6.2 Hepatic Function Abnormality was updated.
28. Appendix 5 MEDI4736 and Tremelimumab Dose Modifications for Toxicity Management was updated according to MedImmune patient safety guidelines.

9.6 Protocol Amendment 6 24Jan2017

The purpose of this amendment was to add a new arm (Arm E) to the Phase 2 portion of the study to evaluate the efficacy and safety of MEDI4736 in combination with tremelimumab in subjects with second- and third-line gastric or GEJ adenocarcinoma with a positive tumor IFN-γ gene expression signature. Major changes to the protocol are summarized below.

1. The EudraCT number was deleted as the study will no longer be opened in the EU.
2. Information for the Medical Monitors was updated.
3. Protocol Synopsis: The synopsis was updated to align with the body of the protocol.
4. Section 1.3.1 (MEDI4736 Nonclinical Experience): The summary of toxicology studies was updated.
5. Section 1.4.1 (MEDI4736 Clinical Experience): The section was revised to include updated data.
6. Section 1.4.2 (Tremelimumab Clinical Experience): The section was revised to include updated data.

[redacted]

8. Section 1.5 (Rationale for Conducting the Study): Rationale was added for patient selection based on tumoral IFN-γ gene expression signature in Arm E.

9. Section 2.1.1 (Primary Objectives): The primary objective for Phase 2 was amended to specify the inclusion of subjects with second and third-line metastatic or recurrent gastric or GEJ adenocarcinoma whose tumors have a positive IFN-γ gene expression signature.
10. Section 2.1.2 (Secondary Objectives, Number 3): Amended to specify the inclusion of subjects with second- and third-line metastatic or recurrent gastric or GEJ adenocarcinoma whose tumors have a positive IFN-γ gene expression signature.

[redacted]

12. Section 2.2.1 (Primary Endpoints): The primary endpoint for Phase 2 was amended to specify the inclusion of subjects with second and third-line metastatic or recurrent gastric or GEJ adenocarcinoma whose tumors have a positive IFN-γ gene expression signature.
13. Section 2.2.2 (Secondary Endpoints): A new secondary endpoint "IFN- gene expression signature and how it correlates with clinical activity of MEDI4736 in combination with tremelimumab." was added.

[redacted]

15. Section 3 (Study Design): The study design section was updated to add a new study flow diagram, add the criteria the subjects must be meet to be enrolled in Arm E, update the approximate number of subjects to be enrolled, add the current status of Phase 1b, describe the addition of Arm E to Phase 2 of the study, and state the subject numbers in Arms A, B, C, and D at the time of the interim analyses. References to the expansion of Arm D up to [redacted] were removed.
16. Section 3.1.2.4 (Criteria for Treatment Beyond Progression, Crossover, and Retreatment in the Follow-up Period): The criteria governing treatment beyond progression and retreatment for subjects who enter follow-up were clarified and details for treatment beyond progression in Arm E were added.
17. Section 3.1.3 (Phase 1b): A status update for Phase 1b was added.
18. Section 3.1.4 (Phase 2): A status update for Phase 2 was added, including the addition of Arm E and the removal of the expansion of Arm D by up to [redacted] additional subjects.
19. Section 3.2.3 (Rationale for Endpoints): The rationale for the new secondary endpoint "IFN- gene expression signature and how it correlates with clinical activity of MEDI4736 in combination with tremelimumab." was added. [redacted]
20. Section 4.1.1 (Number of Subjects): The approximate number of subjects to be enrolled in Phase 1b/2 was updated [redacted].
21. Section 4.1.2 (Inclusion Criteria),the following changes were made:
    - Inclusion criterion 5 was updated to specify prior lines of therapy for subjects in Arm E.
    - Inclusion criterion 6 was added to describe pre-screening for IFN-α expression for enrollment into Arm E of Phase 2 and to specify the requirement for subjects enrolling to Arm E to provide archival tumor tissue for IFN-γ testing.

- Inclusion criterion 7 (was inclusion criterion 6) revised to remove requirement for measurable disease at baseline confirmed by [redacted] for the planned expansion in Arm D, which has now been removed from the protocol.
- Inclusion criteria 11 and 12 (were criteria 10 and 11, respectively) revised to update text regarding contraception.
- Inclusion criterion 13 was added to specify requirements regarding blood donation for subjects participating in this study.

22. Section 4.1.4 (Subject Enrollment and Randomization): The text was revised to include pre-screening evaluations where appropriate.
23. Section 4.2.1 (Enrollment/Screening Period), Table 4.2.1-1: The table title was amended to clarify that [redacted]; a footnote was added to provide a list of hepatitis B and C tests, to accommodate global practices; a footnote was added to specify that in Arm E only archival tumor tissue (no older than 36 months) will be accepted for biomarker pre-screening.
24. Section 4.2.2 (Randomized Treatment Period), Table 4.2.2-1: The table title was amended to clarify that [redacted] Text was added to specify that the physical examination includes measurement of weight. [redacted] Footnote "d" was modified to remove the requirement to obtain ECGs on Day 1 of Week 1 in triplicate; footnote "f" was modified to clarify details of [redacted] Table 4.2.2-2: The table title was amended to clarify that schedule is applicable as of Amendment 6, text was added to specify that the physical examination includes measurement of weight, [redacted]
25. Section 4.2.3 (Follow-up Period), Table 4.2.3-1: The table title was amended to clarify that [redacted]
26. Section 4.3.1 (Efficacy): Text was added to specify that CT or MRI scans of the head and neck will be performed at screening but that follow-up scans will be optional unless disease is found on the screening examination or clinically indicated.
27. Section 4.3.2.1 (Fresh Tumor Biopsies [Phase 2 Only]): [redacted]
28. Section 4.3.2.2 (Archival Tumor Samples [Phase 1b and Phase 2]): Text was added to state that in Phase 2 Arm E [redacted] will be accepted for biomarker pre-screening; in all other Phase 2 arms and in Phase 1b, when an archival tumor [redacted] cannot be provided then only freshly cut sections should be provided.

29. Section 4.3.4.2 (Electrocardiograms): Text was modified to remove the requirement to obtain ECGs on Day 1 of Week 1 in triplicate.
30. Section 4.3.8 (Biomarker Evaluation and Methods) [redacted]
31. Section 4.3.9 (Estimate of Volume of Blood to be Collected): Blood volumes updated to account [redacted].
32. Section 4.6.1 (Methods for Assigning Treatment Groups): Text revised in line with the addition of Arm E to Phase 2. Text regarding ensuring balance between treatment groups with respect to PD-L1 expression level was deleted.
33. Section 4.8.1 (General Considerations): Arm E was added to the list of arms in which the primary analysis may occur after all subjects in the arm have either discontinued from the study or been on the study for at least 7 months.
34. Section 4.8.2 (Sample Size and Power Calculations): The approximate number of subjects to be enrolled in Phase 2 was updated, the sample size considerations for expansion of Arm D [redacted] was deleted, the sample size calculations for Arm E were added.
35. Section4.8.3 (Efficacy): The text detailing the expansion of Arm D [redacted] was deleted.
36. Section 4.8.3.2 (Secondary Efficacy Analyses): Text was added that detailed the enrollment of subjects whose archival tumor tissue sample showed a positive IFN-γ gene expression signature to Arm E.

[redacted] The text was amended to clarify that the [redacted]

38. Section 4.8.8: Text describing the interim analysis for Arm D was deleted. It was originally planned to perform an interim analysis for Arm D when [redacted] subjects had been enrolled and followed for at least 8 weeks; enrollment could be stopped if ≤ 2 out of the [redacted] subjects experienced a CR/PR or at the Sponsor's discretion. Text describing the interim analysis that will be performed for Arm E was added.
39. Section 5.3: The list of AESIs observed with MEDI4736 was updated. A new subsection on hypersensitivity reactions was added. Text on the the Dosing Modification and Toxicity Management Guidelines (which are presented in Appendix 5) was added.
40. Section8: New references were added and references that are no longer cited were removed.
41. Appendix 5: The guidelines for MEDI4736 and tremelimumab toxicity management were updated according to the 31Aug2016 version.

APPENDICES

Appendix 1 Signatures

Sponsor Signature(s)

A Phase 1b/2 Study of MEDI4736 in Combination with Tremelimumab, MEDI4736 Monotherapy, and Tremelimumab Monotherapy in Subjects with Metastatic or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma

I agree to the terms of this protocol.

Signature and date: electronic signature is appended

[redacted]

Signature of Principal Investigator

A Phase 1b/2 Study of MEDI4736 in Combination with Tremelimumab, MEDI4736 Monotherapy, and Tremelimumab Monotherapy in Subjects with Metastatic or Recurrent Gastric or Gastroesophageal Junction Adenocarcinoma

I, the undersigned, have reviewed this protocol, 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 Council for 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: _____

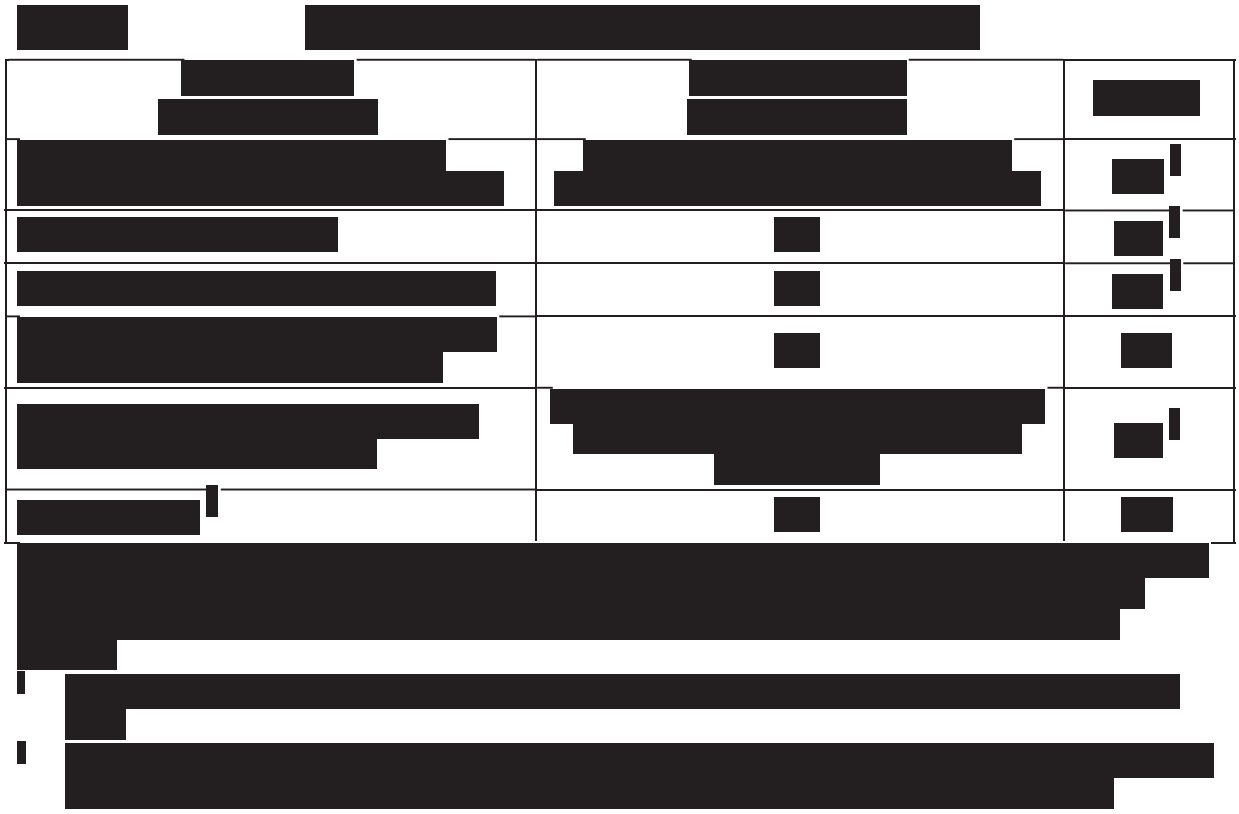
Address including postal code: _____

_____

Telephone number: _____

Site/Center Number (if available):_____

[redacted]



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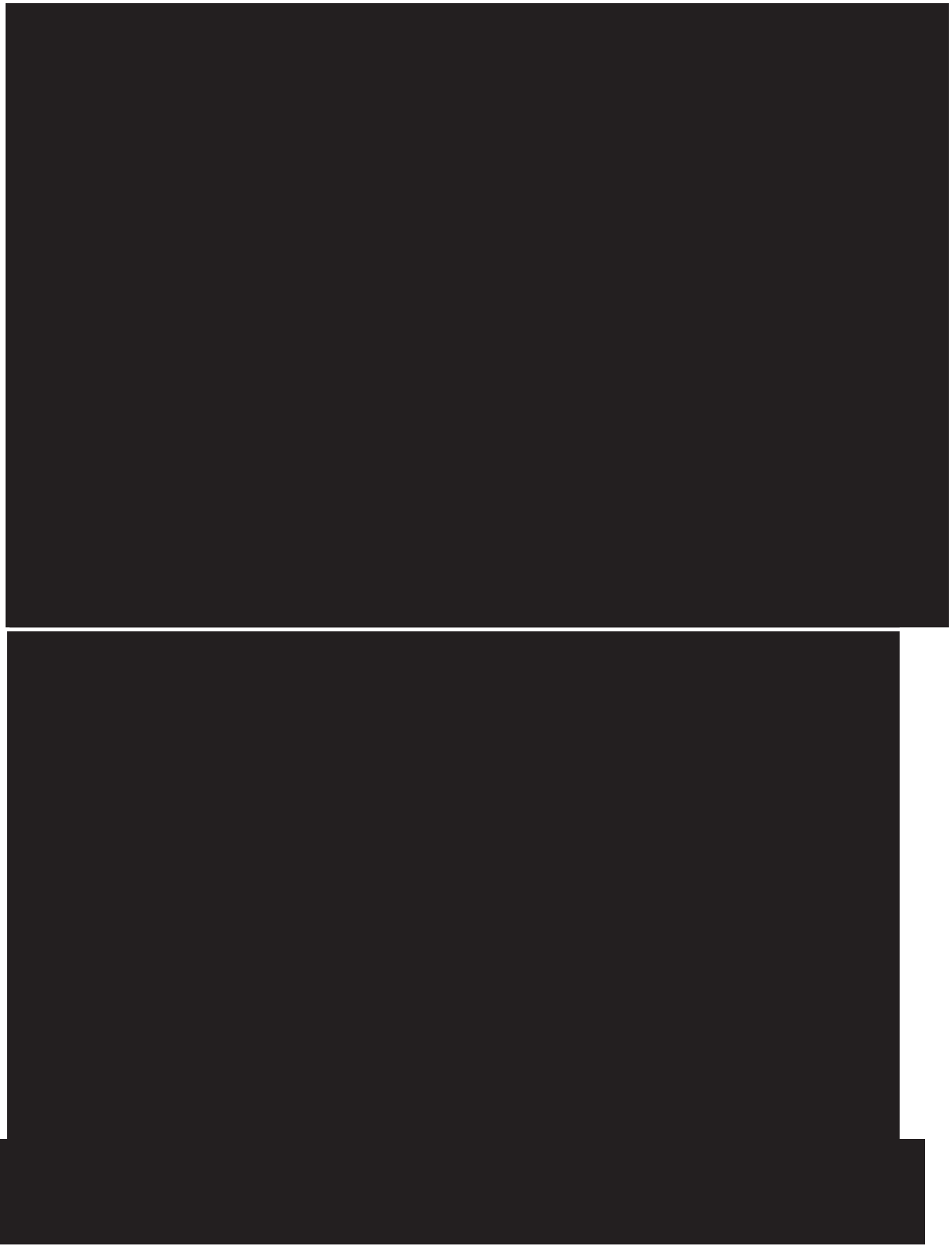

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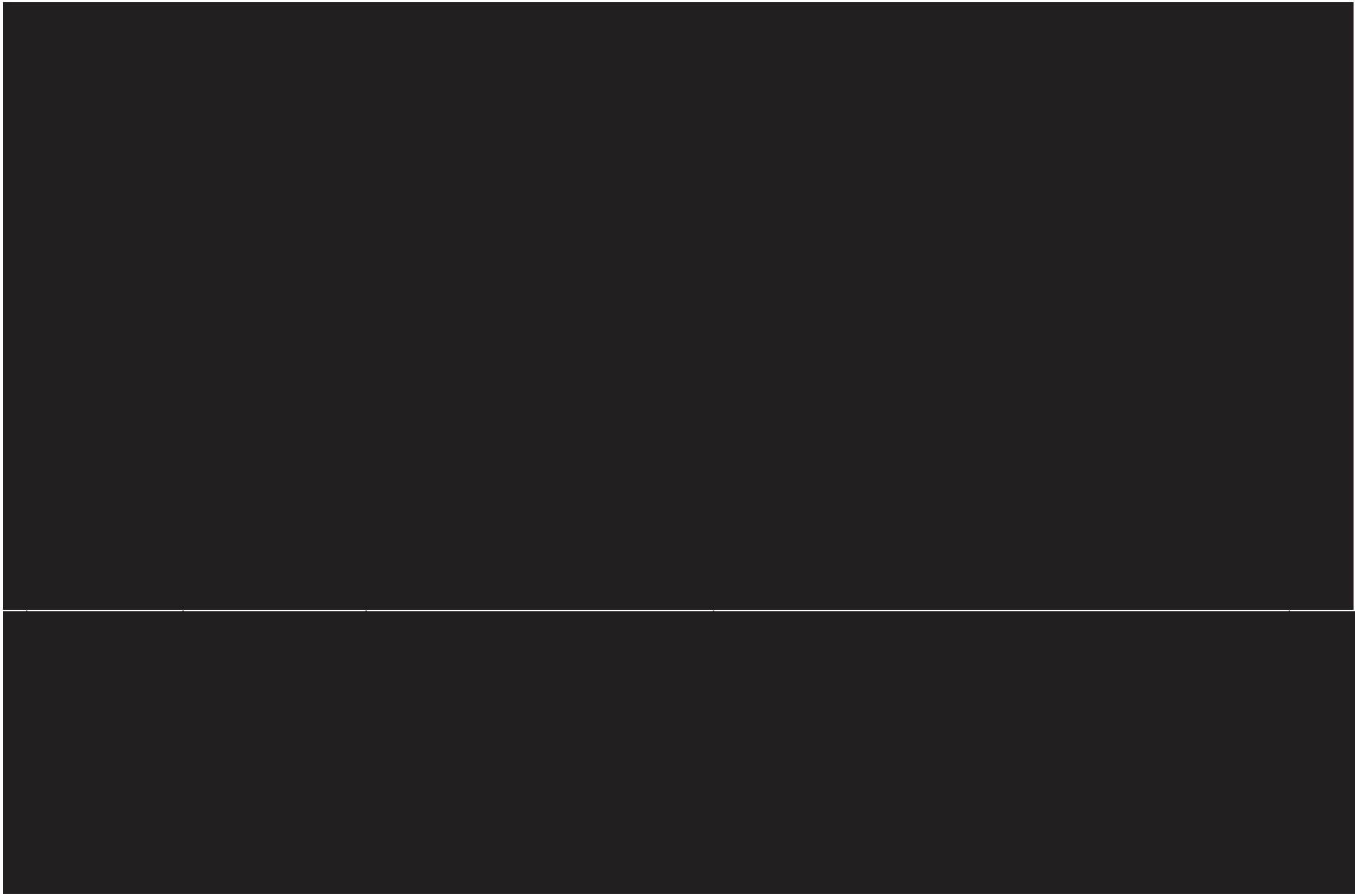
Appendix 5 MEDI4736 and Tremelimumab Dose Modifications for Toxicity Management

[redacted]



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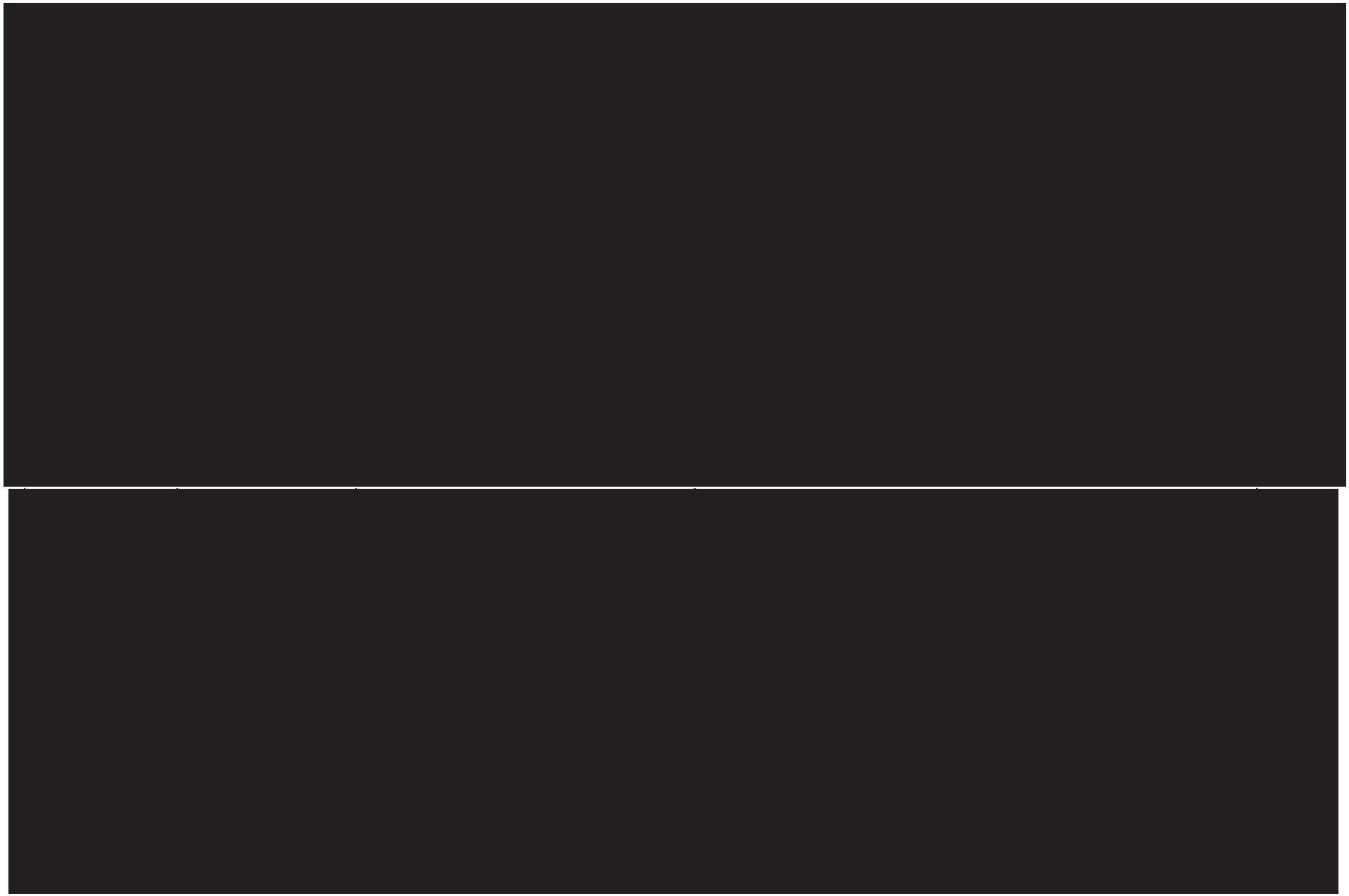

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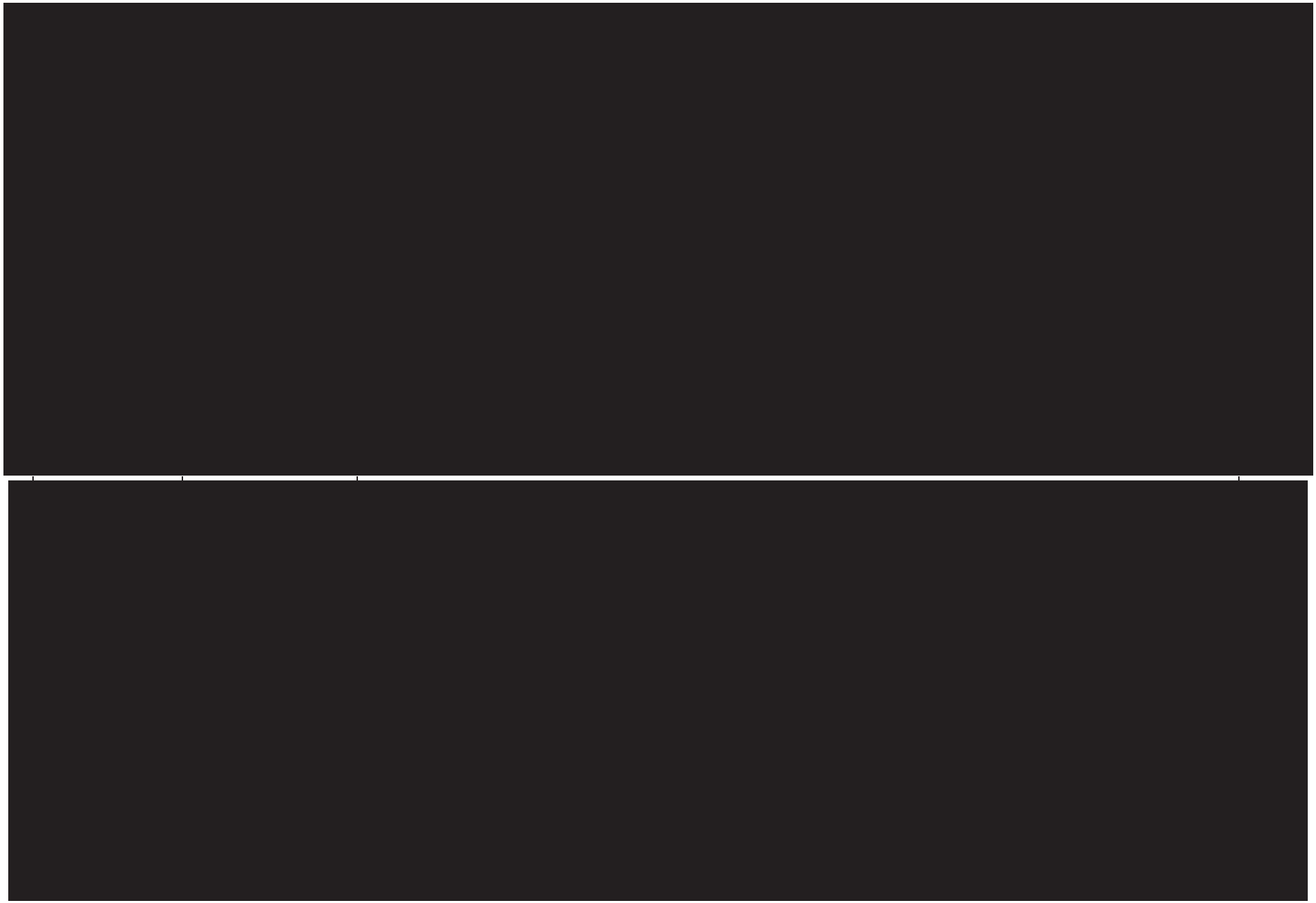
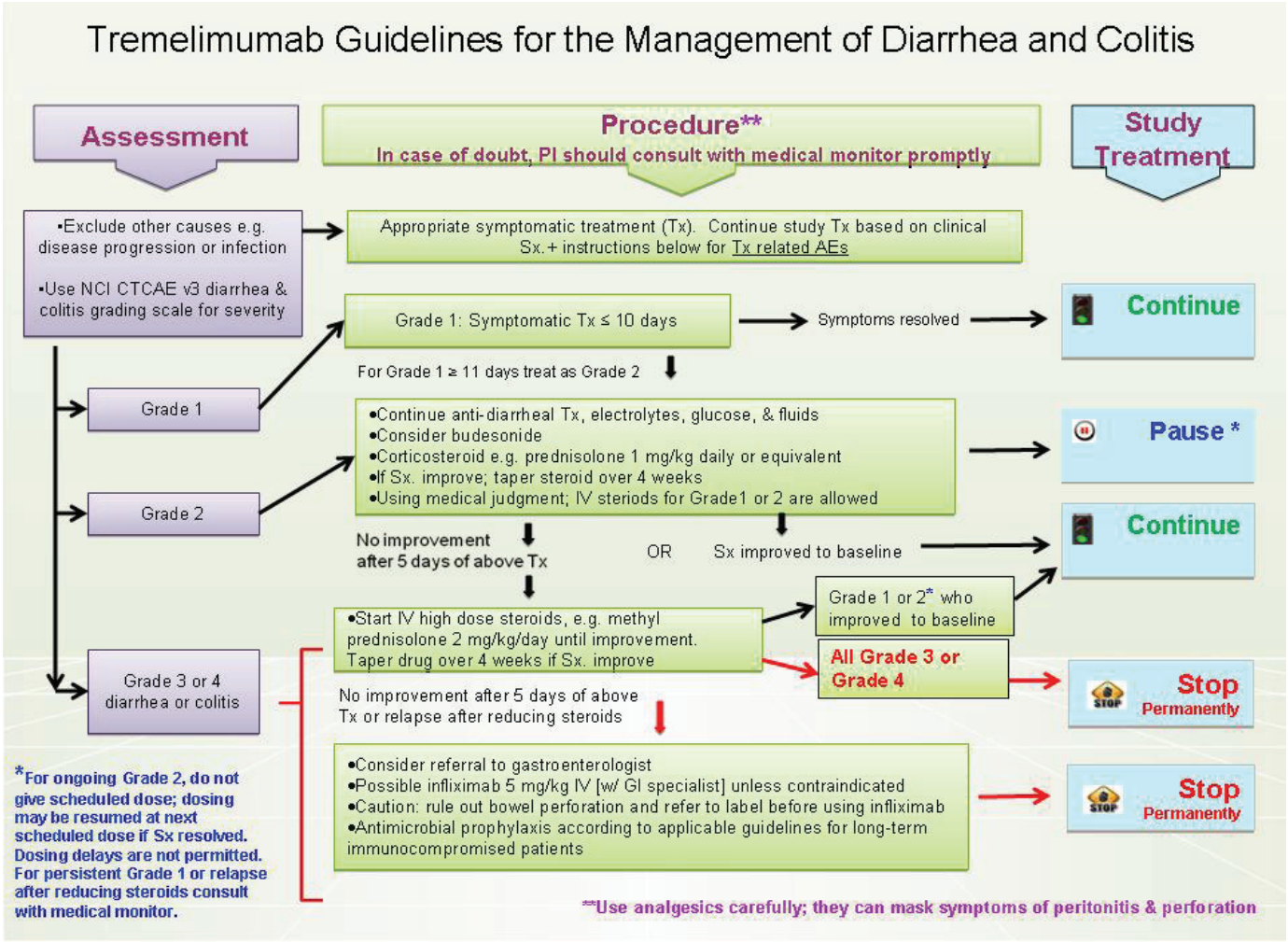


Appendix 6 Diarrhea Management Flowchart



AE = adverse event; GI = gastrointestinal; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PI = principal investigator; Sx = symptom; Tx = treatment; w/ = with.