A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination with Durvalumab versus Nivolumab Monotherapy in Subjects with Select Advanced Malignancies

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PROTOCOL SYNOPSIS

TITLE

A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination with Durvalumab versus Nivolumab Monotherapy in Subjects with Select Advanced Malignancies

HYPOTHESES

Primary hypotheses:

Dose-escalation:

MEDI0680 in combination with durvalumab (MEDI4736) will be adequately tolerated in subjects with select advanced malignancies.

Dose-expansion:

MEDI0680 in combination with durvalumab will have a higher response rate than nivolumab monotherapy in subjects with advanced or metastatic clear cell renal cell carcinoma (ccRCC)

Secondary hypotheses:

Dose-escalation:

MEDI0680 in combination with durvalumab will have antitumor activity in subjects with select advanced malignancies

Dose-expansion:

MEDI0680 in combination with durvalumab will be adequately tolerated in subjects with advanced or metastatic ccRCC

OBJECTIVES

Primary objectives:

Dose-escalation:

To determine the maximum tolerated dose (MTD) or the highest protocol-defined dose in the absence of exceeding the MTD for MEDI0680 in combination with durvalumab and the safety profile of MEDI0680 in combination with durvalumab in subjects with advanced malignancies

Dose-expansion:

To evaluate the antitumor activity of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC as based on investigator assessed response using Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

Secondary objectives:

Dose-escalation:

To evaluate the antitumor activity of MEDI0680 in combination with durvalumab in subjects with advanced malignancies as based on the investigator assessed response using modified RECIST v1.1

Dose-expansion:

To describe the safety and tolerability of MEDI0680 in combination with durvalumab or nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC

To evaluate the antitumor activity of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC as based on blinded independent central review (BICR) assessed response using RECIST v1.1

Dose-escalation and Dose-expansion:

1. To describe the pharmacokinetics (PK) of MEDI0680 in combination with durvalumab
2. To describe the PK of durvalumab in combination with MEDI0680
3. To determine the immunogenicity of MEDI0680 in combination with durvalumab
4. To determine the immunogenicity of durvalumab in combination with MEDI0680
5. To determine whether PD-L1 is a predictive biomarker for response to therapy with MEDI0680 in combination with durvalumab

Exploratory objectives:

1. To identify biomarkers that are predictive of antitumor response to MEDI0680 in combination with durvalumab
2. To profile gene expression changes that may correlate with antitumor response to MEDI0680 in combination with durvalumab
3. To evaluate additional biomarkers that may correlate with antitumor activity of MEDI0680 in combination with durvalumab compared with nivolumab monotherapy
4. To evaluate the pharmacodynamic activity of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in the periphery.
5. To compare the pharmacodynamic changes resulting from complete PD-1/PD-L1 pathway blockade versus treatment with nivolumab monotherapy
6. To evaluate the antitumor activity of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in subjects with advanced or metastatic ccRCC as assessed by immune-related Response Evaluation Criteria in Solid Tumors (irRECIST)

STUDY ENDPOINTS

Primary objectives endpoints:

Dose-escalation:

The primary endpoints for safety assessment include adverse events (AEs) and serious adverse events (SAEs), as well as changes from baseline in laboratory evaluations, vital signs, physical examinations, and electrocardiogram (ECG) results.

Dose-expansion:

The primary endpoint is objective response (OR) of MEDI0680 in combination with durvalumab versus nivolumab monotherapy. Secondary endpoints include best overall response (BOR), disease control (DC), time to response (TTR), duration of response (DR), progression free survival (PFS), change from baseline in tumor size and overall survival (OS). Efficacy endpoints except OS are based on an application of RECIST v1.1 to investigator-assessed tumor measurements.

Secondary objectives endpoints:

Dose-escalation:

The endpoints for assessment of antitumor activity include BOR, OR, DC, TTR, DR, PFS, OS, and change from baseline in tumor size. Antitumor activity analyses except OS will be based on investigator-assessed response using modified RECIST v1.1.

Dose-expansion:

The endpoints for assessment of safety include the presence of AEs and SAEs, as well as changes from baseline in laboratory parameters, vital signs, physical examination, and ECG results.

The endpoints for assessment of antitumor activity include BOR, OR, DC, TTR, DR, PFS, and change from baseline in tumor size as based on BICR-assessed response using RECIST v1.1.

Dose-escalation and Dose-expansion:

- The endpoints for assessment of PK include individual MEDI0680 and durvalumab concentrations in serum. PK parameters include peak concentration (C_{max}) and trough concentration (C_{min})
- The endpoints for assessment of immunogenicity of MEDI0680 and durvalumab include the presence of detectable anti-drug antibodies (ADAs).
- PD-L1 expression / localization on tumor membrane and tumor-infiltrating immune cells within the tumor microenvironment

Exploratory endpoints:

1. The endpoints related to candidate predictive and/or prognostic biomarkers in dose-expansion will focus on tissue-based, protein or gene expression measures and peripheral gene signatures including, but not limited to immunohistochemistry (IHC) measures of markers associated with infiltrating immune cells (eg, cluster of differentiation 80)

2. Gene expression signatures associated with response to therapy will include expression of messenger ribonucleic acid in blood and tumor samples before and after treatment to examine gene expression patterns at baseline and changes in response to treatment. Analysis may also include but is not limited to: evaluation of key oncogenic mutations and/or mutations in immune-related molecules.
3. Levels of circulating free DNA and/or circulating soluble factors which may include cytokines, chemokines, growth factors, soluble receptors, and antibodies against tumor and self-antigens, may be evaluated before and after treatment to evaluate response to treatment with MEDI0680 and durvalumab compared with nivolumab monotherapy
4. Pharmacodynamic assessments of MEDI0680 and durvalumab combination in the periphery include:
    a. Flow cytometric assessment of cell populations such as T cells and B cells before and after treatment to evaluate their association with drug exposure and response to treatment; analysis may include characterization of phenotype, expression of activation markers, proliferation, and production of cytokines and effector molecules
    b. Dose escalation only: Serum soluble PD-L1 levels before and after treatment may be measured to evaluate their association with drug exposure and response to treatment with MEDI0680 and durvalumab
    c. Dose escalation only: MEDI0680 receptor occupancy on peripheral blood T cells before and after treatment may be measured to evaluate associations with drug exposure and response to treatment with MEDI0680 and durvalumab
5. Expression and localization of key molecules such as PD-L1, PD-L2, and PD-1 within the tumor microenvironment, as well as the frequency, localization, and phenotype of tumor-infiltrating lymphocytes, may be examined in biopsy specimens by IHC, immunofluorescence, and/or flow cytometry and correlated with response to treatment
6. Antitumor activity, including OR, DR, DC, and PFS, may be assessed by irRECIST

STUDY DESIGN

This is a multicenter, open-label, Phase 1/2 study to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of MEDI0680 in combination with durvalumab or nivolumab monotherapy in adult immunotherapy-naïve subjects with selected advanced malignancies. The study will be conducted at approximately 50 study centers globally.

The study includes 2 phases, dose-escalation and dose-expansion. In the dose-escalation phase, subjects with selected solid tumors will receive MEDI0680/durvalumab combination therapy. In the dose-expansion phase, subjects with ccRCC will receive either MEDI0680/durvalumab combination therapy or nivolumab monotherapy.

In the dose-escalation phase, subjects may receive treatment for up to 12 months; in the dose expansion phase, subjects may remain on treatment until unacceptable toxicity, confirmed progressive disease (PD), or development of other reason for treatment discontinuation. Subjects in dose expansion may receive study drug(s) for a maximum of 2 years. At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug(s). Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of the sponsor. The sponsor reserves the right to terminate access to study drug if any of the following occur: a) the marketing application is rejected by responsible health authority; b) the study is terminated due to safety concerns; c) the subject can obtain medication from a government sponsored or private health program; or d) therapeutic alternatives become available in the local market. All subjects will be evaluated regularly. Clinical status will be classified according to modified RECIST v1.1 for subjects in the dose-escalation phase and by RECIST v1.1 for subjects in the dose expansion phase, and other disease-specific assessments. All subjects will be followed for survival until the end of study. Adverse events and SAEs will be followed.

In the dose-escalation phase, sequential cohorts of 3 to 6 subjects will be enrolled in 1 of 6 dose-level cohorts: 0.1 mg/kg MEDI0680 Q2W with 3 mg/kg durvalumab Q2W, and increasing dose levels of MEDI0680 Q2W (0.1, 0.5, 2.5, 10, and 20 mg/kg) with 10 mg/kg durvalumab Q2W. The dose-escalation phase will initially include immunotherapy-naïve subjects with solid tumors. As of Protocol Amendment 2, only subjects with non-small cell lung cancer NSCLC, squamous cell carcinoma of the head and neck (SCCHN), microsatellite instability-high (MSI high) colorectal cancer (CRC), bladder cancer, ovarian cancer, esophageal cancer, gastric

cancer, or renal cell carcinoma (RCC) will be enrolled.

The dose-escalation phase will be executed according to a 3 + 3 design. If ≥ 2 of 6 subjects experience a dose limiting toxicity (DLT), a dose level from the intermediate zone-based cohort(s) that does not exceed the MTD or the highest protocol defined dose for each investigational product in the absence of exceeding the MTD may be explored. Based on emerging safety, PK, pharmacodynamic, and clinical activity data for the MEDI0680 Q2W treatment schedule, the dosing interval for MEDI0680 could have been increased to every 4 weeks (Q4W).

Any dose-level cohort in the dose-escalation phase that did not exceed the MTD can be expanded up to a maximum of 18 subjects for further evaluation of safety, PK, pharmacodynamics, and antitumor activity.

Based on 6 dose-level cohorts in the main 3 + 3 dose-escalation design on a Q2W treatment schedule, up to 36 subjects may be enrolled. Additional subjects could be required if dose de-escalation occurs, intermediate dosing using the modified zone-based design is explored or any dose-level cohort is expanded beyond 6 subjects.

As of Protocol Amendment 3, the dose-escalation phase completed enrollment. Subjects were treated through the highest planned dose-level cohort of 20 mg/kg MEDI0680 Q2W in combination with durvalumab Q2W and the MTD was not reached.

The dose-expansion phase will begin after the dose-escalation phase. As of Amendment 5, immunotherapy-naïve subjects with ccRCC will be randomized in a 2:1 ratio to 1 of 2 treatment arms: (1) MEDI0680/durvalumab combination therapy or (2) nivolumab monotherapy. Stratification factors will include the Memorial Sloan Kettering Cancer Center (MSKCC) risk group (0 = favorable risk; 1 or 2 = intermediate risk; 3 = poor risk) and PD-L1 expression status (≤ 1% and > 1%). Up to 40 subjects may be randomized in to the MEDI0680/durvalumab combination therapy arm and up to 20 subjects in the nivolumab monotherapy arm based on evaluation of emerging safety and efficacy parameters in the current study as well as other ongoing studies. An interim futility analyses will be performed for the MEDI0680/durvalumab combination therapy arm in the dose-expansion phase after 20 subjects have been randomized and have reached their second post-baseline disease assessment or have completed study.

An evaluation of a possible correlation between clinical activity of MEDI0680 in combination with durvalumab or nivolumab and potential biomarkers (eg, PD-L1 expression on tumor) will be ongoing throughout the study. Randomization into the dose expansion phase may be discontinued at the discretion of the sponsor should emerging clinical or pre-clinical data suggest that continued treatment may not be beneficial.

TARGET SUBJECT POPULATION

For the dose-escalation phase, subjects will be immunotherapy-naïve adults with selected solid tumors who are refractory or intolerant to standard therapy or for which no standard therapy exists. As of Protocol Amendment 2, only subjects with NSCLC, SCCHN, MSI-high CRC, bladder cancer, ovarian cancer, esophageal cancer, gastric cancer, or RCC will be enrolled. No more than 3 prior lines of systemic therapy in the recurrent or metastatic setting, including standard and investigational agents, will be allowed.

For the dose-expansion phase, subjects will be immunotherapy-naïve adults with advanced or metastatic RCC with a clear cell component who have received and experienced disease progression after at least 1 and no more than 2 prior anti-angiogenic therapy regimens (including, but not limited to, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab) in the advanced or metastatic setting; must have received no more than 3 total prior systemic treatment regimens in the advanced or metastatic setting (prior mammalian target of rapamycin [mTOR] regimens are not allowed); and must have evidence of radiographic progression on or after the last treatment regimen received within 6 months prior to study enrollment.

Subjects in the dose-expansion phase will be required to provide formalin fixed paraffin embedded archival or fresh tumor tissue deemed to be evaluable for PD-L1 expression status in order to be randomized to study treatment. Subjects will not be excluded based on PD-L1 status. Subjects with non-evaluable PD L1 status will be excluded.

INVESTIGATIONAL PRODUCT, DOSAGE, AND MODE OF ADMINISTRATION

Subjects will be treated in either the dose-escalation or dose-expansion phase. Both MEDI0680 and durvalumab will be administered via IV infusion. Nivolumab will be administered per the dosing information in the package insert. In the dose-escalation phase, sequential cohorts of subjects will receive 1 of 6 MEDI0680/durvalumab combination dose levels: 0.1 mg/kg MEDI0680 Q2W with 3 mg/kg durvalumab Q2W, or increasing dose levels of MEDI0680 Q2W (0.1, 0.5, 2.5, 10, and 20 mg/kg) with 10 mg/kg durvalumab Q2W. Subjects will remain on

treatment for up to 12 months. Subjects in the dose-escalation phase who achieve and maintain DC (ie, CR, PR, or stable disease SD) through the end of the 12-month treatment period will enter follow-up. During the first 12 months of follow-up, if the subject has PD, the subject may be re-administered MEDI0680 and durvalumab for up to another 12 months with the same treatment guidelines followed during the initial 12-month period if the subject fulfills the criteria for retreatment in the setting of PD, has not received other anticancer treatments for their disease, and does not meet any of the investigational product discontinuation criteria. Only 1 round of retreatment will be allowed.

In the dose-expansion phase, subjects will receive either 20 mg/kg MEDI0680 in combination with 750 mg (fixed dose) durvalumab Q2W or nivolumab Q2W monotherapy. Subjects in the dose-expansion phase will remain on treatment until unacceptable toxicity, confirmed PD, or development of other reason for treatment discontinuation.

Prior to the removal of a MEDI0680 monotherapy arm in this protocol amendment, some subjects were randomized and began receiving MEDI0680 monotherapy. These subjects are to continue receiving 20 mg/kg MEDI0680 Q2W monotherapy until unacceptable toxicity, confirmed progressive disease (PD), or development of other reason for treatment discontinuation and will follow the schedule of study procedures for MEDI0680/durvalumab combination therapy.

In the event of an initial assessment of PD (based on RECIST v1.1) in either the dose-escalation or dose-expansion phases, a subject may continue to receive the assigned study treatment until confirmation of PD if the subject fulfills the criteria for treatment in the setting of PD and does not meet any of the investigational product discontinuation criteria. If the lesions included in the tumor burden subsequently regress to the extent that the criteria for PD are no longer met, then treatment may continue according to the treatment schedule. Initial observation of PD must be confirmed by a subsequent scan no earlier than 4 weeks from the initial scan. Subjects with confirmed PD must discontinue treatment.

STATISTICAL ANALYSIS PLAN

Sample Size

Initially, a total of approximately 96 subjects could be required for both dose-escalation and dose-expansion phases of the study.

For dose-escalation (enrollment completed), the number of subjects will depend upon the toxicities observed as the study progresses. Up to approximately 36 evaluable subjects could be required by the 3 + 3 design with 6 dose cohorts in the main dose escalation design. Additional subjects could be required if dose de-escalation occurs, intermediate dosing using the modified zone-based design is explored, the dosing interval of MEDI0680 is changed, or expansion of a dose-escalation cohort occurs. Subjects in the dose escalation phase are considered evaluable if they receive the protocol-assigned doses of both durvalumab and MEDI0680, and complete the DLT-evaluation period or experience a DLT during the DLT-evaluation period. Non-evaluable subjects will be replaced. The table below provides the probability of dose-escalation to the next higher level for each underlying true DLT rate. For example, for a common toxicity that occurs in 10% of subjects, there is a greater than 90% probability of escalating to the next higher dose level. Conversely, for a toxicity that occurs with a rate of 60%, the probability of escalating to the next higher dose level is less than 10%.

Probability of Escalating Dose for Different True Underlying Dose-limiting Toxicity Rate at Given Dose Level

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

For dose-expansion, up to approximately 60 subjects (40 subjects in the MEDI0680/durvalumab combination therapy arm and 20 subjects in the nivolumab monotherapy arm) may be randomized at the selected combination dose (ie, MTD or highest protocol-defined dose for each agent in the absence of exceeding the MTD) in a 2:1 ratio. The primary objective of the dose-expansion phase is to evaluate the antitumor activity based on objective response rate (ORR) of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC based on an application of RECIST v1.1 to investigator-assessed tumor measurements. Assuming an ORR for nivolumab monotherapy of 21.5%, the sample size is chosen to detect a difference in ORR of 26.0% (ie, ORR = 47.5%) with 76% power at a 1-sided significance level of 0.10. The 95% confidence interval of a 47.5% ORR (19 responders / 40 subjects)

is 31.5%, 63.9%).

Safety

The MTD evaluation will be based on the DLT-evaluable Population (Q2W schedule) which includes all subjects enrolled in the dose-escalation phase who receive 2 protocol-assigned doses of durvalumab and MEDI0680 and complete the safety follow-up through the end of the DLT-evaluation period, or experience a DLT during the DLT-evaluation period (defined as the time period starting with the first dose of study drugs until the planned administration of the third dose of durvalumab and MEDI0680).

The safety evaluation will be based on the As-treated Population and will include AEs, SAEs, laboratory evaluations, vital signs, and physical examinations. Summary statistics will be provided for AEs, SAEs, and AE grade, severity, and relationship to investigational product, reported from the start of treatment with durvalumab and MEDI0680 or nivolumab. Adverse events will be graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) v4.03 and described by system organ class using the Medical Dictionary for Regulatory Activities preferred term. Laboratory abnormalities with toxicity grades according to the NCI CTCAE v4.03 will be derived and summarized. Safety analyses will be descriptive in nature and no formal statistical comparison will be made.

Efficacy

For the dose-escalation phase, efficacy analyses will be based on an application of modified RECIST v1.1 to investigator-assessed tumor measurements. RECIST v1.1 has been modified to require confirmation of PD. A confirmed PD will be a PD confirmed by a consecutive repeat assessment no fewer than 4 weeks later. A PD that occurs without follow-up scans to provide confirmation or only non-evaluable follow-up scans will also be considered a confirmed PD. The efficacy analysis will be based on the As-treated Population.

For the dose-expansion phase, efficacy analyses will be based on an application of RECIST v1.1 to investigator-assessed tumor measurements and BICR. The efficacy analysis will be based on the As-treated Population.

The following efficacy endpoints will be analyzed. More details will be provided in the statistical analysis plan.

- ORR is defined as the proportion of subjects with a BOR of confirmed CR or confirmed PR. ORR will be estimated with a 95% CI using the exact probability method. For the dose-expansion phase, comparison of arms will be obtained from Fisher's exact test.
- DCR16 is defined as the proportion of subjects with a BOR of confirmed CR, confirmed PR, or SD (maintained for ≥ 16 weeks). A similar definition applies to DCR24. DCR16 and DCR24 will be estimated with a 95% CI using the exact probability method.
- TTR is defined as the time from the first dose of treatment until the first documentation of a subsequently confirmed objective response. Only subjects who have achieved OR will be evaluated for TTR. The median TTR and its 95% CI will be assessed using the Kaplan-Meier method.
- DR is defined as the time from the first documentation of a subsequently confirmed objective response until the first documentation of a disease progression (subsequently confirmed for dose escalation phase) or death due to any cause, whichever occurs first. Only subjects who have achieved OR will be evaluated for DR. The median DR and its 95% CI will be estimated using the Kaplan-Meier method.
- PFS is defined as the time from the first dose of treatment until the first documentation of a disease progression (subsequently confirmed for dose escalation phase) or death due to any cause, whichever occurs first. The median PFS and its 95% CI will be estimated using the Kaplan-Meier method. The Kaplan-Meier method will be used to estimate the PFS curve and the PFS rate at time points of interest.
- OS is defined as the time from the first dose of treatment with durvalumab and MEDI0680 or nivolumab until death due to any cause. The median OS and its 95% CI will be estimated using the Kaplan-Meier method. The Kaplan-Meier method will be used to estimate the OS curve and the OS rate at time points of interest.

Immunogenicity

Only subjects who receive at least one dose of both durvalumab and MEDI0680 and provide at least one posttreatment sample will be evaluated. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-durvalumab or anti-MEDI0680 antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-durvalumab or anti-MEDI0680 antibodies. The impact of ADAs on PK and pharmacodynamics will also be assessed if data

allow. Samples will be collected and banked for evaluating neutralizing capacity of ADAs in the future.

Pharmacokinetics

Only subjects who receive at least one dose of investigational product and provide at least one posttreatment sample will be evaluated. Individual durvalumab and MEDI0680 concentrations will be tabulated by dose cohort along with descriptive statistics. The PK of durvalumab and MEDI0680 will be assessed using parameters including C_{max} and C_{min} after the first dose. Durvalumab and MEDI0680 steady-state PK parameters including concentrations at peak concentration at steady state ($C_{max,ss}$) and trough concentration at steady state ($C_{min,ss}$) will be estimated. Accumulation to steady state will be assessed as the ratio of $C_{max,ss}$:C_{max} and $C_{min,ss}$:C_{min}. All PK parameters will be estimated by non-compartmental analysis. Descriptive statistics of non-compartmental PK parameters will be provided.

Exploratory Analyses

Descriptive statistics will be the primary methods for the exploratory analyses. Depending on the nature of the data, geometric mean and other appropriate statistical summaries might be used as well. Tumor responses by irRECIST, immune-related complete response, immune-related partial response, immune-related stable disease, and immune-related progressive disease will be summarized and analyzed descriptively. Tumor response by irRECIST will be compared with that by RECIST v1.1. The irRECIST is similar to RECIST v1.1 except that measurements of the new lesions are included in the sum of the measurements of all target lesions and do not automatically constitute progressive disease under irRECIST, whereas new lesions are not measured and automatically constitute progressive disease under RECIST v1.1.

Interim Analysis

An interim futility analyses will be performed for the MEDI0680/durvalumab combination therapy arm in the dose-expansion phase after 20 subjects have been randomized and have reached their second post-baseline disease assessment or have completed study. Subject accrual may be paused in both cohorts to evaluate the MEDI0680/durvalumab combination therapy arm for futility. Continued randomization of subjects in both arms will be terminated if 2 (10%) or fewer responses within the MEDI0680/durvalumab combination arm are observed. For the futility analysis, a response is defined as either a confirmed or unconfirmed CR or PR as per RECIST v1.1.

TABLE OF CONTENTS

LIST OF IN-TEXT TABLES

LIST OF IN-TEXT FIGURES

LIST OF APPENDICES

LIST OF ABBREVIATIONS

Abbreviation or Specialized Term	Definition
ADA	anti-drug antibody
AE	adverse event
AESI	adverse event of special interest
ALK	anaplastic lymphoma kinase
ALT	alanine aminotransferase
APC	antigen-presenting cells
AST	aspartate aminotransferase
BICR	blinded independent central review
BOR	best overall response
BP	blood pressure
ccRCC	clear-cell renal cell carcinoma
CD80	cluster of differentiation 80
CI	confidence interval
C_{max}	peak concentration
$C_{max,ss}$	peak concentration at steady state
C_{min}	trough concentration
$C_{min,ss}$	trough concentration at steady state
CNS	central nervous system
CR	complete response and remission
CRC	colorectal cancer
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen 4
DC	disease control
DCR	disease control rate
DEHP	di(2-ethylhexyl) phthalate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
EGFR	epidermal growth factor receptor
EOI	end of infusion
EOT	end of treatment
EU	European Union
FAAN	Food Allergy and Anaphylaxis Network
FACT-G	Functional Assessment of Cancer Therapy General

Abbreviation or Specialized Term	Definition
Fc	fragment crystallizable
FFPE	formalin fixed paraffin embedded
FTIH	first-time-in-human
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IF	immunofluorescence
IFN	interferon
IGF	insulin-like growth factor
IgG	immunoglobulin G
IHC	immunohistochemistry
IL	interleukin
imAE	immune-mediated adverse event
IPSS	International Prognostic Scoring System
IRB	Institutional Review Board
irRECIST	immune-related Response Evaluation Criteria in Solid Tumors
IV	intravenous(ly)
IVBP	intravenous bag protectant
IXRS	interactive voice response system/interactive web response system (collectively)
KRAS	Kirsten rat sarcoma oncogene homolog
mAb	monoclonal antibody
MDS	myelodysplastic syndrome
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MSI-high	microsatellite instability-high
MSKCC	Memorial Sloan Kettering cancer center
MTD	maximum tolerated dose
mTOR	mammalian target of rapamycin
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
NRAS	neuroblastoma RAS viral oncogene homologue
NSCLC	non-small cell lung cancer
OR	objective response

Abbreviation or Specialized Term	Definition
ORR	objective response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PEF	peak expiratory flow
PFS	progression-free survival
PK	pharmacokinetic(s)
PR	partial response
PT	prothrombin time
PTPN11	Protein tyrosine kinase phosphatase non-receptor Type 11
Q2W	every 2 weeks
Q3W	every 3 weeks
Q4W	every 4 weeks
RANKL	receptor activator of nuclear factor kappa-B ligand
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	serious adverse event
SCCHN	squamous cell carcinoma of the head and neck
SD	stable disease
SHP2	Src homology domain containing phosphatase 2
SID	subject identification
sPD-L1	soluble programmed cell death ligand 1
TKI	tyrosine kinase inhibitor
TNF-α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
TTR	time to response
ULN	upper limit of normal
US or USA	United States
USP	US Pharmacopeia
WFI	water for injection
WT	weight
w/v	weight per volume

1 INTRODUCTION

1.1 Immunotherapy

In the United States (US), cancer is the second most common cause of death after heart disease, accounting for nearly 1 in every 4 deaths (Siegel et al, 2013). There has been a 20% lower death risk rate from cancer in 2009 in comparison to 1991, likely reflecting progress in diagnosing certain cancers earlier and improvements in treatment (Siegel et al, 2013). Unfortunately, despite this progress, there continues to be an unmet medical need for more effective and less toxic therapies, especially for patients with advanced refractory disease.

Recent advances in immunotherapy offer promise for improving clinical outcomes in patients with advanced malignancies. It is increasingly appreciated that cancers are recognized by the immune system, and under some circumstances, the immune system may control or even eliminate tumors (Dunn et al, 2004). Studies in mouse models of transplantable tumors have demonstrated that manipulation of co-stimulatory or co-inhibitory signals can amplify T-cell responses against tumors (Peggs et al, 2009). This may be accomplished by blocking co-inhibitory molecules such as cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) or programmed cell death 1 (PD-1) from binding with their ligands, B7 or B7-H1 (programmed cell death ligand 1 [PD-L1]).

The human CTLA-4 blocking antibody ipilimumab has demonstrated an overall survival (OS) benefit in two Phase 3 studies (Hodi et al, 2010; Robert et al, 2011). Based on these data, ipilimumab was approved in 2011 by the US Food and Drug Administration and the European Medicines Agency for the treatment of advanced (unresectable or metastatic) melanoma. Ipilimumab, in a sequenced combination with carboplatin and paclitaxel, improved clinical outcomes in non-small cell lung cancer (NSCLC) compared to carboplatin and paclitaxel alone (Lynch et al, 2012). Additionally, clinical activity across a range of tumor types, including NSCLC, for PD-1 blocking and PD-L1 blocking antibodies have been reported from Phase 1 studies (Brahmer et al, 2010; Brahmer et al, 2012; Topalian et al, 2012; Hamid et al, 2013).

1.2 MEDI0680 and Durvalumab (MEDI4736) Background

1.2.1 MEDI0680 Background

MEDI0680 is a humanized modified IgG4 kappa monoclonal antibody (mAb) specific for human PD-1. MEDI0680 may help to promote an effective anti-tumor immune response by two mechanisms. Like other anti-PD-1 antibodies in clinical development, MEDI0680 blocks

the interactions between PD-1 and its ligands (PD-L1 and programmed cell death ligand 2 [PD-L2]), thereby relieving inhibitory signaling downstream of PD-1. In addition, MEDI0680 improves the intrinsic functionality of T cells by triggering internalization of PD-1, thereby reducing levels of cell-surface PD-1 and membrane proximal Src homology domain containing phosphatase 2 (SHP2), also known as protein tyrosine phosphatase non-receptor type 11 (PTPN11). This mechanism has not been described for other PD-1 targeted agents and may be unique to MEDI0680 (AMP 514).

1.2.2 Durvalumab Background

Durvalumab is a human immunoglobulin G (IgG) 1 kappa mAb directed against human PD-L1. Durvalumab selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and cluster of differentiation 80 (CD80). The fragment crystallizable (Fc) domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fcγ receptors responsible for mediating antibody-dependent cell-mediated cytotoxicity (Oganesyan et al, 2008).

1.3 Summary of Nonclinical Experience

Programmed cell death 1 (CD279) is a member of the immunoglobulin superfamily of molecules involved in regulation of T-cell activation. Programmed cell death 1 expression is induced in activated T cells and is strongly upregulated following chronic antigen stimulation in the context of chronic infections and cancer. Programmed cell death 1 is also expressed on activated B cells and can be induced on natural killer (NK) cells, dendritic cells, and monocytes. Programmed cell death 1 binds to 2 ligands, PD-L1 (CD274) and PD-L2 (CD273). Programmed cell death ligand 1 binds to two receptors, PD-1 and CD80 (B7-1), while PD-1 is the only known receptor for PD-L2 apart from RGMb. Programmed cell death ligand 1 is widely expressed and can be induced in many hematopoietic and non-hematopoietic cells in response to inflammatory stimuli, especially interferon (IFN)-γ. It is expressed in a variety of normal tissues and in both solid and hematologic tumors. It has also been described on peripheral tissues including cardiac endothelium, lung, small intestine, keratinocytes, islet cells of the pancreas, and syncytiotrophoblasts in the placenta as well as a variety of tumor cell types (Hamanishi et al, 2007; Inman et al, 2007; Ishida et al, 2002; Keir et al, 2008; Latchman et al, 2001; Liu et al, 2007; Nakanishi et al, 2007; Ohigashi et al, 2005; Parsa et al, 2007; Schreiner et al, 2004; Thompson et al, 2004; Yamazaki et al, 2002). Programmed cell death ligand 2 expression is more limited; it is largely restricted to subsets of B cells, monocytes, dendritic cells, and macrophages, where it is induced by T-helper cell 2 cytokines such as interleukin (IL)-4. Programmed cell death ligand 2 expression has also been reported in the lung, certain cancers, and cancer-associated fibroblasts. CD80 is

primarily expressed by professional antigen-presenting cells (APC), including B cells, dendritic cells, and monocytes, and can also be expressed on T cells. CD80 expression is generally low in the tumor microenvironment; however CD80 is present on APC in the draining lymph nodes (Blank, 2014; Hamid and Carvajal, 2013; Kamphorst and Ahmed, 2013; Maj et al, 2013; Quezada and Peggs, 2013).

Engagement of PD-1 on T cells inhibits activation with downstream effects on cytokine production, proliferation, cell survival, and transcription factors associated with effector T-cell function (Bennett et al, 2003; Carter et al, 2002; Fife and Bluestone, 2008; Freeman et al, 2000; Nurieva et al, 2006; Saunders et al, 2005).

1.3.1 MEDI0680 Nonclinical Experience

The pharmacology of MEDI0680 has been studied in a variety of in vitro and in vivo systems to support its use as an investigational drug in oncology. MEDI0680 binds to human PD-1 with an affinity of 2.4 nM, determined using flow cytometry saturation binding experiments. MEDI0680 blocks the interactions between PD-1 and its ligands, PD-L1 and PD-L2; the half maximal inhibitory concentrations are 2.6 and 3.6 nM, respectively. MEDI0680 is internalized following binding to PD-1, while appreciable internalization was not observed with comparator anti PD-1 antibodies. Both blocking and internalization may contribute to the functional activity of MEDI0680.

In the single-dose and repeat-dose toxicology studies of MEDI0680 performed in cynomolgus monkeys, there were no test-article effects on mortality, clinical observations, body weights, food consumption, ophthalmology, cardiovascular profiling, electrocardiography, hematology, urinalysis, gross pathology or organ weights. The most notable finding was a test article-related increase in prothrombin time (PT), which was observed on Study Day 3, Study Day 31, and Study Day 100 in males and females given $\geq$ 1 mg/kg MEDI0680. This finding was considered non-adverse, as values remained within the historical control range and there were no correlating findings. The increase in PT was partially reversible.

Please refer to the current Edition of the Investigator's Brochure for additional information.

1.3.2 Durvalumab Nonclinical Experience

Durvalumab has shown the following activity as an anti-PD-L1 molecule:

- Durvalumab binds to PD-L1 and blocks its interaction with PD-1 and CD80
- Durvalumab can relieve PD-L1-mediated suppression of human T-cell activation in vitro

- Durvalumab inhibits human tumor growth in a xenograft model via a T-cell dependent mechanism
- A surrogate anti-mouse PD-L1 antibody resulted in improved survival in a syngeneic tumor model as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy

In general, there were no durvalumab-related adverse effects in toxicology studies conducted in cynomolgus monkeys with durvalumab that were of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) pharmacokinetic (PK)/pharmacodynamic and dose range-finding study (4 doses over 5 weeks), and a GLP 4-week repeat-dose toxicity study were consistent with anti-drug antibody (ADA)-associated morbidity and mortality in individual animals. The spectrum of findings, especially the microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA:durvalumab immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry study. Similar effects have been observed by MedImmune in cynomolgus monkeys administered human mAbs unrelated to durvalumab. Given that immunogenicity of human mAbs in nonclinical species is not generally predictive of responses in humans, the ADA-associated morbidity and mortality were not taken into consideration for the determination of the no-observed-adverse-effect level (NOAEL) of durvalumab. In the GLP 13-week IV repeat-dose toxicity study, treatment with durvalumab was not associated with any adverse effects. Therefore, the NOAEL of durvalumab in all the general toxicity studies was considered to be 200 mg/kg loading dose followed by 4 or 13 weekly doses of 100 mg/kg, respectively, the highest dose tested in these studies. In addition to the in vivo toxicology data, no unexpected membrane binding of durvalumab to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues. In vitro cytokine release studies showed that durvalumab did not induce cytokine release in blood from any donor. Additionally, an enhanced pre- and postnatal development study in cynomolgus monkeys showed that treatment with durvalumab from confirmation of pregnancy until natural delivery was not associated with maternal toxicity, effects on pregnancy outcome, embryofetal development, or effects on infant growth and development during the 6 month postnatal phase.

1.4 Summary of Clinical Experience

Clinical experience with durvalumab and MEDI0680 is briefly described below. Refer to the current Investigator's Brochures for details.

1.4.1 MEDI0680 Clinical Experience

Study D6020C00001

In Study D6020C00001, the dose-escalation phase for immunotherapy-naïve subjects is complete. All dose-level cohorts were enrolled and 30 subjects were exposed to MEDI0680 in combination with durvalumab. Dose levels included 0.1 mg/kg MEDI0680 Q2W with 3 mg/kg durvalumab Q2W, and increasing doses of MEDI0680 Q2W (0.1, 0.5, 2.5, 10, and 20 mg/kg) with 10 mg/kg durvalumab Q2W. The maximum tolerated dose (MTD) was not identified and the highest combination dose level administered was 20 mg/kg MEDI0680 Q2W with 10 mg/kg durvalumab Q2W. The study is ongoing and data are included as of the data cut-off date of 30Nov2016. One subject received MEDI0680 20 mg/kg Q2W in combination with durvalumab 750 mg Q2W in dose expansion. Two subjects received MEDI0680 20 mg/kg monotherapy in dose expansion.

The mean (range) exposure to MEDI0680 in combination with durvalumab as of the data cut-off date was 23.9 (2 to 52) weeks.

Across all cohorts of subjects receiving MEDI0680 in combination with durvalumab, the most frequently reported AEs (≥ 5 subjects), regardless of causality, were anemia, arthralgia, back pain, constipation, cough, decreased appetite, diarrhea, dyspnea, edema peripheral, fatigue, nausea, pruritus, pyrexia, rash, upper respiratory tract infection, and vomiting. There was no trend towards a dose relationship in incidence of AEs.

A total of 18 (58.1%) subjects receiving MEDI0680 in combination with durvalumab in the As-treated Population had at least 1 AE ≥ Grade 3 in severity (regardless of causality). All of these events were Grade 3.

AEs ≥ Grade 3 considered related to MEDI0680 or durvalumab according to the investigator were reported in 6 (19.4%) subjects receiving MEDI0680 in combination with durvalumab in the As-treated Population. These included: increased lipase (0.1 mg/kg MEDI0680 Q2W + 3 mg/kg durvalumab Q2W and 10 mg/kg MEDI0680 Q2W + durvalumab 10 mg/kg Q2W); prolonged ECG QT (0.5 mg/kg MEDI0680 Q2W + 10 mg/kg durvalumab Q2W); and increased alanine aminotransferase (ALT), increased aspartate aminotransferase (AST), atrial fibrillation, increased γ-glutamyltransferase, and nausea (10 mg/kg MEDI0680 Q2W + 10 mg/kg durvalumab Q2W).

A dose limiting toxicity (DLT) was reported in 1 subject (10 mg/kg MEDI0680 Q2W + 10 mg/kg durvalumab Q2W). The subject had Grade 3 increased ALT and Grade 3 increased AST; both considered related to MEDI0680 and durvalumab by the investigator. Study

treatment was discontinued and the events resolved. Dose escalation continued to the highest protocol defined dose. The MTD was not identified.

Overall, 10 (32.3%) subjects receiving MEDI0680 in combination with durvalumab died during the study; 9 died due to disease under study and 1 due to "other" reason. Twelve subjects experienced treatment emergent serious adverse events (SAEs), of whom 3 subjects had events considered related to MEDI0680 and durvalumab by the investigator. A total of 7 (22.6%) subjects receiving MEDI0680 in combination with durvalumab permanently discontinued investigational product as a result of an AE. No AEs leading to discontinuation were reported in more than 1 subject across cohorts. AEs included: ALT increased, AST increased, blood alkaline phosphatase increased, dyspnea, ECG QT prolonged, headache, intracranial mass, and pleural effusion.

As of the data cut-off date across all cohorts in subjects receiving MEDI0680 in combination with durvalumab, 1 (3.2%) subject had a confirmed complete response (CR) and 8 (25.8%) subjects had a confirmed partial response (PR). The objective response rate (ORR) was 29.0% (95% CI 14.2%, 48.0%). The rate of disease control (DC; CR + PR + stable disease for ≥ 8 weeks) was 48.4% (15 subjects; 95% CI 30.2%, 66.9%).

Study D6020C00002

As of 30Nov2016, 58 subjects received MEDI0680 monotherapy. All cohorts except dose de-escalation 3 mg/kg Q2W were enrolled. Dose levels included 0.1, 0.5, 2.5, 10, and 20 mg/kg Q3W, 10 and 20 mg/kg Q2W, 20 mg/kg QW × 2 and 20 mg/kg QW × 4. Enrollment was completed in August 2015 and the study is ongoing. Overall, mean (range) exposure as of the data cut-off date was 23.1 (2 to 105) weeks.

Across all cohorts, the most frequently reported AEs (≥ 10 subjects; regardless of causality) were arthralgia, anemia, asthenia, constipation, decreased appetite, dyspnea exertional, fatigue, nausea, pyrexia and vomiting. A total of 35 (60.3%) subjects in the As-treated Population had at least 1 AE ≥ Grade 3 in severity regardless of causality. The majority of these events were Grade 3. Six subjects experienced Grade 4 AEs: hyperbilirubinemia (0.5 mg/kg MEDI0680 Q3W), lacunar infarction (0.5 mg/kg MEDI0680 Q3W), atrial fibrillation (10 mg/kg MEDI0680 Q3W), myositis and blood creatinine phosphokinase increased (both events in the same subject; 20 mg/kg MEDI0680 Q2W), sepsis and respiratory distress (both events in the same subject; 20 mg/kg MEDI0680 Q2W) and pulmonary embolism (20 mg/kg MEDI0680 QW x 4).

The database includes 2 subjects with a Grade 5 AE. One subject died from superior vena cava syndrome (0.1 mg/kg MEDI0680 Q3W), and 1 subject died from respiratory failure (20 mg/kg MEDI0680 Q2W). Neither AE was considered related to MEDI0680. Overall, 18 (31.0%) subjects died during the study; the additional 16 subjects died due to disease under study. Twenty-nine (50.0%) subjects experienced treatment emergent SAEs, of whom 8 had events considered related to MEDI0680 by the investigator.

AEs ≥ Grade 3 considered related to MEDI0680 according to the investigator were reported in 12 (20.7%) subjects in the As-treated Population. These included: anemia, autoimmune hepatitis, fatigue, increased ALT, increased AST, and increased blood alkaline phosphatase (0.5 mg/kg MEDI0680 Q3W); anemia, asthenia, dehydration, fatigue, hypercalcemia, and increased lipase (20 mg/kg MEDI0680 Q3W); abdominal pain, anemia, arthralgia, blood creatinine phosphokinase increased, increased AST, diarrhea, hyperkalemia, hypertension, myasthenia gravis, myositis and urinary tract infection (20 mg/kg MEDI0680 Q2W); and anemia (20 mg/kg MEDI0680 QW × 4).

An MTD was not identified and the highest dose administered was MEDI0680 20 mg/kg Q2W.

A total of 13 (22.4%) subjects permanently discontinued MEDI0680 as a result of an AE, with no apparent relationship to MEDI0680 dose level. Events reported in more than 1 subject across cohorts included increased blood creatinine and fatigue (2 subjects each).

Assessment of antitumor response was based on Response Evaluation Criteria in Solid Tumors (RECIST) v1.1 (Eisenhauer et al, 2009). Across all cohorts, 1 (1.7%) subject had a confirmed CR, 8 (13.8%) subjects had a confirmed PR, and 1 (1.7%) subject had an unconfirmed PR. For these 10 subjects, the ORR was 17.2% (95% confidence interval [CI] 8.6%, 29.4%). The ORR with confirmed CR and confirmed PR was 15.5% (9 subjects; 95% CI 7.3%, 27.4%). The rate of DC (CR + PR + stable disease for ≥ 8 weeks) was 39.7% (23 subjects; 95% CI 27.0%, 53.4%).

1.4.2 Durvalumab Clinical Experience

As of the data cut-off date of 12Jul2016 reported in the current durvalumab (MEDI4736) Investigator's Brochure, an estimated 5,225 subjects have been exposed to one or more doses of durvalumab in AstraZeneca or MedImmune sponsored studies, either as monotherapy or in combination, including 2,878 subjects in open-label trials, and 2,347 subjects as an estimate based on the randomization scheme in studies where the treatment arm is blinded. Additionally, more than 1,700 subjects have been exposed to one or more doses of

durvalumab in externally sponsored/investigator-initiated clinical trials. Of the 2,878 subjects exposed to durvalumab in ongoing AstraZeneca- or MedImmune-sponsored open-label studies, 1,744 received durvalumab monotherapy, 808 received durvalumab in combination with tremelimumab, 140 received durvalumab in combination with other investigational products and 186 received durvalumab in combination with approved products. No study has been terminated prematurely due to toxicity.

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Most adverse drug reactions seen with the immune checkpoint inhibitor class of agents are thought to be due to the effects of inflammatory cells on specific tissues. These immune-mediated risks seen with immune checkpoint inhibitors such as durvalumab can include gastrointestinal AEs such as colitis and diarrhea, pancreatitis, pneumonitis/interstitial lung disease, renal AEs such as nephritis and increases in serum creatinine, hepatic AEs such as hepatitis and liver enzyme elevations, dermatitis/rash, endocrinopathies such as hypo- and hyper-thyroidism, hypophysitis, adrenal insufficiency and type I diabetes mellitus, and neurotoxicities such as myasthenia gravis and Guillain Barre syndrome. These events are manageable by available/established treatment guidelines as described in the toxicity management guidelines contained in each of the study protocols.

Data from Study CD-ON-MEDI4736-1108 (durvalumab monotherapy) is presented below. Please refer to the durvalumab Investigator's Brochure for data from all studies.

Study CD-ON-MEDI4736-1108

Study CD-ON-MEDI4736-1108 is a Phase 1/2, first-time-in-human (FTIH), multicenter, open-label, dose-exploration, dose-escalation, and dose-expansion study to determine the maximum tolerated dose (MTD) or optimal biologic dose, safety, PK, pharmacodynamics, immunogenicity, and antitumor activity of durvalumab in adult subjects with advanced solid tumors refractory to standard therapy or for which no standard therapy exists. A total of 1,012 subjects with advanced solid tumors have been treated in Study CD-ON-MEDI4736-1108 as of 24Jul2016. Of these subjects, 970 have received durvalumab at 10 mg/kg every 2 weeks (Q2W), either in the dose-escalation or dose-expansion phase of the study. The 10 mg/kg Q2W cohort comprises subjects with NSCLC, urothelial carcinoma, squamous cell carcinoma of head and neck (SCCHN), microsatellite instability high, gastroesophageal cancer, ovarian cancer, hepatocellular carcinoma (HCC), pancreatic adenocarcinoma, triple-negative breast cancer , uveal melanoma, non-SCCHN

human papilloma virus (positive) , advanced cutaneous melanoma, small cell lung cancer, glioblastoma multiforme, soft tissue sarcoma, and nasopharyngeal carcinoma. Subjects in the 10 mg/kg Q2W dose cohort were exposed to a median of 6 doses of durvalumab (range, 1–27).

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. The safety profile of durvalumab monotherapy in the 970 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108 was manageable and generally consistent with the known safety profile of the anti-PD-L1/PD-1 drug class. Immune-mediated AEs were manageable and generally reversible by delaying or interrupting the durvalumab dose, treating with immunosuppression and/or endocrine therapy per the toxicity management guidelines, or, infrequently, by permanently discontinuing durvalumab treatment.

As of 24Jul2016, among the 970 subjects treated with durvalumab 10 mg/kg Q2W in Study CD-ON-MEDI4736-1108, a total of 554 subjects (57.1%) experienced a treatment-related AE, with the most frequent (occurring in ≥ 5% of subjects) being fatigue (18.7%), nausea (7.9%), diarrhea (7.6%), pruritus (6.8%), decreased appetite (6.7%), hypothyroidism (6.3%) and rash (6.0%). The majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with Grade 3 or higher AEs reported in 88 subjects (9.4%). Treatment-related ≥ Grade 3 or 4 events reported in ≥ 2 subjects were fatigue (1.6%), increased AST (1.0%), increased ALT (0.8%), increased γ glutamyl transferase (0.7%), hyponatraemia and diarrhea (0.5% each), colitis (0.4%), decreased appetite and vomiting (0.3% each), and increased ALP, anemia, arthralgia, autoimmune hepatitis, increased blood bilirubin, dyspnea, hyperglycemia, infusion related reaction, leukopenia, nausea, neutropenia, nervous system disorder, maculo-papular rash, thrombocytopenia, transaminases increased and weight decreased (0.2% each). Four subjects had a treatment-related Grade 5 event (autoimmune hepatitis, immune thrombocytopenic purpura, pneumonia, and pneumonitis). Treatment related SAEs that occurred in ≥ 2 subjects were colitis and pneumonitis (4 subjects each); nervous system disorder (3 subjects); and acute kidney injury, AST increased, and diarrhea (2 subjects each). The majority of the treatment-related SAEs were ≥ Grade 3 in severity and resolved with or without sequelae. Treatment-related AEs that resulted in permanent discontinuation were seen in 24 subjects (2.5%) with colitis being the most frequent (3 subjects). Approximately half of the treatment-related AEs resulting in discontinuation were ≥ Grade 3 in severity and the majority of these resolved with or without sequelae.

Tumor assessments were based on RECIST v1.1. There are different data cut-offs for efficacy data from the different cohorts in the study.

- NSCLC: As of 29Apr2016, 304 NSCLC subjects had received durvalumab monotherapy, 144 (47%) subjects with non-squamous and 160 (53%) subjects with squamous histology. Subjects with tumors defined as PD-L1 high (defined as tumor tissue samples that had ≥ 25% of tumor cells with membrane staining for PD-L1 [tumor cells ≥ 25%]) had improved ORR and OS. The ORR was 25% and 6% in subjects with PD-L1 high and low/negative (defined as tumor cells < 25%) tumors, respectively and 18% in the overall population, regardless of PD-L1 expression. The ORR in first-line subjects was 29%, 11%, and 27% for PD-L1 high, PD-L1 low/negative, and the overall population, respectively. In the second-line setting ORR was 26%, 4%, and 19% and in the third-line plus setting it was 22%, 6% and 13% for PD L1 high, PD-L1 low/negative and the overall population, respectively. The 12-month OS rate was 71% and 44% in subjects with PD-L1 high and low/negative tumors, respectively, in the first-line setting. In the second-line setting the 12-month OS rate was 56% and 39% and in the third-line plus setting it was 51% and 37%, in subjects with PD L1 high and low/negative tumors, respectively.
- SCCHN: As of 29Apr2016, 62 subjects with recurrent/metastatic squamous cell carcinoma of the head and neck had received durvalumab monotherapy. ORR was 11% across all subjects, 18% in subjects with PD-L1 high tumors (tumor cells ≥ 25%) and 8% in subjects with PD-L1 low/negative tumors (< 25%). Among the 7 responders (all subjects), 6 subjects had a duration of response (DoR) of ≥ 12 months, with the longest DoR being 19.8 months. Six- and 12-month OS were 62% and 42%, respectively, for the all treated subject population and 53% and 45%, respectively, for the subjects with PD-L1 high tumors, and 66% and 41%, respectively, for the subjects with PD-L1 low/negative tumors.
- Urothelial Carcinoma: As of 20Nov2015, 61 subjects had been enrolled into the urothelial cell cohort. Forty-two subjects who initiated study therapy ≥ 12 weeks prior to data cut-off were evaluable for response. Confirmed ORR was 46% in the PD-L1 high subgroup compared to 0% in the PD-L1 low/negative subgroup. ORR in the entire response evaluable population was 31% (13/42 subjects).
- Other indications: In PD-L1 unselected subjects, the ORR, based on investigator assessment per RECIST v1.1, ranged from 0% in uveal melanoma to 17.4% in advanced cutaneous melanoma, and disease control rate (DCR) at 24 weeks (DCR24) ranged from 4.2% in triple negative breast cancer to 39.1% in advanced cutaneous melanoma. Across the PD-L1 high tumors, ORR was > 10% for advanced cutaneous melanoma and HCC (33.3% each). In the PD-L1 high subset, DCR24 was > 10% in advanced cutaneous melanoma (66.7%) and HCC (33.3%).

As of 24Jul2016, PK data were available for 977 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-MEDI4736-1108 following treatment with durvalumab 0.1 to 10 mg/kg Q2W, 15 mg/kg every 3 weeks (Q3W), or 20 mg/kg every

4 weeks (Q4W). The peak concentration (C_{max}) increased in an approximately dose-proportional manner over the dose range examined. The area under the concentration curve from zero to 14 hours increased dose-proportionally at doses of 3 to 20 mg/kg and more than dose-proportionally at doses of < 3 mg/kg, likely due to saturable target-mediated clearance. The steady state was achieved at approximately Week 16. Accumulation of durvalumab was observed following repeated dosing. Mean accumulation ratio ranged from 0.64 to 1.87 and 3.15 to 4.93 for C_{max} and trough concentration, respectively. Near complete target saturation (soluble PD-L1 [sPD-L1] and membrane bound) is expected with durvalumab ≥ 3 mg/kg Q2W. As of 24Jul2016, a total of 790 subjects provided evaluable samples for ADA analysis. Overall, 25 of 790 subjects (3.2%) tested positive for treatment emergent ADAs in the ADA evaluable population; 19 (2.4%) subjects were persistently positive for the presence of ADA. Three subjects (0.4%) were neutralising ADA positive. Based on population PK covariate analysis, ADA positive status was not associated with a clinically relevant reduction of exposure to durvalumab. There was no apparent effect of immunogenicity on the PK profile. At the 10 mg/kg Q2W dose, sPD-L1 suppression in ADA positive subjects was similar to that observed in ADA negative subjects.

1.5 Rationale for Conducting the Study

There is sound rationale for evaluating the combination of durvalumab and MEDI0680 for the treatment of advanced malignancies. Both anti-PD-1 and anti-PD-L1 agents have shown clinical activity across a number of tumor types, such as melanoma, NSCLC, and renal cell carcinoma (RCC) (Weber et al, 2012; Topalian et al, 2012; Brahmer et al, 2010; Brahmer et al, 2012; Hamid et al, 2013; Motzer et al 2015). Previous studies have shown that PD-L1 expression is associated with a poor prognosis in RCC, presumably because of its immunosuppressive function (Thompson et al, 2006). In a recent Phase 3 study involving subjects with advanced RCC who received previous treatment, an improvement in median OS was shown for patients that received nivolumab compared to patients that received everolimus. The ORR was greater with the anti-PD-1 checkpoint inhibitor than with the mammalian target of rapamycin (mTOR) inhibitor (based on independent review, 21.5% [95% CI: 17.6%, 25.8%] vs 3.9% [95% CI: 2.2%, 6.2%]; Opdivo [nivolumab] Package Insert, 2015).

The mechanisms of action of anti-PD-1 and anti-PD-L1 antibodies are distinct: while both inhibit the interaction between PD-1 and PD-L1, only anti-PD-1 blocks PD-1/PD-L2 and only anti-PD-L1 blocks PD-L1/CD80. All three interactions may contribute to immunosuppression in the tumor and tumor-draining lymph nodes. The interaction between PD-L1 and CD80 may be especially important in the context of anti-PD-1 treatment.

The blockade of PD-1 can lead to increased release of the pro-inflammatory cytokine IFN-γ at the tumor site (Peng et al, 2012). Interferon-γ enhances the expression of PD-L1 in a range of cell types (Lee et al, 2006) and so PD-1 blockade may result in increased PD-L1 mediated blockade of co-stimulatory CD80 within the tumor microenvironment. Similarly, PD-1/PD-L2 signaling may be more pronounced in the context of PD-L1 blockade. Further support for the combination strategy is provided by mouse models of cancer (Curran et al, 2010). This includes significantly enhanced activity of a PD-1/PD-L1 combination relative to maximally efficacious doses of PD-1 or PD-L1 monotherapies in a murine syngeneic sarcoma model as described in the current edition of the MEDI0680 Investigator's Brochure. Based upon these observations, the complex feedback between pathways and differences in pathway blockade between agents, combination therapy with durvalumab and MEDI0680 may generate superior antitumor activity compared to either monotherapy. This may translate into high rates of response in tumors known to respond to immunotherapies or increased likelihood of activity in tumors that have previously not shown high levels of responsiveness to immunotherapy. However, the combination of these two agents may increase the frequency or severity of toxicities, and thus a dose-escalation study in the appropriate setting to explore this combination is indicated.

In the dose-expansion phase of the study, nivolumab is included as a comparator as it is now the standard of care in the metastatic RCC setting in some markets.

Benefit-risk Evaluation

Potential Benefits

Emerging data with both durvalumab and MEDI0680 in a monotherapy setting across a range of tumor types demonstrate encouraging clinical activity with a manageable safety profile (Sections 1.4.1, Section 1.4.2). In Study D6020C00002, MEDI0680 monotherapy showed an ORR of 24.1% among 29 subjects with advanced RCC. Of the 14 RCC subjects who received MEDI0680 at the 20 mg/kg dose level, 4 (28.6%) subjects had an objective response (OR).

Anti-PD-1 monoclonal antibodies such as MEDI0680 block the interaction of PD-1 with its ligands PD-L1 and PD-L2, but leave the interaction between PD-L1 and CD80 intact. PD-L1 targeting strategies, such as the anti-human PD-L1 mAb durvalumab, block the interaction between PD-L1 and CD80 as well as between PD-L1 and PD-1, but do not block the interaction between PD-L2 and PD-1. The combination of durvalumab with MEDI0680 in nonclinical models that have shown superior antitumor activity of combination therapy over monotherapy. These observations suggest that a complete pathway blockade with

combination therapy may generate superior antitumor activity compared to monotherapy, which may yield more complete and more durable antitumor activity. The results from this study will inform the design of future studies of the combination of durvalumab and MEDI0680. The rationale for the study design and starting doses is described in Section 3.2.

Summary of Risks

As of 30Nov2016, 58 subjects have received MEDI0680 monotherapy in Study D6020C00002 and 31 subjects have received MEDI0680 in combination with durvalumab in Study D6020C00001. One DLT was observed in Study D6020C00001 and none in Study D6020C00002.

Most frequently reported AEs (≥ 10 subjects) in subjects receiving MEDI0680 monotherapy in Study D6020C00002 were fatigue, decreased appetite, anemia, constipation, nausea, arthralgia, asthenia, dyspnea exertional, vomiting and pyrexia. Twenty-nine subjects in Study D6020C00002 (MEDI0680 monotherapy) had at least 1 SAE. SAEs reported in more than 1 subject across cohorts included pneumonia (5 subjects), fatigue and hypotension (4 subjects), pyrexia (3 subjects), abdominal pain, cellulitis, diarrhea, disease progression, pleural effusion, and vomiting (2 subjects).

Most frequently reported AEs (≥ 5 subjects) for MEDI0680 in combination with durvalumab (Study D6020C00001) were anemia, arthralgia, back pain, constipation, cough, decreased appetite, diarrhea, dyspnea, fatigue, nausea, edema peripheral, pruritus, pyrexia, rash, upper respiratory tract infection, and vomiting. Twelve subjects in Study D6020C00001 receiving MEDI0680 in combination with durvalumab had at least 1 SAE. The only SAE reported in more than 1 subject across cohorts was pleural effusion (2 subjects). One subject in Study D6020C00001 received MEDI0680 monotherapy in expansion and had an SAE of abdominal pain.

Immune-mediated reactions/immune-mediated adverse events (imAEs) are considered to be AEs of special interest (AESIs). ImAEs are important risks of immune checkpoint inhibitors, and are being closely monitored in clinical studies with durvalumab and MEDI0680 monotherapy and combination therapy. See Section 5.3 for a summary of AESIs.

The proposed combination of durvalumab with MEDI0680 has the potential to increase the frequency or severity of toxicities of monotherapy with either agent.

Overall Benefit-risk and Ethical Assessment

There continues to be a high unmet need for new treatment options in advanced solid malignancies. An estimated 338,000 new cases of RCC are diagnosed worldwide, approximately 30% of patients present with metastatic disease at the time of diagnosis (Ferlay et al, 2015; Fisher et al, 2013; Motzer 2015). Recent approval of a check-point inhibitor monotherapy has afforded RCC patients an increased number of treatment options. However, there is an unmet need for additional treatment strategies for patients that do not respond or have limited clinical response to current therapeutic options. The study design aims to minimize potential risks by incorporating intensive monitoring. Early safety assessment is in place for risks deemed most likely based on prior experience with durvalumab and MEDI0680.

Based upon the available nonclinical and clinical safety data, the limited survival benefit provided by the currently available treatment options to patients, the limited life expectancy due to malignant disease, and the strength of the scientific hypotheses under evaluation, combination therapy with MEDI0680 and durvalumab proposed for evaluation in this study may provide meaningful clinical benefit with a manageable safety and tolerability profile by generating durable and improved rate of clinical responses, as compared with monotherapy.

Therefore, the investigation of the potential therapeutic efficacy of the combination of MEDI0680 with durvalumab in patients with selected solid tumors, including RCC is acceptable, and the overall benefit/risk assessment supports the proposed study design.

1.6 Research Hypotheses

1.6.1 Primary Hypotheses

Dose-escalation:

MEDI0680 in combination with durvalumab will be adequately tolerated in subjects with select advanced malignancies.

Dose-expansion:

MEDI0680 in combination with durvalumab will have a higher response rate than nivolumab monotherapy in subjects with advanced or metastatic clear-cell renal cell carcinoma (ccRCC).

1.6.2 Secondary Hypotheses

Dose-escalation: MEDI0680 in combination with durvalumab will have antitumor activity in subjects with select advanced malignancies.

Dose-expansion: MEDI0680 in combination with durvalumab will be adequately tolerated in subjects with advanced or metastatic ccRCC.

2 OBJECTIVES AND ENDPOINTS

2.1 Primary Objectives and Endpoints

Table 2.1-1 Primary Objectives and Associated Endpoints

Type	Objectives	Endpoints
Dose escalation		
Safety	1. To determine the MTD or the highest protocol-defined dose in the absence of exceeding the MTD for MEDI0680 in combination with durvalumab, and the safety profile of MEDI0680 in combination with durvalumab in subjects with advanced malignancies	1.1. Presence of AEs and SAEs, as well as changes from baseline in laboratory evaluations, vital signs, physical examinations, and ECG results
Dose expansion		
Efficacy	2. To evaluate the antitumor activity of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC as based on investigator assessed response using RECIST v1.1 (Eisenhauer et al, 2009)	2.1. Primary endpoint: OR of MEDI0680 in combination with durvalumab versus nivolumab monotherapy. Secondary endpoints include BOR, DC, TTR, DR, PFS change from baseline in tumor size and OS. Efficacy endpoints except OS are based on an application of RECIST v1.1 to investigator-assessed tumor measurements.

AE = adverse event; BOR = best overall response; ccRCC = clear-cell renal cell carcinoma; DC = disease control; DR = duration of response; ECG = electrocardiogram; MTD = maximum tolerated dose; OR = objective response; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TTR = time to response.

2.2 Secondary Objectives and Endpoints

Table 2.2-1 Secondary Objectives and Associated Endpoints

Type	Objectives	Endpoints
Dose escalation		
Efficacy	1. To evaluate the antitumor activity of MEDI0680 in combination with durvalumab in subjects with advanced malignancies as determined by the	1.1 BOR, OR, DC, TTR, DR, PFS, OS, and change from baseline in tumor size. Antitumor activity analyses except OS

Table 2.2-1 Secondary Objectives and Associated Endpoints

Type	Objectives	Endpoints
	investigator based on modified RECIST v1.1	will be based on investigator-assessed response using modified RECIST v1.1
Dose expansion		
Safety	2. To describe the safety and tolerability of MEDI0680 in combination with durvalumab or nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC	2.1 Presence of AEs and SAEs, as well as changes from baseline in laboratory parameters, vital signs, physical examination, and ECG results
Efficacy	3. To evaluate the antitumor activity of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC as based on BICR assessed response using RECIST v1.1	3.1 BOR, OR, DC, TTR, DR, PFS, and change from baseline in tumor size as based on BICR-assessed response using RECIST v1.1.
Dose escalation and dose expansion		
PK	4. To describe the PK of MEDI0680 in combination with durvalumab 5. To describe the PK of durvalumab in combination with MEDI0680	4.1 and 5.1 The endpoints for assessment of PK include individual MEDI0680 and durvalumab concentrations in serum. PK parameters include C_{max} and C_{min}.
Immunogenicity	6. To determine the immunogenicity of MEDI0680 in combination with durvalumab 7. To determine the immunogenicity of durvalumab in combination with MEDI0680	6.1 and 7.1 Presence of detectable ADAs to MEDI0680 and durvalumab.
Pharmaco-dynamics	8. To determine whether PD-L1 is a predictive biomarker for response to therapy with MEDI0680 in combination with durvalumab	8.1 PD-L1 expression / localization on tumor membrane and tumor-infiltrating immune cells within the tumor microenvironment

ADA = anti-drug antibody; AE = adverse event; BICR = blinded independent central; review; BOR = best overall response; C_{max} = peak concentration; C_{min} = trough concentration; ccRCC = clear-cell renal cell carcinoma; DC = disease control; DR = duration of response; ECG = electrocardiogram; MTD = maximum tolerated dose; OR = objective response; OS = overall survival; PD-L1 = programmed cell death ligand 1; PFS = progression-free survival; PK = pharmacokinetics; RECIST = Response Evaluation Criteria in Solid Tumors; SAE = serious adverse event; TTR = time to response.

2.3 Exploratory Objectives and Endpoints

Exploratory assessments will be performed to examine the relationship between a subject's health and immune status prior to treatment and clinical outcome, as well as to characterize any changes in immune status which may occur during and/or following treatment relative to clinical outcome.

Table 2.3-1 Exploratory Objectives and Associated Endpoints

Type	Objectives	Endpoints
PD	1. To identify biomarkers that are predictive of antitumor response to MEDI0680 in combination with durvalumab	1.1 The endpoints related to candidate predictive and/or prognostic biomarkers in dose-expansion will focus on tissue-based, protein or gene expression measures and peripheral gene signatures including, but not limited to IHC measures of markers associated with infiltrating immune cells (eg, CD80)
PD	2. To profile gene expression changes that may correlate with antitumor response to MEDI0680 in combination with durvalumab	2.1 Gene expression signatures associated with response to therapy will include expression of messenger ribonucleic acid in blood and tumor samples before and after treatment to examine gene expression patterns at baseline and changes in response to treatment. Analysis may also include but is not limited to: evaluation of key oncogenic mutations and/or mutations in immune-related molecules.
PD	3. To evaluate additional biomarkers that may correlate with antitumor activity of MEDI0680 in combination with durvalumab compared with nivolumab monotherapy	3.1 Levels of circulating free DNA and/or circulating soluble factors which may include cytokines, chemokines, growth factors, soluble receptors, and antibodies against tumor and self-antigens, may be evaluated before and after treatment to evaluate response to treatment with MEDI0680 and durvalumab compared with nivolumab monotherapy.
PD	4. To evaluate the pharmacodynamic activity of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in the periphery.	4.1 Pharmacodynamic assessments of MEDI0680 and durvalumab combination in the periphery include: a. Flow cytometric assessment of cell populations such as T cells and B cells before and after treatment to evaluate their association with drug exposure and response to treatment; analysis may include characterization of phenotype, expression of activation markers, proliferation, and production of cytokines and effector molecules b. Dose escalation only: Serum soluble PD-L1 levels before and after treatment may be measured to evaluate their association with drug exposure and response to treatment with MEDI0680 and durvalumab c. Dose escalation only: MEDI0680 receptor occupancy on peripheral blood T cells before and after treatment may

Table 2.3-1 Exploratory Objectives and Associated Endpoints

Type	Objectives	Endpoints
		be measured to evaluate associations with drug exposure and response to treatment with MEDI0680 and durvalumab
PD	5. To compare the pharmacodynamic changes resulting from complete PD-1/PD-L1 pathway blockade versus treatment with nivolumab monotherapy	5.1 Expression and localization of key molecules such as PD-L1, PD-L2, and PD-1 within the tumor microenvironment, as well as the frequency, localization, and phenotype of tumor-infiltrating lymphocytes, may be examined in biopsy specimens by immunohistochemistry, immunofluorescence, and/or flow cytometry and correlated with response to treatment
Efficacy	6. To evaluate the antitumor activity of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in subjects with advanced or metastatic ccRCC as assessed by irRECIST	6.1 Antitumor activity, including OR, DR, DC, and PFS, may be assessed by irRECIST (Nishino et al, 2013).

ccRCC = clear-cell renal cell carcinoma; CD80 = cluster of differentiation 80; DC = disease control; DR = duration of response; IHC = immunohistochemistry; irRECIST = immunerelated Response Evaluation Criteria in Solid Tumors; OR = objective response; PD-1 = programmed cell death 1; PD-L1 = programmed cell death ligand 1; PD-L2 – programmed cell death ligand 2.

3 STUDY DESIGN

3.1 Description of the Study

3.1.1 Overview

This is a multicenter, open-label, Phase 1/2 study to evaluate the safety, tolerability, PK, immunogenicity, and antitumor activity of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in adult immunotherapy naïve subjects with select advanced malignancies. The study will be conducted at approximately 50 study centers globally.

The study includes 2 phases, dose-escalation and dose-expansion. In the dose-escalation phase, subjects with selected solid tumors will receive MEDI0680/durvalumab combination therapy. In the dose-expansion phase, subjects with ccRCC will receive either MEDI0680/durvalumab combination therapy or nivolumab monotherapy. Changes initiated to the dose-escalation and dose-expansion phases as of Protocol Amendment 5 are described in Section 9.1.

In the dose-escalation phase, subjects may receive treatment for up to 12 months; in the dose-expansion phase, subjects may remain on treatment until unacceptable toxicity, confirmed PD, or development of other reason for treatment discontinuation. All subjects will be evaluated regularly. Clinical status will be classified according to modified RECIST v1.1 (Eisenhauer et al, 2009) for subjects in the dose-escalation phase and by RECIST v1.1 for subjects in the dose-expansion phase, and other disease-specific assessments (see Appendix 4). All subjects will be followed for survival until the end of study (see Section 6.3). Adverse events and SAEs will be followed as per Section 5.

3.1.1.1 Dose-escalation Phase

In the dose-escalation phase, sequential cohorts of 3 to 6 subjects will be enrolled in 1 of 6 dose-level cohorts: 0.1 mg/kg MEDI0680 Q2W with 3 mg/kg durvalumab Q2W, and increasing dose levels of MEDI0680 Q2W (0.1, 0.5, 2.5, 10, and 20 mg/kg) with 10 mg/kg durvalumab Q2W. The dose-escalation phase will include immunotherapy-naïve (defined in Section 4.1.2) with solid tumors. As of Protocol Amendment 2, only subjects with NSCLC, squamous cell carcinoma of the head and neck (SCCHN), microsatellite instability-high (MSI-high) colorectal cancer (CRC), bladder cancer, ovarian cancer, esophageal cancer, gastric cancer, or RCC will be enrolled.

The dose-escalation phase will be executed according to a 3 + 3 design. If ≥ 2 of 6 subjects experience a DLT, a dose level from the intermediate zone-based cohort(s) that does not exceed the MTD or the highest protocol-defined dose for each investigational product in the absence of exceeding the MTD may be explored (see Section 3.1.3.2 for description of modified zone-based dose-escalation). Based on emerging safety, PK, pharmacodynamic, and clinical activity data for the MEDI0680 Q2W treatment schedule, the dosing interval for MEDI0680 could have been increased to every 4 weeks (Q4W; however, as of Protocol Amendment 3, this dosing schedule will not be implemented since dose-escalation is considered complete, see earlier versions of the protocol for more information on this dosing schedule).

Any dose-level cohort in the dose-escalation phase that did not exceed the MTD can be expanded up to a maximum of 18 subjects for further evaluation of safety, PK, pharmacodynamics, and antitumor activity.

Based on 6 dose-level cohorts in the main 3 + 3 dose-escalation design on a Q2W treatment schedule, up to 36 subjects may be enrolled. Additional subjects could be required if dose de-escalation occurs, intermediate dosing using the modified zone-based design is explored, or any dose-level cohort is expanded beyond 6 subjects.

As of Protocol Amendment 3, the dose-escalation phase completed enrollment. Subjects were treated through the highest planned dose-level cohort of 20 mg/kg MEDI0680 Q2W in combination with durvalumab Q2W and the MTD was not reached (See Section 1.4.1 for the number of subjects enrolled as of this amendment).

3.1.1.2 Dose-expansion Phase

The dose-expansion phase will begin after the dose-escalation phase. Immunotherapy-naïve subjects (defined in Section 4.1.2) with ccRCC will be randomized in a 2:1 ratio to 1 of 2 treatment arms: (1) MEDI0680/durvalumab combination therapy or (2) nivolumab monotherapy. Stratification factors will include the Memorial Sloan Kettering Cancer Center (MSKCC) risk group (0 = favorable risk; 1 or 2 = intermediate risk; 3 = poor risk; Motzer et al, 2002; see Appendix 7), and PD-L1 expression status (≤ 1% and > 1%). Up to 40 subjects may be randomized in the MEDI0680/durvalumab combination therapy arm and up to 20 subjects may be randomized in the nivolumab monotherapy arm based on evaluation of emerging safety and efficacy parameters in the current study as well as other ongoing studies. An interim futility analyses will be performed for the MEDI0680/durvalumab combination therapy arm in the dose-expansion phase after 20 subjects have been randomized and have reached their second post-baseline disease assessment or have completed study. Randomization into the dose-expansion phase may be discontinued at the discretion of the sponsor should emerging clinical or pre-clinical data suggest that continued treatment may not be beneficial.

The endpoints to be measured in this study are described in Section 2.

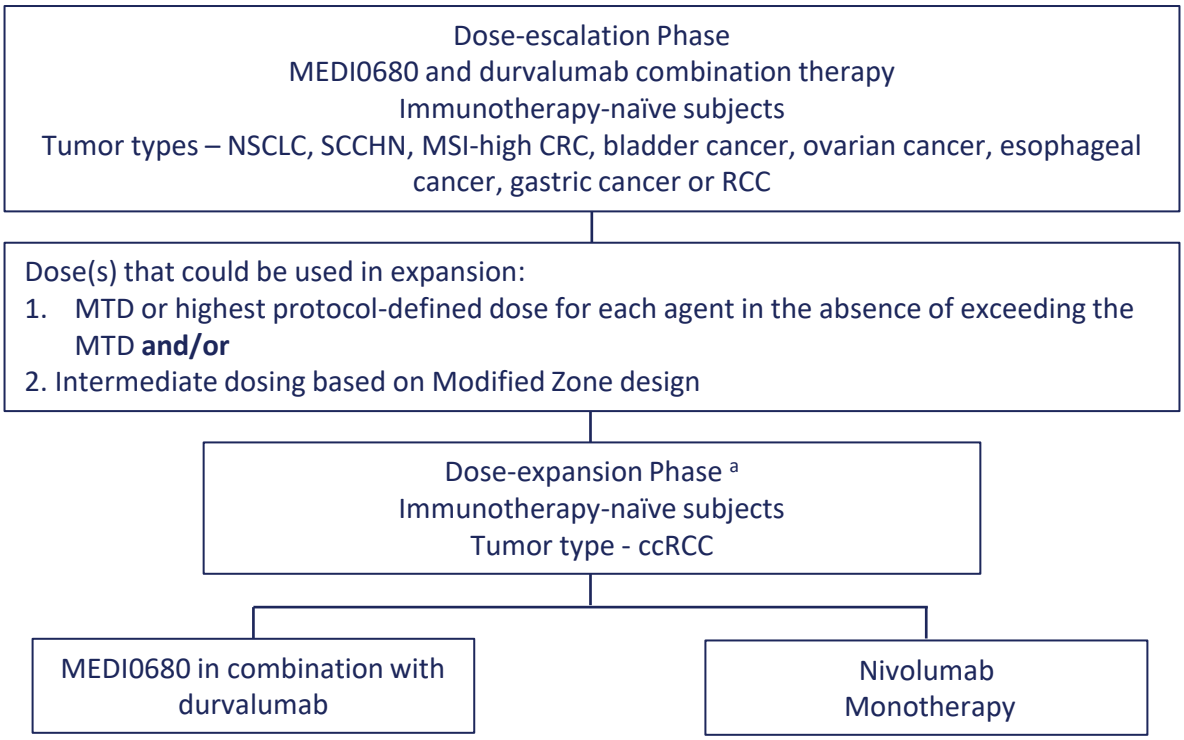

Figure 3.1.1-1 Study Flow Diagram

ccRCC = clear-cell RCC; CRC = colorectal cancer; MSI = microsatellite instability; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; RCC = renal cell carcinoma; SCCHN = squamous cell carcinoma of head and neck.

[a] Up to a total of 60 subjects with ccRCC will be randomized in a 2:1 ratio to receive either MEDI0680/durvalumab combination therapy or nivolumab monotherapy.

3.1.2 Treatment Regimen

Subjects will be treated in either the dose-escalation or dose-expansion phase. MEDI0680, durvalumab and nivolumab will be administered via IV infusion. In dose-escalation phase, subjects will remain on treatment for up to 12 months. In the dose-expansion phase, subjects will remain on treatment until unacceptable toxicity, confirmed PD, or development of other reason for treatment discontinuation.

For subjects receiving MEDI0680 in combination with durvalumab, durvalumab will be administered first. The IV infusion of durvalumab will be approximately 1 hour in duration. MEDI0680 infusion will start approximately 30 minutes after the end of durvalumab infusion. MEDI0680 will be administered by IV infusion over a minimum of 30 minutes at dose levels of 0.1, 0.5, and 2.5 mg/kg, over a minimum of 60 minutes at dose levels of > 2.5 mg/kg up to a total dose of 1200 mg, and over a minimum of 90 minutes at total doses > 1200 mg. In the dose-escalation phase only, subjects who achieve and maintain DC (ie,

CR, PR, or stable disease [SD]) through the end of the 12-month treatment period will enter follow-up. During the first 12 months of follow-up, if the subject has PD, the subject may be re-administered MEDI0680 and durvalumab for up to another 12 months with the same treatment guidelines followed during the initial 12-month period if the subject fulfills the criteria for retreatment in the setting of PD, has not received other anticancer treatments for their disease, and does not meet any of the investigational product discontinuation criteria (Section 4.1.6). Only 1 round of retreatment will be allowed.

Nivolumab will be administered according to the package insert guidelines.

3.1.2.1 Treatment Beyond Progression

For subjects treated with MEDI0680 monotherapy or in combination with durvalumab, in the event of an initial assessment of PD (based on an application of RECIST v1.1 to investigator-assessed tumor measurements), a subject may continue to receive the assigned study treatment as long as none of the criteria listed below are met.

- 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 and must be discontinued.
- Meets any of the investigational product discontinuation criteria (Section 4.1.6).
- Clinical symptoms or signs indicating significant PD such as the benefit-risk ratio of continuing therapy is no longer justified.
- Decline in Eastern Cooperative Oncology Group (ECOG) performance status.
- Threat to vital organs/critical anatomical sites (eg, spinal cord compression) requiring urgent alternative medical intervention, and continuation of study therapy would prevent institution of such intervention.

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.

Nivolumab will be administered according to the package insert guidelines.

3.1.2.2 Dosing Schedule

In the dose-escalation phase, durvalumab will be administered Q2W for 12 months and MEDI0680 will be administered Q2W for 12 months (Figure 3.1.2.2-1). In the dose-expansion phase, MEDI0680 in combination with durvalumab (depending on assigned treatment arm) will be administered Q2W until unacceptable toxicity, documentation of confirmed PD, or development of other reason for treatment discontinuation.

In the dose expansion phase, nivolumab (depending on assigned treatment arm) will be administered Q2W as per the local (country-specific) package insert (or similar) until unacceptable toxicity, documentation of confirmed PD, or development of other reason for treatment discontinuation, according to the local (country-specific) package insert (or similar).

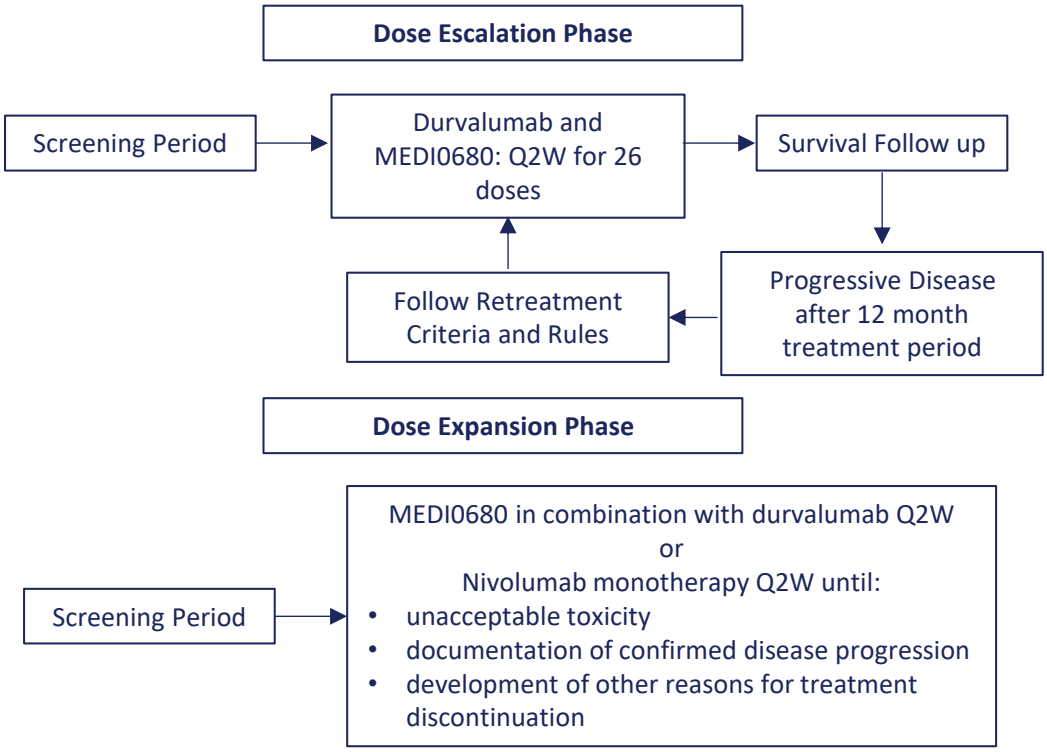

Figure 3.1.2.2-1 Study Flow for Primary MEDI0680 Schedule (Every 2-week Dosing)

Q2W = every 2 weeks.

3.1.3 Dose-escalation Phase: Dose-escalation and Modified Zone-based Design

3.1.3.1 Dose-escalation

As of Protocol Amendment 3, enrollment in the dose-escalation phase is complete.

Rules for dose-escalation and de-escalation are as follows:

1. A minimum of 3 subjects will be enrolled in each dose cohort.
2. The administration of durvalumab and MEDI0680 to the first and second subjects of each cohort will be separated by at least 24 hours.
3. All safety data will be reviewed by a study-specific dose-escalation committee before proceeding with an escalation or de-escalation decision.
4. A 3 + 3 dose-escalation design will be followed as summarized below:
   a. If 0 out of the 3 subjects in a dose cohort experience a DLT during the DLT-evaluation period, dose-escalation may proceed to the next planned cohort(s) with approval of the dose-escalation committee.
   b. If 1 of the 3 subjects in any dose cohort experiences a DLT during the DLT-evaluation period, that dose cohort will be expanded to a total of 6 subjects. If no more than 1 of 6 subjects in the dose cohort experiences a DLT, dose-escalation may proceed to the next planned dose cohort(s) with the approval of the dose-escalation committee.
   c. If 2 or more subjects in a dose cohort experience a DLT during the DLT-evaluation period, the MTD will have been exceeded and no further subjects will be enrolled into that dose cohort. The following options could be evaluated:
   - In the Primary Q2W schedule (see Figure 3.1.3.2-1):
     - A previous lower dose cohort or an intermediate dose cohort
     - A switch to Q4W dosing for MEDI0680
     - An intermediate dose using the modified zone-based design
   - In the Alternative Q4W schedule:
     - A previous lower dose cohort or an intermediate dose cohort
     - An intermediate dose using the modified zone-based design
5. Intermediate doses may be explored based on a zone-based design (Huang et al, 2007). The modified zone-based design takes the initial dose-escalation along a predefined path (ie, main dose-escalation) until the MTD is exceeded or the highest protocol-defined doses for each agent in the absence of exceeding the MTD are reached. Lower zones or doses in the same zone as the MTD or the highest protocol-defined doses for each agent in the absence of exceeding the MTD may be explored simultaneously with the dose-expansion cohort (Section 3.1.3.2)
6. If the MTD is exceeded for Cohort 1 (starting dose level):
   a. Based on ongoing review of emerging data from the current study as well as ongoing clinical studies with durvalumab and MEDI0680 (MEDI0680; monotherapy and

combination therapy), the dosing interval of MEDI0680 may be changed in which longer dosing intervals may be evaluated in combination with durvalumab. For example, if the emerging safety profile of the combination precludes the Q2W dosing interval for MEDI0680, a longer dosing interval for MEDI0680 (MEDI0680; ie, Q4W) may offer the possibility of better tolerability for the combination. There can be escalation to explore higher dose cohorts based on a 3 + 3 escalation design (see Figure 3.1.3.2-1)

   b. Dependent on emerging subject data, including safety, PK, pharmacodynamics, biomarker, and response among subjects on the Q4W dosing regimen, higher doses of MEDI0680 may be explored.

7. If the MTD is not exceeded for Cohort 1, then higher cohorts will be explored using the 3 + 3 escalation design.
   a. A switch to Q4W dosing for MEDI0680 could potentially permit additional time for recovery from any observed toxicities.
   b. The dose that would be used for the Q4W schedule would be the highest dose evaluated on the Q2W schedule that did not exceed the MTD or a lower dose based on evaluation of emerging PK, pharmacodynamics, safety, and efficacy parameters in the current study and other ongoing studies.
8. Any dose-escalation cohort that has not exceeded the MTD can be expanded up to a maximum of 18 subjects for further evaluation of safety, PK, pharmacodynamics, and efficacy

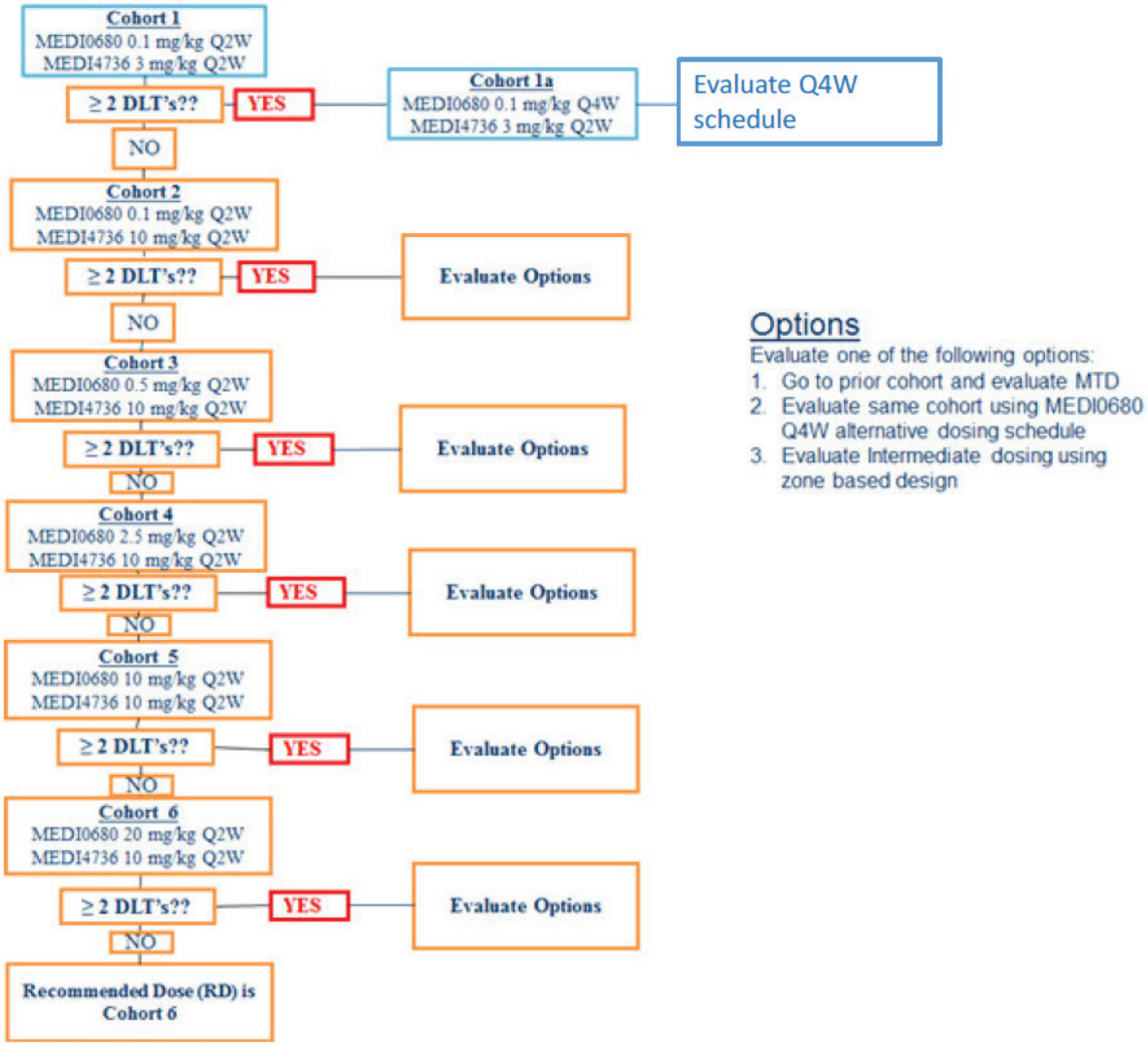

Figure 3.1.3.1-1 Primary (Every 2-week Dosing of MEDI0680) Dose-escalation Design

DLT = dose-limiting toxicity; MTD = maximum tolerated dose; MEDI4736 = durvalumab; Q2W = every 2 weeks; Q4W = every 4 weeks.

3.1.3.2 Modified Zone-based Design

In general, the zone-based design allows for the exploration of cohorts in lower zones or within a zone (see Figure 3.1.3.2-1). The current dosing would be considered during the dose-escalation or dose-expansion phase dependent on clinical or safety data.

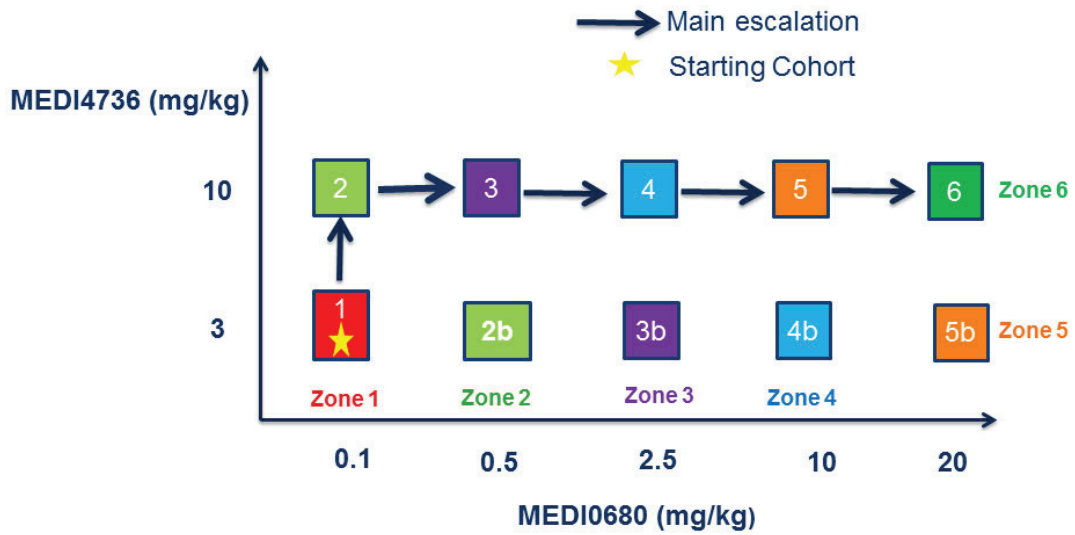

Figure 3.1.3.2-1 Dose-escalation (Zone-based) for Primary Q2W Schedule

MEDI4736 = durvalumab; Q2W = every 2 weeks.

3.1.3.3 Dose-limiting Toxicity

Dose-limiting toxicities will be evaluated during the dose-escalation phase. Non-evaluable subjects will be replaced in the same dose cohort (see Section 4.1.7). Grading of DLTs will be 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 treatment-related toxicity that occurs during the DLT-evaluation period, including but not limited to:

- Any Grade 4 imAE regardless of duration
- Any ≥ Grade 3 colitis regardless of duration
- Any Grade 3 or Grade 4 non-infectious pneumonitis irrespective of duration
- Any Grade 3 imAE, excluding colitis and pneumonitis, that does not downgrade to ≤ Grade 2 within 3 days after onset of the event despite maximal supportive care including systemic corticosteroids or downgrade to ≤ Grade 1 or baseline within 14 days
- Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care
- Liver transaminase elevation higher than 8 × upper limit of normal (ULN) or total bilirubin higher than 5 × ULN
- Grade 4 neutropenia and thrombocytopenia that does not resolve to ≤ Grade 3 within ≤ 7 days and Grade 3 thrombocytopenia associated with any clinically important bleeding

- Any other toxicity that is greater than baseline grade, is clinically significant and/or unacceptable, and is judged to be a DLT by the dose-escalation review committee

The definition excludes the following conditions:

- Grade 3 endocrinopathy, 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) that resolves to ≤ Grade 1 within 30 days
- Concurrent vitiligo or alopecia of any AE grade

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

While the rules for adjudicating DLTs in the context of dose-escalation are 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.

Primary Escalation (Every 2-week Dosing of MEDI0680) Dose-limiting Toxicity Period

The period for evaluating DLTs is the time period starting with the first dose of study drugs until the planned administration of the third dose of durvalumab and MEDI0680 during Q2W dosing. Subjects are considered evaluable for assessment of DLT if they receive the protocol-assigned doses of both durvalumab and MEDI0680 (ie, 2 doses of both durvalumab Q2W and MEDI0680 Q2W) and complete the safety follow-up through the end of the DLT-evaluation period, or experience a DLT during the DLT-evaluation period.

3.1.3.4 Maximum Tolerated Dose

The MTD is defined as the highest dose within a dose-escalation cohort where no more than 1 of 6 subjects experiences a DLT.

Dose-escalation is complete (see Section 1.4.1). An MTD was not identified and the highest combination dose administered was 20 mg/kg MEDI0680 Q2W with 10 mg/kg durvalumab Q2W.

3.1.4 Dose-expansion Phase

Dose-expansion will be initiated following completion of the dose-escalation phase. Immunotherapy-naïve subjects with ccRCC will be randomized in a 2:1 ratio to receive either 20 mg/kg MEDI0680 in combination with 750 mg durvalumab Q2W or nivolumab Q2W. Dose levels of MEDI0680 and durvalumab were selected based on data from the dose-escalation phase of this study, the ongoing FTIH MEDI0680 Study D6020C00002, and ongoing durvalumab studies and analyses (see Section 3.2.1). The dose level of nivolumab is the recommended dose for treatment of patients with advanced RCC.

Prior to the removal of a MEDI0680 monotherapy arm in this protocol amendment, some subjects were randomized and began receiving MEDI0680 monotherapy. These subjects are to continue receiving 20 mg/kg MEDI0680 Q2W monotherapy until unacceptable toxicity, confirmed PD, or development of other reason for treatment discontinuation, and will follow the study procedures outlined in Section 4.2 for MEDI0680/durvalumab combination therapy (with the exception of durvalumab specific procedures).

During the dose-expansion phase, subjects will be monitored for safety according to the same criteria employed during dose-escalation. If during the treatment period, ≥ 33% of subjects in the MEDI0680/durvalumab combination arm experience safety events meeting DLT criteria (even if outside of the DLT-evaluation period [see Section 3.1.3.2]), randomization 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 randomization.

3.1.5 Management of Study Medication Related Toxicities

3.1.5.1 Dose Modifications of Durvalumab and MEDI0680

Based on the mechanism of action of durvalumab and MEDI0680 leading to T-cell activation and proliferation, there is the possibility of observing imAEs during the conduct of this study. Potential imAEs may be similar to those seen with the use of ipilimumab, BMS-936558, 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). Subjects should be monitored for signs and symptoms of imAEs. In the absence of an alternate etiology (eg, infection or PD), an immune-mediated etiology should be considered for signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy. Subjects should be evaluated to identify any alternative etiology

1. In the absence of clear alternative etiology, all events of an inflammatory nature should be considered to be immune-mediated
1. Symptomatic and topical therapy should be considered for low-grade events
2. Systemic corticosteroids should be considered for a persistent low-grade event or for a severe event
3. More potent immunosuppressives should be considered for events not responding to systemic steroids (eg, infliximab, mycophenolate, etc)

If the investigator has any question in regards to an AE being an imAE, the investigator should immediately contact the medical monitor. Dose modifications may not be required for AEs that are clearly not attributed to durvalumab or MEDI0680 (such as an accident) or for laboratory abnormalities that are deemed asymptomatic, not deemed to be clinically significant, 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 durvalumab and MEDI0680 are not permitted.

Treatment modifications of MEDI0680/durvalumab may be required in the event of treatment-related toxicity. General treatment modification and toxicity management guidelines are provided in Appendix 6. Additionally, management guidelines for adverse events of special interest (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.

3.1.5.2 Dose Modifications of Nivolumab

The investigator should follow the recommendations in the local (country-specific) package insert (or similar).

3.2 Study Design and Dose Rationale

3.2.1 Dose Rationale (MEDI0680 and Durvalumab)

3.2.1.1 Dose-escalation Phase

MEDI0680

MEDI0680 monotherapy Study D6020C00002 (AMP-514-01), the ongoing FTIH study, will evaluate MEDI0680 doses of 0.1, 0.5, 2.5, 10, and 20 mg/kg Q3W; and 10 and 20 mg/kg Q2W. Provided the MTD is not exceeded at 20 mg/kg Q3W or Q2W, higher doses may be explored based on clinical efficacy, safety, and PK/pharmacodynamic data, but will not

exceed double the maximum dose. Based on available data from Study D6020C00002, the proposed starting dose of MEDI0680 in the current study will be given Q2W in order to align with the durvalumab schedule, and will be the lowest dose on a Q3W dosing schedule in the ongoing FTIH study. The MEDI0680 starting dose will be 0.1 mg/kg administered by IV on Day 1 and then Q2W (± 3 days) for 12 months. As of 02Nov2015, 58 subjects received MEDI0680 monotherapy (see Section 1.4.1). Dose levels included 0.1, 0.5, 2.5, 10, and 20 mg/kg Q3W, 10 and 20 mg/kg Q2W, 20 mg/kg QW × 2 and 20 mg/kg QW × 4. One DLT was reported.

Durvalumab

Durvalumab dose levels were selected based on data from the FTIH Study CD-ON-MEDI4736-1108. The dose selected for further evaluation in the dose-expansion phase of Study CD-ON-MEDI4736-1108 is 10 mg/kg administered Q2W. This was based on evaluation of the current PK data in the subjects enrolled in Study CD-ON-MEDI4736-1108 where doses of 0.1, 0.3, 1.0, 3.0, and 10 mg/kg Q2W were evaluated. Durvalumab exhibited nonlinear (dose-dependent) PK consistent with target-mediated drug disposition. Linear PK was observed at doses of 3.0 mg/kg and above and is consistent with near complete target suppression, which is supported by sPD-L1 suppression data. Further, the 10 mg/kg Q2W dose was not associated with any DLTs in the dose-escalation phase and was, therefore, selected for further evaluation in the dose-expansion phase of Study CD-ON-MEDI4736-1108. For the current study, the starting dose of durvalumab was 3 mg/kg, one dose level below the 10 mg/kg referenced above.

Durvalumab will be administered by IV on Day 1 and then Q2W (± 3 days) for 12 months.

3.2.1.2 Dose-expansion Phase

MEDI0680/Durvalumab Combination Therapy

The dose-escalation phase of this study (D6020C00001) was completed as of the date of this amendment with the highest MEDI0680/durvalumab combination dose level administered being 20 mg/kg MEDI0680 Q2W with 10 mg/kg durvalumab Q2W. A dose limiting toxicity (DLT) was reported in 1 subject. An MTD was not identified and no significant AE trends were observed across the dose levels evaluated.

Following IV infusion of MEDI0680 in combination with durvalumab, mean C_{max}, trough concentration, and AUC_{τ} values of MEDI0680 increased approximately dose proportionally from 0.1 to 20 mg/kg. Co-administration of durvalumab did not affect MEDI0680 PK

compared to MEDI0680 monotherapy. Preliminary data from MEDI0680/durvalumab combination therapy in the dose-escalation phase of this study suggest that target receptor occupancy is achieved at both the 10 + 10 mg/kg and 20 + 10 mg/kg dose levels of MEDI0680 in combination with durvalumab in early assessments (first cycle). MEDI0680 PK was linear with dose-proportional increases in serum concentrations from 0.1 to 20 mg/kg in combination with 10 mg/kg durvalumab administered Q2W.

Durvalumab Weight-based Dosing to Fixed Dosing

A population PK model was developed for durvalumab using monotherapy data from Study CD-ON-MEDI4736-1108 (solid tumors; N = 292; doses = 0.1 to 10 mg/kg Q2W or 15 mg/kg every 3 weeks). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5^{th}, median and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of approximately 75 kg). A total of 1000 subjects were simulated using body WT distribution of 40 to 120 kg. Simulation results demonstrate that body WT-based and fixed-dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen. Thus, a fixed dosing of durvalumab 750 mg will be explored in the dose-expansion phase of this study. The dose of 20 mg/kg MEDI0680 Q2W with 750 mg durvalumab (fixed dose) Q2W was selected for the dose-expansion phase to maximize the likelihood of observing robust efficacy with tolerable safety profiles based on available PK, PD, and clinical response data.

3.2.2 Rationale for Study Population

Despite considerable advancements made during the last decade, patients with advanced solid tumors have poor outcomes with currently available therapies. Although many of the solid tumor types have approved first-line treatments, further therapeutic options are limited with second- and third-line treatments generally providing short OS.

Tumors that have historically shown responsiveness to immunotherapy (IMT) may benefit from complete pathway blockade. Solid tumors such as melanoma (MEL), RCC and NSCLC are known to respond to IMT (Brahmer et al, 2012; Hodi et al, 2010; Motzer et al, 2015; Topalian et al, 2012).

Rationale for RCC Population

An estimated 338,000 new cases of RCC are diagnosed worldwide, with approximately 30% of patients presenting with metastatic disease (Ferlay et al, 2015; Fisher et al, 2013; Motzer et al, 2015). A number of targeted therapies have been approved for the treatment of patients with advanced or metastatic RCC, however, these treatments are associated with limited OS (< 2 years). A PD-1-targeting agent, nivolumab, recently received approval for the treatment of patients with advanced RCC with its Phase 3 study stopped early after it was determined that nivolumab improved OS versus everolimus in subjects with advanced RCC (Motzer et al, 2015). The confirmed ORR (95% CI) in this Phase 3 study was 21.5% (17.6, 25.8) based on independent review, suggesting that some RCC patients are primarily nonresponsive or are only minimally responsive to nivolumab monotherapy (Opdivo [nivolumab] Package insert, 2015). Thus, exploration of new therapies in patients who are candidates for nivolumab monotherapy is warranted. Following Protocol Amendment 5, nivolumab monotherapy was added as a comparator arm in the dose expansion phase to enable comparison of MEDI0680/durvalumab activity with the current standard of care.

The mechanisms of action of anti-PD-1 and anti-PD-L1 antibodies are distinct: while both inhibit the interaction between PD-1 and PD L1, only anti-PD-1 blocks PD-1/PD-L2 and only anti-PD-L1 blocks PD-L1/CD80 and support for the combination strategy is provided by mouse models of cancer (Curran et al, 2010). Based upon these observations, the complex feedback between pathways and differences in pathway blockade between agents, combination therapy with durvalumab and MEDI0680 may generate superior antitumor activity compared to either monotherapy. This may translate into high rates of response in tumors known to respond to therapeutic agents that target PD-1 or increased likelihood of activity in tumors that have previously not shown high levels of responsiveness to PD-1 targeting agents.

3.2.3 Rationale for Endpoints

Primary Endpoints

The primary endpoints for this study are to determine the MTD or highest protocol-defined dose for each agent in the absence of exceeding the MTD for MEDI0680 in combination with durvalumab and to determine the safety of this combination. Ensuring the safety of the combination, and defining a dose for dose-expansion, is important prior to progressing to the next stage of clinical development. Standard safety parameters, and enhanced monitoring for imAEs, will be employed to assess the safety profiles of MEDI0680 in combination with durvalumab or nivolumab monotherapy.

The primary efficacy endpoint for the dose-expansion phase is a standard measure used to assess efficacy in oncology studies.

Secondary Endpoints

The secondary endpoints for this study include antitumor activity, PK, and immunogenicity. Antitumor activity is being examined to determine the effect of MEDI0680 in combination with durvalumab versus nivolumab monotherapy treatment on tumor burden which will help to further explore the benefit-risk profile for the combination. The PK of durvalumab and MEDI0680 are being examined to determine the effect of MEDI0680 on durvalumab PK parameters and the effect of durvalumab on MEDI0680 PK parameters. Immunogenicity will be examined to assess its impact on safety and efficacy. Expression and localization of PD-L1 will be examined to determine if it is a predictive biomarker for response to therapy. The endpoints chosen to assess secondary objectives are commonly used in oncology studies.

Pharmacodynamic and Predictive Exploratory Endpoints

The goals of exploratory assessments are to identify predictive markers (measures of a subject's health or immune status prior to treatment that correlate with clinical response) and to characterize the pharmacodynamic effects of MEDI0680 and durvalumab (changes in a subject's immune status following treatment and correlations with drug exposure and clinical response). The rationale for the exploratory endpoints is based on ongoing studies of MEDI0680 and durvalumab, as well as knowledge gained in clinical studies with other cancer immunotherapies. The collections are being synchronized in the monotherapy and combination treatment studies to enable comparisons of the pharmacodynamic markers and predictive markers among the two monotherapies and the combination treatment.

Collection of tumor biopsy specimens, as well as whole blood, and plasma specimens, are needed to assess the requested pharmacodynamic and predictive markers. Peripheral blood mononuclear cells (PBMC) were also analyzed in dose escalation but were removed for dose expansion as of Amendment 5. Tumor biopsy specimens provide critical information about the status of the antitumor immune response, at the site of disease. Since the antitumor immune response can evolve with time and in response to different therapies, fresh pre-treatment biopsies, when clinically feasible, provide more relevant information than archival biopsies. During dose-expansion, optional posttreatment biopsies will be collected at approximately Day 57 and end of treatment (EOT). If available, the pretreatment and Day 57 biopsies will be compared to assess changes in the tumor microenvironment after one cycle of treatment, at a time when active tumor regression has occurred in subjects receiving durvalumab monotherapy treatment. The EOT biopsy specimens will be evaluated to

understand potential mechanisms of resistance in tumors that remain following treatment. Peripheral specimens (whole blood, PBMC, and plasma) indicate a subject's overall immune status and can provide insight into the antitumor immune response.

Pharmacodynamic Markers

Receptor targeting and occupancy is being evaluated using the sPD-L1 assay (durvalumab) and the PD-1 flow cytometry assay (MEDI0680). These assays are especially useful during dose-escalation and may help to inform dose selection for the dose-expansion phase; these assays will not be conducted in the dose-expansion phase as of Protocol Amendment 5.

The functional consequences of complete pathway blockade will be evaluated by assessing immune responses in the tumor microenvironment and periphery. Similar evaluations are being conducted in conjunction with monotherapy studies, to understand the functional consequences of each agent alone.

Changes in the immune response in the tumor microenvironment will be assessed using multiple approaches. Expression and localization of key molecules such as PD-L1, PD-L2, and PD-1 within the tumor microenvironment may be examined by immunohistochemistry (IHC). Biopsy specimens may also be evaluated for changes in the frequency, phenotype, and/or localization of infiltrating T cells and APC. Gene expression profiling will be used to evaluate a broader panel of markers that indicate the level of inflammation within the tumor microenvironment and the balance between markers of immune suppression versus action in T cells and APC.

Changes in the immune responses in the periphery are also being evaluated using multiple approaches. Flow cytometry assays may be used to evaluate factors such as phenotype, expression of activation markers, proliferation, and production of cytokines and effector molecules, by cell populations such as T cells, B cells, and myeloid-derived suppressor cell (MDSC). Gene expression analysis (evaluation of messenger ribonucleic acid [mRNA] and/or micro ribonucleic acid [miRNA]) of peripheral blood specimens and/or cryopreserved PBMC may also be conducted. Plasma specimens will also be collected prior to treatment and at several posttreatment time points to enable evaluation of circulating soluble factors indicative of immune response (eg chemokines, cytokines, soluble receptors, and antibodies to self-antigens and tumor antigens), cancer biomarkers, and tumor DNA.

Other pharmacodynamic markers may be evaluated as determined by additional data.

Predictive Markers

Candidate biomarkers for subject selection will be assessed to determine whether these markers predict which subjects are most likely to respond to treatment with durvalumab and MEDI0680. Similar evaluations are being conducted in conjunction with monotherapy studies for both agents.

Tumors can express PD-L1 as a mechanism of adaptive resistance to an activated immune response within the tumor microenvironment. Fresh and/or archival pre-treatment biopsies will be collected from all subjects and analyzed by IHC to evaluate whether the expression of PD-L1 may be a predictive marker for response to treatment with durvalumab and MEDI0680.

The combination of durvalumab and MEDI0680 may be especially beneficial in cases where PD-1, PD-L1, PD-L2, and CD80 are all expressed in the tumor microenvironment. Expression of PD-1, PD-L2, and CD80 may be evaluated using IHC and/or other methods, to determine whether expression of multiple pathway molecules may be a predictive marker for response to treatment with durvalumab and MEDI0680.

Expression of additional immune-related markers in the tumor microenvironment may also be conducted by IHC and/or other methods. Gene expression analysis of pre-treatment biopsy specimens may also be conducted to determine whether certain baseline patterns of mRNA/miRNA expression, such as markers of an inflammatory tumor microenvironment, correlate with response. Results of these exploratory studies may suggest predictive markers for response to the combination treatment.

Pre-treatment biopsy specimens may be analyzed for the presence of key mutations; these may include but are not limited to epidermal growth factor receptor, Kirsten rat sarcoma oncogene homolog (K-ras), neuroblastoma RAS viral oncogene (N-ras), APC, B catenin, anaplastic lymphoma kinase, and C-MNNG HOS transforming gene, as mutational status may impact tumor immunogenicity and mechanisms of tumor immune evasion. Correlations between key mutations and response to the durvalumab and MEDI0680 treatment combinations may be evaluated.

The general status of the immune system may also affect responsiveness to immunotherapies, including MEDI0680 and durvalumab. Pre-treatment numbers of total T cells, CD4 T cells, CD8 T cells, B cells, and NK cells per mL of peripheral blood, the relative populations of these lymphocyte subsets, and the relative frequency of proliferating, naïve, effector, and memory T cells, will be evaluated by flow cytometry to determine whether baseline

characteristics of peripheral leukocytes may be a predictive marker for response to treatment with durvalumab and MEDI0680.

Other predictive biomarkers may be evaluated as determined by additional data.

4 MATERIALS AND METHODS

4.1 Subjects

4.1.1 Number of Subjects

A total of approximately 96 subjects could be enrolled at approximately 50 study centers globally.

4.1.2 Inclusion Criteria

Subjects must meet *all* of the following criteria:

1. Age ≥ 18 years at the time of screening
2. ECOG performance status of 0 - 1
3. For dose escalation:
    a. Histologically confirmed metastatic or recurrent NSCLC, SCCHN, MSI-high CRC, bladder cancer, ovarian cancer, esophageal cancer, gastric cancer, or RCC that are refractory or intolerant to standard therapy or for which no standard therapy exists
    b. No more than 3 prior lines of systemic therapy in the recurrent or metastatic setting, including standard and investigational agents (additional criteria apply for NSCLC, see item 3e)
    c. Subjects with at least one measurable lesion according to RECIST v1.1
    d. Immunotherapy naïve: Subjects must have no prior exposure to immunotherapy including but not limited to other anti-CTLA-4, anti-PD-1, or anti-PD-L1 antibodies
    e. For NSCLC subjects:
        i. NSCLC subjects with metastatic or recurrent disease must have received no more than 3 prior lines of therapy, or either failed to respond, relapsed, or were unable to tolerate standard treatment
        ii. Subjects with EGFR-activating mutations must have received an EGFR tyrosine kinase inhibitor (TKI) and subjects with anaplastic lymphoma receptor tyrosine kinase (ALK) rearrangement positive tumors must have received an ALK TKI
        iii. Subjects with wild-type EGFR and ALK mutation must have failed a platinum-based regimen. NOTE: Maintenance therapy following platinum doublet-based chemotherapy is not considered a separate line of therapy. Prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease is considered first line therapy only if recurrent (local or metastatic) disease developed within 6 months of completing therapy. Subjects

with recurrent disease > 6 months must also have progressed after a subsequent platinum-based chemotherapy regimen given to treat the recurrence

4. For dose-expansion:
   a. Histological confirmation of advanced or metastatic RCC with a clear-cell component
   b. Must have received at least 1 and no more than 2 prior anti-angiogenic therapy regimens (including, but not limited to, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab) in the advanced or metastatic setting.
   c. Must have received no more than 3 total prior systemic treatment regimens in the advanced or metastatic setting, and must have evidence of radiographic progression on or after the last treatment regimen received and within 6 months prior to study enrollment.
   d. No prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or checkpoint pathways
   e. No prior treatment with an mammalian target of rapamycin (mTOR) inhibitor (including, but not limited to everolimus, temsirolimus, sirolimus, and ridaforolimus)
   f. Prior cytokine therapy (eg, IL-2, IFN-α) or treatment with cytotoxics is allowed.
   g. Subjects must have at least 1 measurable lesion according to RECIST v1.1. A previously irradiated lesion cannot be considered a target lesion. Radiographic disease assessment can be performed up to 28 days prior to the first dose
5. Biopsy requirements:
   a. For dose escalation, subjects must consent to provide archival tumor tissue (initial and subsequent tumor biopsy samples, if possible) for correlative biomarker studies if available
   b. Able and willing to give valid written consent for fresh tumor samples if required. 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). Sites are encouraged to confirm adequacy of tumor biopsy material at the time of the procedure. Fine-needle aspirate specimens are not acceptable.
   c. For dose-expansion:
      i. Tumor tissue (formalin fixed paraffin embedded [FFPE] archival or fresh tumor tissue) must be received by the central vendor (block or unstained slides) and evaluable for PD-L1 expression status in order to randomize a subject to study treatment.
      ii. All subjects are encouraged to consent to and provide both pre-treatment and on-treatment fresh tumor biopsies; however, on-treatment biopsies are optional
6. For dose-escalation and dose-expansion: (If evaluations performed as part of standard of care for other purposes prior to obtaining informed consent are suitable for screening and occurred within 7 days prior to starting treatment, those evaluations do not need to be repeated if the subject consents to their use):
   a. Adequate organ and marrow function, as defined below:
      i. Hemoglobin ≥ 9 g/dL

ii. Absolute neutrophil count ≥ 1,500/mm^3
iii. Platelet count ≥ 100,000/mm^3
iv. Total bilirubin ≤ 1.5 × ULN except subjects with documented Gilbert's syndrome (> 3 × ULN) or liver metastasis, who must have a baseline total bilirubin ≤ 3.0 mg/dL
v. Alanine aminotransferase (ALT) and AST ≤ 2.5 × ULN; for subjects with hepatic metastases, ALT and AST ≤ 5 × ULN
vi. Calculated creatinine clearance or 24-hour urine creatinine clearance ≥ 40mL/min determined by the Cockcroft-Gault formula (using actual body weight)

7. Written informed consent and any locally required authorization (eg, Health Insurance 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)
8. Female subjects of childbearing potential who are sexually active with a nonsterilized male partner must use at least one highly effective method of contraception from screening and must agree to continue using such precautions for 120 days after the subject's last dose of MEDI0680 or durvalumab or 150 days after the subject's last dose of nivolumab. It is strongly recommended for the male partner of a female subject to also use male condom plus spermicide throughout this period. Cessation of contraception after this point should be discussed with a responsible physician. Effective methods (including highly effective methods) of contraception are described in Table 4.1.2-1. Not engaging in sexual activity for the total duration of the study is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female subjects should refrain from egg cell donation and breastfeeding throughout this period.
   a. Females of childbearing potential are defined as those who are not surgically sterile (ie, have not undergone bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or who are not post-menopausal
      i. Females < 50 years of age will be considered postmenopausal 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 postmenopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
      ii. Females ≥ 50 years of age will be considered postmenopausal 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. A highly effective method of contraception is defined as one that results in a low failure rate (ie, less than 1% per year) when used consistently and correctly. Note that some contraception methods are not considered highly effective.
9. Nonsterilized males who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from Day 1 through 120 days after the

subject's last dose of MEDI0680 or durvalumab or 150 days after the subject's last dose of nivolumab. It is highly recommended for a female partner of childbearing potential of a male subject to use a highly effective method of contraception throughout this period, as described in Table 4.1.2-1. In addition, male subjects must refrain from fathering a child or donating sperm while on study and for 120 days after the subject's last dose of MEDI0680 or durvalumab or 150 days after the subject's last dose of nivolumab.

Table 4.1.2-1 Effective Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
• Male or female condom with or without spermicide [a, b] • Cap, diaphragm, or sponge with spermicide [a, b] • Copper T intrauterine device [d] • Levonorgesterel-releasing intrauterine system) (eg, Mirena®) [c, d]	• Implants [d] • Hormone shot or injection [d] • Combined pill [d] • Minipill [a] • Patch [d]

Note: A highly effective method of contraception has a failure rate of < 1% per year.

[a] Not highly effective (failure rate of ≥ 1% per year)

[b] A male condom plus cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods

[c] Also considered a hormonal method.

[d] Highly effective (failure rate of < 1% per year).

4.1.3 Exclusion Criteria

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

1. Concurrent enrollment in another clinical study, unless in a follow-up period or it is an observational study
2. Central nervous system (CNS) metastatic disease and leptomeningeal disease are excluded. (Note: spinal cord compression which has been stabilized is allowed).
3. Any concurrent chemotherapy, immunotherapy, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (eg, insulin for diabetes and hormone replacement therapy) is acceptable
   (NOTE: Local treatment of isolated lesions for palliative intent is acceptable [eg, by local surgery or radiotherapy])
4. Any investigational anticancer therapy received within 28 days prior to the first dose of durvalumab and MEDI0680 or nivolumab
5. Major surgical procedure (as defined by the investigator) within 28 days prior to the first dose of durvalumab and MEDI0680 or nivolumab or still recovering from prior surgery
6. Unresolved toxicities from prior anticancer therapy, defined as having not resolved to NCI CTCAE v4.03 Grade 0 or 1 with the exception of alopecia and laboratory values listed per the inclusion criteria. Subjects with prior endocrine toxicities (eg, hypothyroidism) who are stable on replacement therapy are not excluded. Subjects

with irreversible toxicity that is not reasonably expected to be exacerbated by durvalumab and MEDI0680 or nivolumab may be included (eg, hearing loss)
7. Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab and MEDI0680 or nivolumab with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent
8. Active or prior documented autoimmune or inflammatory disease (including inflammatory bowel disease, diverticulitis with the exception of diverticulosis, celiac disease, irritable bowel disease; Wegener's granulomatosis; Hashimoto syndrome) within the past 3 years. Subjects with vitiligo, alopecia, Grave's disease, or psoriasis not requiring systemic treatment (within the past 3 years) are not excluded
9. History of primary immunodeficiency or tuberculosis
10. Test results indicating active infection with human immunodeficiency virus (HIV), or hepatitis A, B, or C
11. Receipt of live, attenuated vaccine within 28 days prior to the first dose of durvalumab and MEDI0680 or nivolumab. NOTE: Subjects, if enrolled, should not receive live vaccine during the study and 90 days after the last dose of durvalumab and MEDI0680 or nivolumab
12. Females who are pregnant, lactating, or intend to become pregnant during the participation to the study
13. Uncontrolled inter-current illness including, but not limited to, ongoing or active infection, current pneumonitis, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, interstitial lung disease, or psychiatric illness/social situations that would limit compliance with study requirement substantially increase risk of incurring AEs from durvalumab or MEDI0680 or nivolumab, or compromise the ability of the subject to give written informed consent
14. Diagnosis of a second malignancy within the last 2 years prior to Cycle 1, Day 1, with the exception of those with a negligible risk of metastasis or death, treated with expected curative outcome (such as adequately treated carcinoma in situ of the cervix, basal or squamous cell skin cancer, localized prostate cancer treated surgically with curative intent, ductal carcinoma in situ treated surgically with curative intent)
15. Known allergy or hypersensitivity to study drug formulations
16. Any condition that, in the opinion of the investigator, would interfere with evaluation of the investigational product or interpretation of subject safety or study results
17. Subjects with advanced NSCLC with tumors harboring anaplastic lymphoma kinase gene rearrangements or epidermal growth-factor receptor-sensitizing mutations who have not received appropriate TKI therapy. These subjects can be enrolled after documented progression or intolerance to appropriate TKIs

4.1.4 Subject Enrollment

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 voice response system/interactive web response system [IXRS]) and the screening evaluations may begin to assess study eligibility

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

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

Subjects who fail to meet the inclusion/exclusion criteria (ie, screening failures) should not receive investigational product. 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 at any time free to withdraw from the study (investigational product and assessments), without prejudice to further treatment (withdrawal of consent). Such subjects will always be asked about the reason(s) and the presence of any AEs. If possible, they will be seen and assessed by an investigator. Adverse events will be followed. If a subject withdraws from further participation in the study, then no further study visits or data collection should take place.

4.1.5.1 Withdrawal of Consent

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

4.1.5.2 Withdrawal from Treatment

Subjects who are permanently discontinued from further receipt of investigational product (see Section 4.1.6) regardless of the reason (withdrawal of consent from further treatment, due to an AE, other), will be identified as having permanently discontinued treatment.

Subjects who are permanently discontinued from treatment in the absence of disease progression will be asked to come in for every protocol-specified visit and will follow all protocol procedures with the exception of dosing. For subjects refusing to return to the site, they should be contacted every 3 months by phone to assess for survival unless consent is withdrawn. The time period for recording toxicity can be found in Section 5.4.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 4.1.6, including the collection of any protocol-specified blood, or urine specimens, unless consent is withdrawn, the subject is lost to follow-up, starts

alternative treatment, or 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 as an alternative.

4.1.5.3 Lost to Follow-up

Subjects will be considered lost to follow-up only if no contact has been established by the time the study is completed (as defined in Section 6.3) such that there is insufficient information to determine the subject's status at that time.

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

4.1.6 Discontinuation of Investigational Product

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

1. Withdrawal of consent from further participation in study-related assessments and follow-up
2. Withdrawal of consent from further treatment with investigational product
3. Lost to follow-up
4. An AE that, in the opinion of the investigator or the sponsor, contraindicates further dosing
5. Any AE that meets criteria for discontinuation as defined in Section 3.1.5.1
6. Dose-limiting toxicity (see Section 3.1.3.3 for definition of DLT)
7. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk
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 (solid tumors) and retreatment criteria in setting of PD are not fulfilled see Section 3.1.2)

Subjects who are permanently discontinued from receiving investigational product will be followed for protocol-specified assessments including follow-up of any AEs unless consent

is withdrawn specifically from further study participation (Section 4.1.5.1), the subject is lost to follow-up, the subject starts alternative treatment, or the subject is enrolled in another clinical study.

4.1.7 Replacement of Subjects

Subjects in the Phase 1/dose-escalation cohorts are considered evaluable if they receive the protocol-assigned dose(s) of both durvalumab and MEDI0680 (ie, 2 doses of durvalumab Q2W and 2 doses of MEDI0680 Q2W) and complete the safety follow-up through the end of the DLT-evaluation period or they experience a DLT during the DLT-evaluation period. Non-evaluable subjects in the dose-escalation cohorts will be replaced in the same dose cohort. No subjects will be replaced in the dose-expansion phase.

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 but will not be labeled with personal identifiers such as the subject's name. If the subject withdraws consent for participating in the future research, this link will allow the sponsor to locate the subject's sample and destroy it. The coding of samples and results is to ensure that these research results are kept confidential by keeping the subject's identity and these results separate.

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

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

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

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. Assessments should be performed in the order shown in the table.

Whenever vital signs, 12-lead electrocardiograms (ECGs), and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then blood draws.

Table 4.2.1-1 Schedule of Screening Procedures Following Protocol Amendment 5

Study Period	**Screening**
Visit Number	**V1**
Procedure / Study Day	**Day -28 to Day -1**
Written informed consent/ assignment of SID number	X
Medical history	X
Physical examination (full), weight, height	X
ECOG performance status	X
Smoking questionnaire (Appendix 4; dose-escalation only)	X
ECG [a]	X
MRI brain (solid tumors) [c]	X
Disease assessment [c]	X
Vital signs, including pulse oximetry	X
Serum chemistry	X

Table 4.2.1-1 Schedule of Screening Procedures Following Protocol Amendment 5

Study Period	Screening
Visit Number	**V1**
Procedure / Study Day	**Day -28 to Day -1**
Hematology	X
Urinalysis	X
Pregnancy test	X
Hepatitis A, B, C; HIV-1	X
TSH, free T4, free T3	X
Flow cytometry	X
Circulating soluble factors	X
mRNA/miRNA	X
Archival/fresh tumor biopsy [b]	X
Assessment of AEs/SAEs	X
Concomitant medications	X
Verify eligibility criteria	X

AE = adverse event; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; HIV = human immunodeficiency virus; miRNA = micro ribonucleic acid; MRI = magnetic resonance imaging; mRNA = messenger ribonucleic acid; SAE = serious adverse event; SID = subject identification; T3 = thyroxine 3; T4 = thyroxine 4; TSH = thyroid stimulating hormone; V = Visit.

[a] At screening, ECGs will be obtained in triplicate (all 3 within a 5-minute time period, at least 1 minute apart).

[b] For all subjects, if an archival tumor biopsy is available then fresh tumor biopsy is not required at screening. If a subject is unable to verify availability of archival tumor samples or where the tumor samples are unsuitable for use, then baseline fresh tumor biopsies will need to be obtained prior to administration of the first dose of study drugs for subjects in the dose-escalation phase or prior to randomization for subjects in the dose-expansion phase.

[c] A computed tomography or MRI scan performed as part of standard of care prior to written informed consent may be used for this assessment if performed within 42 days prior to Day 1 (ie, Day -42 to Day -1).

4.2.2 Treatment Period

Study procedures to be conducted during the primary Q2W dose-escalation treatment period and the dose-expansion treatment period are presented in Table 4.2.2-1 for Cycles 1 through 6 and in Table 4.2.2-2 for Cycles 7 through 13, as well as beyond Cycle 13 for subjects who continue treatment. Assessments should be performed in the order shown in the table when possible.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, the assessments should occur in the following order: 12-lead ECG, vital signs, and then

blood draws. The timing of the first two assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

Subjects who are assigned to MEDI0680 monotherapy should follow procedures outlined for the combination arm, except where it is a durvalumab specific procedure (eg. durvalumab PK collection).

Table 4.2.2-1 Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 1-6 Following Protocol Amendment 5

Procedure	Treatment											
	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
	D1	D15 ± 1	D29 ± 3	D43 ± 3	D57 ± 3	D71 ± 3	D85 ± 3	D99 ± 3	D113 ± 3	D127 ± 3	D141 ± 3	D155 ± 3
Study procedures and examinations												
Abbreviated physical exam (including weight)	X [a]	X	X	X	X	X	X	X	X	X	X	X
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X
ECG [b]	X		X		X				X			
Vital signs [c]	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
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X
Labs												
Hematology	X	X	X	X	X	X	X		X		X	
Serum chemistry	X	X	X	X	X	X	X		X		X	
TSH, free T4, free T3	X		X		X		X		X		X	
Urinalysis	X		X		X		X		X		X	
Blood or urine pregnancy test (females of child bearing potential)[c]	X		X		X		X		X		X	
Pharmacokinetics												
Durvalumab PK (Combination arm only)	X [d]		X [d]						X			
MEDI0680 PK (Combination arm only) [e]	X [f]		X [f]						X			

Table 4.2.2-1 Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 1-6 Following Protocol Amendment 5

Procedure	Treatment											
	Cycle 1		Cycle 2		Cycle 3		Cycle 4		Cycle 5		Cycle 6	
	D1	D15 ± 1	D29 ± 3	D43 ± 3	D57 ± 3	D71 ± 3	D85 ± 3	D99 ± 3	D113 ± 3	D127 ± 3	D141 ± 3	D155 ± 3
Other labs and assays												
Immunogenicity durvalumab (Combination arm only)	X		X						X			
Immunogenicity MEDI0680 (Combination arm only)	X		X						X			
Flow cytometry	X [g]	X			X							
Circulating soluble factors	X		X		X							
miRNA/mRNA	X	X	X									
Tumor biopsy (dose escalation and dose expansion) [h]					X							
Disease assessment (Q8W) [i]					X (-7 to -1)				X (-7 to -1)			
Durvalumab administration (Combination arm only)	X	X	X	X	X	X	X	X	X	X	X	X
MEDI0680 administration [j]	X	X	X	X	X	X	X	X	X	X	X	X
Nivolumab administration (Dose expansion monotherapy arm only)	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; D = Day; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; miRNA = micro ribonucleic acid; mRNA = messenger ribonucleic acid; PK = pharmacokinetic; Q2W = every 2 weeks; Q8W = every 8 weeks; SAE = serious adverse event; T3 = thyroxine 3; T4 = thyroxine 4; TSH = thyroid stimulating hormone.

Note: Evaluations and sample collections should be conducted prior to administration of MEDI0680 and durvalumab or nivolumab unless otherwise indicated. Cycles are 28 days in length and dosing is Q2W.

[a] If physical exam was performed within 3 days prior to Dose 1, it does not need to be repeated. Abbreviated physical exam includes disease specific examination or if clinically indicated.

[b] On Cycle 1 Day 1 single ECGs will be obtained within 60 minutes prior to start of infusion of durvalumab or nivolumab, and within 10 minutes post-EOI of MEDI0680, and within 10 minutes post-EOI of nivolumab. At all other timepoints, single ECGs will be obtained within 60 minutes prior to start of infusion of each durvalumab or nivolumab and as clinically indicated. If an ECG result is abnormal, collect in triplicate at that time (all within a 5 minutes period, at least 1 minute apart). If clinically indicated, ECGs will be collected in triplicate (all within a 5 minute period, at least 1 minute apart) until resolved

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on durvalumab and MEDI0680 or nivolumab treatment days. On Cycle 1 Day 1 in the durvalumab and MEDI0680 combination arm, vital signs will be measured within 30 minutes prior to the start of durvalumab administration (± 30 minutes), 15 minutes (± 5 minutes) post-EOI of durvalumab, and for the first cycle at 10 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-EOI of MEDI0680. For all other combination dose days, vital signs will be measured 30 minutes (± 30 minutes) prior to durvalumab administration, 15 minutes (± 5 minutes) post durvalumab EOI, and 10 minutes (± 5 minutes) and 30 minutes (± 5 minutes) post MEDI0680 EOI. In the nivolumab arm, on Cycle 1 Day 1 vital signs will be measured within 30 minutes prior to the start nivolumab (± 30 minutes), and at 10 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-EOI of nivolumab. All other nivolumab dose days will measure vital signs 30 minutes (± 30 minutes) prior to infusion and 10 minutes (± 5 minutes) post EOI.

[c] Should be performed within 7 days prior to dosing

[d] Predose and EOI (± 10 minutes) for durvalumab.

[e] For subjects in the escalation phase who will switch from the 60 mg/mL formulation to the 50 mg/mL formulation, predose and EOI (± 10 minutes) MEDI0680 PK samples will be collected for the first 2 doses of MEDI0680 using the new formulation.

[f] Predose and EOI (± 10 minutes) for MEDI0680.

[g] Predose for flow cytometry

[h] Subjects who are in the dose-expansion cohorts are encouraged to provide an optional on-treatment fresh tumor biopsy on Day 57 (could be performed up to 7 days prior to investigational treatment administration, but must not be performed after dosing of investigational treatment) if clinically feasible (ie, repeat biopsy does not pose unacceptable medical risk to a subject as determined by the investigator).

[i] Disease assessments will be performed Q8W (± 3 days) during the treatment period or as indicated by signs/symptoms. Disease assessments should occur within 7 days prior to the planned administration of the scheduled investigational treatment.

[j] MEDI0680 will be administered in the combination arm and to the subjects randomized to the MEDI0680 monotherapy arm prior to Protocol Amendment 5. Subjects who are assigned to MEDI0680 monotherapy should follow the procedures listed for the combination arm, with the exception of durvalumab specific procedures (eg, durvalumab PK)

Table 4.2.2-2 Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 7 to "n" Following Protocol Amendment 5

Procedures	Treatment															
	Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12		Cycle 13		Cycle n	
	D169 ± 3	D183 ± 3	D197 ± 3	D211 ± 3	D225 ± 3	D239 ± 3	D253 ± 3	D267 ± 3	D281 ± 3	D295 ± 3	D309 ± 3	D323 ± 3	D337 ± 3	D351 ± 3	Q4W (unless noted otherwise) starting on D365 ± 3	Q4W (unless noted otherwise) starting on D379 ± 3
Study procedures and examinations																
Disease assessment (Q8W) [a]	X (-7 to -1				X (-7 to -1)				X (-7 to -1)				X (-7 to -1)		Q8W starting D393 (7 to -1)	
Abbreviated physical exam (including weight)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X [b]	X [b]
ECOG performance status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4.2.2-2 Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 7 to "n" Following Protocol Amendment 5

Procedures	Treatment															
	Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12		Cycle 13		Cycle n	
	D169 ± 3	D183 ± 3	D197 ± 3	D211 ± 3	D225 ± 3	D239 ± 3	D253 ± 3	D267 ± 3	D281 ± 3	D295 ± 3	D309 ± 3	D323 ± 3	D337 ± 3	D351 ± 3	Q4W (unless noted otherwise) starting on D365 ± 3	Q4W (unless noted otherwise) starting on D379 ± 3
ECG [c]	X				X				X				X [c]		Q12W starting D421 [d]	
Vital signs [e]	X	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	
Assessment of AEs/SAEs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Labs																
Hematology	X		X		X		X		X		X		X		X [f]	
Chemistry	X		X		X		X		X		X		X		X [f]	
TSH, free T4, free T3	X		X		X		X		X		X		X		Q8W [f]	
Urinalysis	X		X		X		X		X		X		X		Q8W [f]	
Blood or urine pregnancy test (females of child bearing potential)	X		X		X		X		X		X		X		X [f]	
Pharmacokinetics																
Durvalumab PK (combo arm only)			X						X							
MEDI0680 PK (combo arm only) [g]			X						X							

Table 4.2.2-2 Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 7 to "n" Following Protocol Amendment 5

Procedures	Treatment															
	Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12		Cycle 13		Cycle n	
	D169 ± 3	D183 ± 3	D197 ± 3	D211 ± 3	D225 ± 3	D239 ± 3	D253 ± 3	D267 ± 3	D281 ± 3	D295 ± 3	D309 ± 3	D323 ± 3	D337 ± 3	D351 ± 3	Q4W (unless noted otherwise) starting on D365 ± 3	Q4W (unless noted otherwise) starting on D379 ± 3
Other labs and assays																
Durvalumab immunogenicity (combo arm only)			X						X							
MEDI0680 immunogenicity (combo arm only)			X						X							
Durvalumab administration (combo arm only) [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
MEDI0680 administration (combo arm only) [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

Table 4.2.2-2 Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 7 to "n" Following Protocol Amendment 5

Procedures	Treatment															
	Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12		Cycle 13		Cycle n	
	D169 ± 3	D183 ± 3	D197 ± 3	D211 ± 3	D225 ± 3	D239 ± 3	D253 ± 3	D267 ± 3	D281 ± 3	D295 ± 3	D309 ± 3	D323 ± 3	D337 ± 3	D351 ± 3	Q4W (unless noted otherwise) starting on D365 ± 3	Q4W (unless noted otherwise) starting on D379 ± 3
Nivolumab administration (Dose expansion monotherapy arm only) [h]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

AE = adverse event; D = Day; ECG = electrocardiogram;; ECOG = Eastern Cooperative Oncology Group;; PK = pharmacokinetic; Q2W = every 2 weeks; Q4W = every 4 weeks; Q8W = every 8 weeks; SAE = serious adverse event; T3 = thyroxine 3; T4 = thyroxine 4; TSH = thyroid stimulating hormone.

Note: Evaluations and sample collections should be conducted prior to administration of MEDI0680 durvalumab, or nivolumab unless otherwise indicated. Cycles are 28 days in length and dosing is Q2W.

[a] Disease assessments will be performed Q8W (± 3 days) during the treatment period or as indicated by signs/symptoms. Disease assessments should occur within 7 days prior to the planned administration of the scheduled investigational treatment.

[b] From the D365 visit, weight will be collected for dosing information but physical exams (disease focused) are only required on Day 1 of each cycle, or if clinically indicated

[c] A single ECG will be obtained within 60 minutes prior to start of infusion of each investigational product and as clinically indicated. If clinically indicated, ECGs will be collected in triplicate (all within a 5 minute period, at least 1 minute apart) until resolved. If an ECG result is abnormal, collect in triplicate at that time (all within a 5 minutes period, at least 1 minute apart).

[d] To be performed on Day 1 of every third cycle, ie, Cycle 16, Cycle 19, etc.

[e] Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on durvalumab and MEDI0680 or nivolumab treatment days. Vital signs will be measured 30 min (± 30 min) prior to durvalumab administration, 15 min (± 5 min) post durvalumab EOI, and 10 min (± 5 min) and 30 min (± 5 min) post MEDI0680 EOI. In the nivolumab arm, vital signs 30 min (± 30 min) prior to infusion and 10 min (± 5 min) post EOI.

[f] From the D365 visit, samples for analysis of hematology, clinical chemistry, and pregnancy tests are only required on Day 1 of every cycle unless clinically indicated. TSH, free T4, free T3 and urine will be collected every other month beginning on Day 365.

Table 4.2.2-2 Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 7 to "n" Following Protocol Amendment 5

Procedures	Treatment															
	Cycle 7		Cycle 8		Cycle 9		Cycle 10		Cycle 11		Cycle 12		Cycle 13		Cycle n	
	D169 ± 3	D183 ± 3	D197 ± 3	D211 ± 3	D225 ± 3	D239 ± 3	D253 ± 3	D267 ± 3	D281 ± 3	D295 ± 3	D309 ± 3	D323 ± 3	D337 ± 3	D351 ± 3	Q4W (unless noted otherwise) starting on D365 ± 3	Q4W (unless noted otherwise) starting on D379 ± 3

[g] For subjects in the escalation phase who will switch from the 60 mg/mL formulation to the 50 mg/mL formulation, predose and EOI (± 10 minutes) MEDI0680 PK samples will be collected for the first 2 doses of MEDI0680 using the new formulation.

[h] For subjects enrolled in the dose-escalation phase, MEDI0680 and durvalumab may be administered up to 12 months. Subjects randomized in the dose-expansion phase will receive either MEDI0680 Q2W in combination with durvalumab Q2W or nivolumab monotherapy until progressive disease, or other reason for treatment discontinuation.

4.2.3 Follow-up Period

Table 4.2.3-1 shows all procedures to be conducted during the end of treatment visit and during the follow-up period. Assessments should be performed in the order shown in the table.

Whenever vital signs, 12-lead ECGs, and blood draws are scheduled for the same nominal time, it is preferred that assessments are performed in the following order: 12-lead ECG, vital signs, and then blood draws. The timing of the first two assessments should be such that it allows the blood draw (eg, PK blood sample) to occur at the exact nominal time.

All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study. Subjects who decline to return to the site for evaluations should be contacted by phone every 3 months for 12 months and then every 6 months. Subjects who are permanently discontinued from treatment because of toxicity in the absence of disease progression will be asked to come in for every protocol-specified visit and will follow all protocol procedures with the exception of dosing.

Table 4.2.3-1 Schedule of Study Procedures: End of Treatment and Posttreatment Laboratory Follow-Up Following Protocol Amendment 5

Procedure	End of Treatment	Posttreatment Laboratory Follow-up After End of Treatment visit		Long-term Follow-up	
		30 Days (± 3 Days)	60 and 90 Days (± 7 Days)	Every 3 Months (± 1 Week) for 12 Months	12 Months Since Last Dose and Then Every 6 Months (± 2 Weeks)
Tumor and disease assessments					
Disease assessment (Q8W only until disease progression) [a]	X [b]				
Study procedures and examinations					
Physical exam (including weight);full at EOT	X	X [b]	X [b]		
ECOG performance status	X				
ECG [d]	X		X [e]		
Vital signs (temperature, BP, pulse rate, and respiratory rate)	X	X	X		
Concomitant medications	X	X	X		
Assessment of AEs/SAEs	X	X	X		

Table 4.2.3-1 Schedule of Study Procedures: End of Treatment and Posttreatment Laboratory Follow-Up Following Protocol Amendment 5

Procedure	End of Treatment	Posttreatment Laboratory Follow-up After End of Treatment visit		Long-term Follow-up	
		30 Days (± 3 Days)	60 and 90 Days (± 7 Days)	Every 3 Months (± 1 Week) for 12 Months	12 Months Since Last Dose and Then Every 6 Months (± 2 Weeks)
Labs and assays					
Hematology	X	X	X		
Chemistry	X	X	X		
TSH, free T4, free T3	X	X	X		
Blood or urine pregnancy test (females of childbearing potential)	X		X [e]	X [f]	
Pharmacokinetics					
Durvalumab PK (combination arm only)			X [e]	X [g]	
MEDI0680 PK (combination arm only)			X [e]	X [g]	
Other labs and assays					
Immunogenicity (combination arm only)			X [e]	X [g]	
Circulating soluble factors	X [h]				
miRNA/mRNA analysis	X [i]				
Tumor biopsy	X [j]				
Subsequent anticancer therapy				X	X
Survival follow-up phone contact every 3 months				X	X

Table 4.2.3-1 Schedule of Study Procedures: End of Treatment and Posttreatment Laboratory Follow-Up Following Protocol Amendment 5

Procedure	End of Treatment	Posttreatment Laboratory Follow-up After End of Treatment visit		Long-term Follow-up	
		30 Days (± 3 Days)	60 and 90 Days (± 7 Days)	Every 3 Months (± 1 Week) for 12 Months	12 Months Since Last Dose and Then Every 6 Months (± 2 Weeks)
Survival follow-up phone contact with subjects who refuse to return for evaluations and agree to be contacted			X	X	X

AE = adverse event; BP = blood pressure; ECG = electrocardiogram; ECOG = Eastern Cooperative Oncology Group; EOT = end of treatment; miRNA = micro ribonucleic acid; mRNA = messenger ribonucleic acid; PK = pharmacokinetic; Q8W = every 8 weeks; SAE = serious adverse event; T3 = thyroxine 3; T4 = thyroxine 4; TSH = thyroid stimulating hormone.

[a] Subjects discontinued from treatment for a reason other than radiologic disease progression should continue to have disease assessments on a Q8W schedule until radiologic disease progression is observed.

[b] Abbreviated symptom-directed physical examination.

[c] End of treatment disease assessment will not need to be repeated if it was performed ≤ 4 weeks from EOT visit.

[d] A single ECG will be obtained at the specified timepoints. Unless clinically indicated at which time it will be collected in triplicate (all within a 5 minute period, at least 1 minute apart).

[e] Collected on 90-day visit only.

[f] Collected on 120-day visit only. Note that subjects should not become pregnant up to 150 days after the subject's last dose of nivolumab.

[g] Collected on 180-day visit only.

[h] Circulating soluble factors to be collected at time of progression only; delay collection until progression if subject discontinues due to AE or other reasons.

[i] mRNA to be collected at end of treatment and at time of progression if subject discontinues due to AE or other reasons

[j] Optional tumor biopsy upon confirmed progressive disease, providing it is clinically feasible.

4.3 Description of Study Procedures

4.3.1 Efficacy

4.3.1.1 Solid Tumors

See Appendix 5.

4.3.2 Archival Tumor Samples, Bone Marrow Biopsies, and Tumor Biopsies

4.3.2.1 Archival Tumor Samples

Archival tumor samples are required for all subjects (dose-escalation and dose-expansion phases) and must be deemed available during the screening period. FFPE tumor samples will be collected for IHC and additional correlative markers (eg, tumor mutation analysis, ribonucleic acid analysis, and immunodiversity). If a tumor block cannot be provided for this study, then only freshly cut sections should be provided as described in the Laboratory Manual.

4.3.2.2 Tumor Biopsies

If the subjects are unable to verify availability of archival tumor samples, as mentioned in Section 4.3.2.1, then baseline fresh tumor biopsies will need to be obtained prior to administration of the first dose of study drugs for the dose-escalation phase or prior to randomization for the dose-expansion phase.

Subjects in the dose-expansion phase are encouraged to provide on-treatment fresh tumor biopsies on Day 57 (could be performed up to 7 days prior to investigational treatment administration, but must not be performed after dosing of investigational treatment) if clinically feasible (ie, repeat biopsy does not pose unacceptable medical risk to a subject as determined by the investigator). In addition, biopsies may be performed if clinically indicated, at the time of progression and at the end of treatment. For subjects who require serial image-guided core needle tumor biopsy, it will be performed according to institutional practice. These post-treatment biopsies are optional. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions.

An evaluation of a possible correlation between clinical activity of durvalumab and MEDI0680 and potential biomarkers (eg, PD-L1 expression on tumor) will be ongoing throughout the study. For the dose-escalation phase, tumoral PD-L1 expression will be assessed on screening samples after enrollment on an ongoing basis. For the dose-expansion phase, tumor tissue (FFPE archival or fresh tumor tissue) must be received by the central vendor (block or unstained slides) and evaluable for PD-L1 expression status in order to randomize a subject to study treatment.

Tumor lesions used for biopsy should not be lesions used as RECIST target lesions, unless there are no other lesions suitable for biopsy. If a RECIST target lesion is used for biopsy the lesion must be ≥ 2 cm in longest diameter. Additional tumor biopsies are permitted as clinically indicated (eg, for mixed responses or upon PD). If clinically practical, at each time

point, subjects will undergo 4 core biopsies at each protocol-specified time point for tumor biopsy, but a minimum of at least 3 core biopsies are required. The first and third core biopsies will be placed in formalin and processed for FFPE, while the second and fourth core biopsies (fourth biopsy, if available) will be immediately frozen in liquid nitrogen and then stored at -80°C. In exceptional cases, excisional or punch biopsies are permitted and may be substituted for the required minimum of 3 core biopsies if sufficiently large (4 mm or greater in diameter).

Tumor biopsies will be stored at MedImmune or an appropriate vendor selected by MedImmune. Core biopsies may be used for biomarker and pharmacodynamic studies using methods such as IHC, IF, tumor mutation analysis, and gene expression analysis. Additional details for sample collection, processing, storage, and shipment will be provided in the Laboratory Manual.

4.3.3 Medical History and Physical Examination

Physical examinations will be performed on study days noted in Section 4.2. A full physical examination will include assessments of the head, eyes, ears, nose, and throat, respiratory, cardiovascular, gastrointestinal, urogenital, musculoskeletal, neurological, psychiatric, dermatological, hematologic/lymphatic, and endocrine systems; weight; and height (at screening only). A smoking questionnaire will be administered at screening (dose-escalation only). Abbreviated symptom-directed physical examinations will be conducted post-screening, except for a full physical examination at the end of treatment and end of study.

Vital signs (temperature, blood pressure, pulse rate, pulse oximetry [at screening only], and respiratory rate) will be measured on study days noted in Section 4.2. On Cycle 1 Day 1 in the durvalumab and MEDI0680 combination arm, vital signs will be measured within 30 minutes prior to the start of durvalumab administration (± 30 minutes), 15 minutes (± 5 minutes) post-end of infusion (EOI) of durvalumab, and at 10 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-EOI of MEDI0680. For all other combination dose days, vital signs will be measured 30 minutes (± 30 minutes) prior to durvalumab administration, 15 minutes (± 5 minutes) post durvalumab EOI, and 10 minutes (± 5 minutes) and 30 minutes (± 5 minutes) post MEDI0680 EOI.

In the nivolumab arm, on Cycle 1 Day 1 vital signs will be measured within 30 minutes prior to the start of nivolumab (± 30 minutes), and at 10 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-EOI of nivolumab. All other nivolumab dose days will measure vital signs 30 minutes (± 30 minutes) prior to infusion and 10 minutes (± 5 minutes) post EOI.

Electrocardiograms will be recorded on study days as noted in Section 4.2. Electrocardiograms recorded at screening will be obtained in triplicate (all 3 within a 5-minute time period, at least 1 minute apart). On Cycle 1 Day 1 single ECGs will be obtained within 60 minutes prior to start of infusion of durvalumab or nivolumab, and within 10 minutes post-EOI of MEDI0680, and within 10 minutes post-EOI of nivolumab. At all other timepoints, single ECGs will be obtained within 60 minutes prior to infusion of each investigational product or nivolumab and as clinically indicated. For abnormal ECGs or if clinically indicated ECGs are required, they should be obtained in triplicate (all 3 within a 5-minute time period, at least 1 minute apart). In case of clinically significant ECG abnormalities, including an ECG that demonstrates a QTcF value > 500 milliseconds, 2 additional 12-lead ECGs should be obtained over a brief period (eg, 30 minutes) and the average of all 3 ECGs should be used to confirm prolongation.

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 pre-study grade or below.

4.3.4 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 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). Clinically significant 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	• Gamma glutamyl transferase
• Chloride	• Lactic dehydrogenase
• Magnesium	• Creatinine
• Potassium	• Blood urea nitrogen
• Sodium	• Glucose

• Bicarbonate	• Albumin
• Aspartate transaminase (AST)	• Total protein
• Alanine transaminase (ALT)	• Triglycerides
• Alkaline phosphatase (ALP)	• Cholesterol
• Total bilirubin	• Amylase
• Direct Bilirubin	
• Thyroid stimulating hormone (TSH), free thyroxine 4 (T4), free thyroxine 3 (T3)	
• Lipase	

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

Hematology

• White blood cell count with differential (to include absolute neutrophil count)	• Platelet count
• Hemoglobin	• Fibrinogen
• Prothrombin time/partial thromboplastin time	
• Hematocrit	

Urinalysis

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

Pregnancy Test (females of childbearing potential only)

- Urine human chorionic gonadotropin (hCG) or serum beta-hCG

Other Safety Tests

- Hepatitis A IgM antibody, hepatitis B surface antigen, hepatitis C antibody
- HIV-1 antibody

4.3.5 Pharmacokinetic Evaluation and Methods

Measurement of durvalumab and MEDI0680 concentrations in serum will be performed using validated immunoassays.

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

Blood samples for measurement of durvalumab and MEDI0680 concentrations in serum will be collected in samples taken according to the schedules of procedures presented in Section 4.2. For subjects in the escalation phase who will switch from the 60 mg/mL formulation to the 50 mg/mL formulation, predose and EOI (± 10 minutes) MEDI0680 PK samples will be collected for the first 2 doses of MEDI0680 using the new formulation.

4.3.6 Immunogenicity Evaluation and Methods

Validated electrochemiluminescence assays using a Meso Scale Discovery platform will be used for the determination of anti-durvalumab antibodies in human serum and for determination of anti-MEDI0680 antibodies in human serum.

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

Blood samples for measurement of durvalumab and MEDI0680 ADA concentrations in serum will be collected in samples taken according to the schedules of procedures presented in Section 4.2.

4.3.7 Biomarker Evaluation and Methods

Blood samples will be collected and analyzed to evaluate protein, nucleic acid and cellular biomarkers according to the schedules presented in Section 4.2.

The numbers of T cells, B cells, and NK cells as well as subsets of T cells may be evaluated in whole blood by flow cytometry. Additional flow cytometric assessment of immune-cell phenotypes and function will be conducted; these may include evaluating phenotype, expression of activation markers, proliferation, and production of cytokines and effector molecules, by cell populations such as T cells, B cells, and myeloid-derived suppressor cells.

Blood samples will be collected for analysis of circulating soluble factors in relation to T-cell activation. They may include but are not limited to soluble CTLA-4, soluble B7-1/B7-2, soluble IL-6R, vascular endothelial growth factor, fibroblast growth factor, IL-1 IL-2, IL-4, IL-6, IL-8, IL-10, granzyme B, IFN, C-X-C motif chemokine 10, suppressor of cytokine signaling 3, a proliferation inducing ligand, B-cell activating factor, insulin-like growth factor (IGF)-1, IGF-2, the presence of IFN-γ, tumor necrosis factor alpha (TNF-α), IL-2, IL-6, IL-10, IL-8, and IL-12 as well as antibodies against tumor, self, or viral antigens and autoantibodies to host and tumor antigens and explore their association with treatment and clinical outcome. Additionally, levels of circulating tumor DNA may be evaluated in response to treatment and relationship with clinical outcome.

In the dose escalation phase, peripheral blood mononuclear cells will be isolated from whole blood, preserved, and stored for flow cytometry of additional cell types such as immune regulatory populations which may include myeloid-derived suppressor cells, subsequent functional analysis or assessment of the diversity of the immune cell repertoire, its relationship to clinical responses, and changes in response to treatment with durvalumab and MEDI0680. Peripheral blood mononuclear cells may also be used for gene expression analysis.

Whole blood samples will be collected in PAXgene tubes and stored frozen at -80°C for miRNA and/or mRNA sample preparation. Ribonucleic acid may be used in the analyses of transcript and/or miRNA expression and stored for future analyses. Ribonucleic acid analyses may be conducted to generate hypotheses associated with the mechanisms of action of

durvalumab and MEDI0680 as well as to identify subsets of subjects responsive to the durvalumab plus MEDI0680 treatment combinations evaluated in this protocol.

For dose-expansion randomization, all subjects' tumor tissue will be tested for expression of PD-L1 through a central vendor, as determined by the Ventana (SP263) IHC assay. Subjects with advanced or metastatic ccRCC who are naïve to immunotherapy will be randomized 2:1 into one of two arms with either MEDI0680 in combination with durvalumab or nivolumab monotherapy. Subjects will be stratified by MSKCC risk group (0 = favorable risk; 1 or 2 = intermediate risk; 3 = poor risk; see Appendix 7), and PD-L1 expression status (≤ 1% and > 1%; Motzer, et al 2002).

Tumor biomarkers, including but not limited to the expression level and localization of PD-L1 protein on tumor cells (by IHC analysis) and the T-cell number and phenotype in tumor tissues will be evaluated in archived and fresh tumor samples for any relationship with subject response to treatment.

Archived material and/or fresh biopsies may be analyzed for the presence of key mutations which may include but are not limited to: EGFR, KRAS, NRAS, APC, B catenin, ALK, and C-MNNG HOS transforming gene to evaluate their potential relevance and correlations with response to the treatment combinations used in this protocol. Analysis of mRNA and/or miRNA in archived and/or fresh tumor tissue may be performed to identify a predictive or posttreatment signature of response.

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 Estimate of Volume of Blood to Be Collected

Following Protocol Amendment 5, a total of approximately 29 mL will be required for all screening tests, which may be conducted over 1 to 28 days during screening. No more than 35 mL of blood will be drawn on any visit day after screening. Approximately 35 mL of blood will be collected at all visits related to the first dose. The total volume to be collected will depend on the number of doses administered and the length of follow-up.

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. Any events that, in the judgment of the medical monitor, are deemed serious enough to warrant immediate review by the data safety monitoring committee. This may include any symptomatic and/or irreversible treatment-related Grade 4 pneumonitis, colitis, dermatitis, or hepatitis or any symptomatic treatment-related related Grade ≥ 3 neurological toxicity or uveitis
2. Subject enrollment is unsatisfactory
3. Non-compliance that might significantly jeopardize the validity or integrity of the study
4. Sponsor decision to terminate development
5. Sponsor decision to terminate the study

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 Products

MedImmune will provide the investigators with MEDI0680 and durvalumab (Table 4.5.1-1) using designated distribution centers.

Nivolumab will be obtained from commercial supply and is formulated, administered and labelled according to locally approved prescribing information and guidance.

Table 4.5.1-1 Identification of Investigational Products

Investigational Product	Manufacturer	Concentration and Formulation as Supplied
Durvalumab	MedImmune	Supplied as a lyophilized powder containing 200 mg (nominal) durvalumab. When reconstituted with 4.0 mL of WFI, the solution contains: 50 mg/mL durvalumab, 26 mM histidine/histidine-HCl, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0.
MEDI0680	MedImmune	Supplied as frozen liquid containing 250mg MEDI0680 in 10 mL vial filled with nominal 5 mL at a concentration of 50mg/mL, containing 20 mM sodium phosphate monobasic/dibasic phosphate, 230 mM sucrose, and 0.01% (w/v) polysorbate 80, pH 6.9
IV Bag Protectant for MEDI0680	MedImmune	Supplied as 3cc vials filled with a nominal 1.0 mL containing 3.1 mM citric acid, 21.9 mM sodium citrate dihydrate, 0.65% (w/v) polysorbate 80, pH 6.0

HCl = hydrochloride; IV = intravenous; WFI = water for injection; w/v = weight per volume;

The investigator's or site's designated investigational product manager is required to maintain accurate investigational product accountability records. Commercially available water for injection (WFI) and 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. All unused investigational product will be returned to a MedImmune-authorized depot or disposed of upon authorization by MedImmune according to the investigational site policy. Investigational products should be kept in a secure area.

4.5.1.1 Durvalumab

Durvalumab Dose Preparation

Each vial selected for dose preparation should be inspected.

Durvalumab is supplied as a vial containing 200 mg (nominal) durvalumab as a lyophilized powder. Durvalumab must be stored at 2°C to 8°C (36°F to 46°F) in a secure area with restricted access. When reconstituted with 4.0 mL of WFI, the solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, 0.02% (w/v) polysorbate 80, at pH 6.0. Each carton contains 4 single-dose vials. White labels will be applied to cartons and vials containing durvalumab.

Investigational product 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).

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 4.5.1.5) for further instructions.

Durvalumab Dose Calculation

Dose-escalation Phase

The dose will be calculated using the following formula:

$$\text{By weight: Dose (mL)} = \frac{[\text{subject weight (kg)} \times \text{durvalumab dose level (mg/kg)}]}{50 \text{ mg/mL}}$$

where 50 mg/mL is durvalumab concentration after reconstitution.

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

Dose-expansion Phase

A fixed dose of 750 mg (ie, 15 mL) durvalumab will be administered for all subjects randomized into the MEDI0680/durvalumab combination arm.

Durvalumab Dose Preparation Steps

No incompatibilities between durvalumab and polyethylene, polypropylene, polyvinylchloride, or polyolefin copolymers have been observed. Durvalumab does not contain preservatives and any unused portion must be discarded. Preparation of durvalumab and preparation of the IV bag are to be performed aseptically. Total in-use storage time from needle puncture of durvalumab to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If storage time exceeds these limits, a new dose must be prepared from new vials.

Durvalumab requires reconstitution prior to use. The reconstitution should be performed with 4.0 mL sterile WFI for each vial with the liquid added gently to the side of the vial to minimize product foaming. Commercially available sterile WFI will be supplied by the sites.

The vial should be gently rotated or swirled until dissolution is complete. The vial should not be shaken or vigorously agitated. Reconstituted durvalumab should stand undisturbed at room temperature for a minimum of 5 minutes or until the solution clarifies. The reconstituted solution should appear clear or slightly opalescent. A thin layer of bubbles on the liquid surface is considered normal.

Durvalumab will be administered using a 250 mL IV bag containing 0.9% (w/v) saline and delivered through an IV administration set with a 0.22 or 0.2-µm in-line filter. To prepare the durvalumab saline IV admixture, a volume of 0.9% (w/v) saline equal to the calculated volume of durvalumab to be added to the IV bag must be removed from the IV bag prior to addition of durvalumab. The calculated volume of durvalumab is then added to the IV bag, and the bag is mixed by gentle inversion to ensure homogeneity of the dose in the bag. Following preparation of the dose, the entire contents of the IV bag should be administered as an IV infusion for approximately 1 hour. Flush the IV line with a volume of normal saline equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed. Durvalumab infusion must be completed before MEDI0680 is dosed for subjects assigned to receive both products. MEDI0680 infusion will start approximately 30 minutes after the end of durvalumab infusion.

Durvalumab solution should not be infused through an IV line in which other solutions or medications are being administered. The date, start time, interruption, and completion time of durvalumab administration must be recorded in the source documents.

Durvalumab Administration Guidelines

Each dose of durvalumab should be administered using the following guidelines:

1. Investigational product must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
2. A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available. Investigational product must not be administered via IV push or bolus but as a slow IV infusion. The entire content of each IV bag will be infused using an infusion pump.
3. The infusion lines should be attached only at time of use. Lines used for infusion during dose administration will need to be equipped with 0.22- or 0.2µm in-line filters.

4. Some investigational product may remain in the IV line after the infusion is complete. 15 to 30 mL of 0.9% sodium chloride IV solution should be added to the infusion bag after the investigational product has been administered to flush the line (infusion rate should not be changed) or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed..

The duration of the investigational product administration will be recorded.

4.5.1.2 MEDI0680

Each vial selected for dose preparation should be carefully inspected. MEDI0680 is supplied as a sterile frozen liquid dosage form filled in a glass vial configuration. The product will be supplied to sites in separate multi-subject cartons and must be stored at -15°C to -50°C until ready to use.

MEDI0680 Drug Product is filled in a 10 mL vial with 20 mm opening US Pharmacopeia (USP) Type I Clear Borosilicate glass vial. The 20 mm serum stopper is Teflon coated. The 20 mm aluminum seal has a matte white flip off style top. The label is white.

The IV Bag Protectant (IVBP) is filled in a 3 mL USP Type I Clear Borosilicate glass vial. The 13 mm serum stopper is Teflon coated. The 13 mm aluminum seal has a matte blue flip off style top. Investigational product 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 carton contains 12 single-dose vials. White labels will be applied to cartons and vials containing MEDI0680. No other coding will be included.

Each vial selected for dose preparation should be inspected after thawing. 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 4.5.1.5) for further instructions.

Preparation of MEDI0680 and preparation of the infusion bag are to be performed using aseptic technique. MEDI0680 does not contain preservative and hence any unused portion must be discarded. Total in-use storage time from needle puncture of the first vial of MEDI0680 for investigational product preparation to start of administration should not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F). If storage time exceeds these limits, a new dose must be prepared from new vials and the study monitor must be notified *immediately*.

MEDI0680 Dose Preparation

Thawing techniques include 3 options:

- Option 1 (preferable) – Remove from carton the vial(s) required for the subject's dose and place in a secure refrigerator approximately 3 to 4 hours prior to use. This technique allows MEDI0680 to thaw slowly while still being refrigerated.
- Option 2 – Remove from carton the vial(s) required for the subject's dose and place on a countertop in a secure location and thaw at room temperature. This technique will take approximately 1 to 1.5 hours to thaw MEDI0680.
- Option 3 – Remove from carton the vial(s) required for the subject's dose and place on the counter within a laminar flow hood and thaw via circulating airflow. This technique will take approximately 30 minutes to 1 hour to thaw MEDI0680.

IMPORTANT: Do not remove vial cap until fully thawed and removed from the laminar flow hood.

Mixing - Ensure that the contents of the vial are completely thawed before drawing the subject's dose. **Gently swirl the solution to completely mix the contents. Do not shake the vial. Do not foam the vial contents**.

Infusion of MEDI0680 should begin within 4 hours of completion of thaw.

MEDI0680 Preparation of Intravenous Dose

The IVBP is required for intravenous dose preparation of MEDI0680.

For the 20 mg/kg dose level, the dose will be prepared directly using the investigational product. Calculate MEDI0680 dose using the following formula:

Equation 1:

$$Dose\ (mL) = \frac{Subject\ weight\ (kg) * dose\ level\ (\frac{mg}{kg})}{concentration\ of\ investigational\ product\ (\frac{mg}{mL})}$$

Example of dose calculation with 50mg/mL Investigational Product, assuming a body weight of 40kg and dose level of 20 mg/kg.

$$Dose\ (mL) = \frac{40\ (kg) * 20\ (\frac{mg}{kg})}{50\ (\frac{mg}{mL})}$$

$$= 16.0\ mL\ of\ 50\ \frac{mg}{mL}\ Investigational\ Product$$

Example calculation for number of vials needed for this dose

$$\#\ of\ Vials\ (rounded\ up\ to\ the\ nearest\ whole\ vial) = \frac{Calculated\ dose\ volume\ (mL)}{nominal\ fill\ volume\ (mL)}$$

$$Example: \#\ of\ Vials = \frac{16.0\ (mL)}{5.0\ (mL)} = (3.2)\ 4\ vials$$

MEDI0680 Dose Preparation Steps

The dose of MEDI0680 for administration must be prepared by the investigational product manager or other qualified professional using aseptic technique. Only remove the required MEDI0680 and the IVBP vials required for subject dosing from storage.

No incompatibility between MEDI0680 and plastics (polyolefin, polyethylene and polyvinyl chloride) has been observed when used along with IVBP. IV bags must be free of latex and di(2-ethylhexyl) phthalate (DEHP). Polypropylene and polycarbonate syringes should be used for dose preparation. Infusion line should contain a 0.22 or 0.2 μm in-line filter.

Follow the guidelines of the IV bag manufacturer for maximum number of allowable punctures through the injection port; if needed, use an intermittent adaptor on the injection port for dose preparation.

For all dose levels, IVBP must be used to precondition the IV bag prior to addition of MEDI0680 (specific instructions below).

Preparation of 20 mg/kg dose for IV infusion:

- Add the calculated volume of 0.9% saline (described below) in an empty IV bag to achieve 60 mL dose delivery volume using following equation:
  - **Equation 2:** Volume of 0.9% saline required to add in IV bag = 60 mL – (Investigational Product + 1 mL IVBP)
- To this bag, add 1 mL of IVBP, gently mix the bag, and then add the calculated volume of Investigational Product as described below (Table 4.5.1.2-1).

Table 4.5.1.2-1 Preparation of 20 mg/kg dose for IV infusion

Dose level (mg/kg)	Investigational Product to be added(mL) A	IVBP to be added to IV bag (mL) B	0.9% Saline added (mL) C	Total Delivery Volume (mL) A + B + C
20	Add as per Equation 1	1.0	Add as per Equation 2	60

IV = intravenous; IVBP = intravenous bag protectant.

Dose preparation steps common for all dose levels are as follows:

1. Select the IXRS-assigned number of vials of investigational product required to prepare the subject's dose.
2. After thawing, all investigational product vials should be equilibrated to room temperature for 30 minutes prior to dose preparation.
3. To prepare investigational product, the investigational product manager should remove the tab portion of the vial cap and clean the rubber stopper with 70% ethanol or equivalent and allow to air dry. *To avoid foaming, the vial should not be shaken.*
4. For ease of preparation, a 1.5-inch 19-gauge withdrawal needle is recommended. Use a new needle for withdrawing investigational product from each vial.
5. Gently mix the contents of the infusion bag. The resulting mixture should be inspected to ensure that the solution is clear.

MEDI0680 Administration Guidelines

The day of dosing with investigational product is considered Day 1.

Each dose of MEDI0680 should be administered using the following guidelines:

1. Investigational product must be administered at room temperature by controlled infusion via an infusion pump into a peripheral vein. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.
2. A physician must be present at the site or immediately available to respond to emergencies during all administrations of investigational product. Fully functional resuscitation facilities should be available. Investigational product must not be administered via IV push or bolus but as a slow IV infusion as per Table 4.5.1.2-2. The entire content of each IV bag will be infused using an infusion pump.
3. The infusion lines should be attached only at time of use. Lines used for infusion during dose administration will need to be equipped with 0.22- or 0.2-µm in-line filters.
4. Some investigational product may remain in the IV line after the infusion is completed. 15 to 30 mL of 0.9% sodium chloride IV solution should be added to the infusion bag after the investigational product has been administered to flush the line (infusion rate

should not be changed) or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

The duration of the investigational product administration will be recorded.

Table 4.5.1.2-2 Investigational Product Solution Volume by Treatment Group

Dose level (mg/kg)	Total Investigational Product Solution Volume Per Bag (mL)
20	60

MEDI0680 will be administered by IV infusion over a minimum of 30 minutes at dose levels of 0.1, 0.5, and 2.5 mg/kg, over a minimum of 60 minutes at dose levels of > 2.5 mg/kg up to a total dose of 1200 mg, and over a minimum of 90 minutes at total doses > 1200 mg. During preparation of the investigational product infusion, the capacity of the tubing should be calculated in order to adjust the volume of investigational product solution needed to prime the IV tubing (see example below). This step is necessary because the same volume of saline will be needed at completion of the infusion to flush the IV tubing in order to deliver the complete volume of investigational product solution. Because the IV tubing contains investigational product solution, the flush must be infused using the same infusion rate as that used for the investigational product solution in the infusion bag.

Example:

If the IV tubing capacity is 15 mL, the IV tubing should be primed with 15 mL of investigational product solution from the investigational product infusion bag before initiating the investigational product infusion. Once the investigational product infusion bag is empty, the IV tubing should be flushed with at least 15 mL of 0.9% normal saline via infusion pump at the same rate as dosing.

The start time of the investigational product infusion will be the time the infusion of the investigational product solution from the infusion bag (with IV tubing already primed with investigational product solution) is started. The stop time of the infusion should be the time the IV tubing has been flushed to administer the residual investigational product solution.

4.5.1.3 Nivolumab

For information on nivolumab, refer to the local (country-specific) package insert (or similar).

4.5.1.4 Monitoring of Dose Administration

Subjects will be monitored during and after infusion of durvalumab, MEDI0680, or nivolumab (see Section 4.3.3).

In the event of Grade ≤ 2 infusion-related reaction, the infusion rate of durvalumab or MEDI0680 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.

Refer to the local (country-specific) package insert (or similar) for guidance on dose administration and modification for subjects in the nivolumab arm.

Primary prophylaxis against infusion-related reactions is not permitted during this study in order to avoid obscuring potential safety signal and enable a future assessment regarding whether pre-medications 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 may be administered per institutional standard as secondary at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, treatment with durvalumab and MEDI0680 will be discontinued.

As with any antibody, 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.

4.5.1.5 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:

Email: [redacted]

Phone: [redacted]

Fax: [redacted]

Mail: MedImmune, LLC
Attn: Product Complaint Department
One MedImmune Way
Gaithersburg, MD 20878 USA

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 (GMP) and local regulatory guidelines. The label will fulfill GMP Annex 13 requirements for labeling. Label text will be translated into local languages, as required.

4.5.4 Storage

Store durvalumab at 2°C to 8°C (36°F to 46°F). Do not freeze.

Store MEDI0680 at -15°C to -50°C (5°F to -58°F) and store IVBP at 2°C to 8°C (36°F to 46°F). Do not freeze the IVBP.

For storage of nivolumab, refer to the local (country-specific) package insert (or similar).

4.5.5 Treatment Compliance

Investigational product is administered by qualified 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

During the dose-escalation phase, each subject who meets the eligibility criteria will be assigned open-label investigational product(s). A subject is considered entered into the study when the investigator notifies the IXRS that the subject meets eligibility criteria and is enrolled into the study.

During the dose-expansion phase, subjects will be randomized 2:1 to 1 of 2 arms to either receive MEDI0680 in combination with durvalumab, or nivolumab monotherapy. Subjects are considered randomized into the study when the site confirms eligibility and enters the subject into the IXRS and are assigned unblinded investigational product(s). Subjects will be stratified by MSKCC risk group (0 = favorable risk; 1 or 2 = intermediate risk; 3 = poor risk; see Appendix 7), and PD-L1 expression status (≤ 1% and > 1%; Motzer, et al 2002).

At that time the IXRS will provide the assignment of unblinded investigational product kit numbers to the subject.

The investigational products must be administered or dispensed within 2 days after randomization. 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 study is not blinded.

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 90 days after the last dose of durvalumab, MEDI0680 or nivolumab.

Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the electronic case report form (eCRF).

4.7.1 Permitted Concomitant Medications

Investigators may prescribe concomitant medications or treatments (eg, acetaminophen, diphenhydramine) deemed necessary to provide adequate supportive care except for those medications identified as "excluded" as listed in Section 4.7.2. Specifically, subjects should receive full supportive care during the study, including transfusions of blood and blood products, and treatment with antibiotics, anti-emetics, anti-diarrheals, and analgesics, and other care as deemed appropriate, and in accordance with their institutional guidelines.

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. 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
3. Any growth factor support except during hospitalization for neutropenic fevers
4. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses not 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 and intranasal corticosteroids is permitted. A temporary period of steroids could be allowed for different indications (eg, chronic obstructive pulmonary disease, radiation, nausea, etc) after discussion with the sponsor.
5. Live attenuated vaccines during the study and 30 days after the last dose
6. Herbal and natural remedies should be avoided

4.8 Statistical Evaluation

4.8.1 General Considerations

Tabular summaries will be presented by cohorts. Categorical data will be summarized by the number and percentage of subjects in each category. Continuous variables will be summarized by descriptive statistics. All analyses will be based on the As-treated Population,

which includes all subjects who receive any dose of investigational product analyzed according to the treatment they actually receive. Additional details of statistical analyses will be described in the statistical analysis plan.

4.8.2 Sample Size and Power Calculations

A total of approximately 96 subjects could be required for both the dose-escalation and dose-expansion phases. For dose-escalation, the number of subjects will depend upon the toxicities observed as the study progresses. Up to approximately 36 evaluable subjects could be required by the 3 + 3 design with 6 dose cohorts in the main dose-escalation design. Additional subjects could be required if dose de-escalation occurs, intermediate dosing using the modified zone-based design is explored, the dosing interval of MEDI0680 is changed, or expansion of a dose-escalation cohort occurs. Subjects in the dose-escalation phase are considered evaluable if they receive the protocol-assigned doses of both durvalumab and MEDI0680, and complete the DLT-evaluation period or experience a DLT during the DLT-evaluation period. Non-evaluable subjects will be replaced. The table below provides the probability of dose-escalation to the next higher level for each underlying true DLT rate. For example, for a common toxicity that occurs in 10% of subjects, there is a greater than 90% probability of escalating to the next higher dose level. Conversely, for a toxicity that occurs with a rate of 60%, the probability of escalating to the next higher dose level is less than 10%.

Table 4.8.2-1 Probability of Escalating Dose for Different True Underlying Dose-limiting Toxicity Rate at Given Dose Level

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

DLT = dose-limiting toxicity.

For the dose-expansion phase, up to approximately 60 subjects (40 subjects in the MEDI0680/durvalumab combination therapy arm and 20 subjects in the nivolumab monotherapy arm) may be randomized at the selected combination dose (ie, MTD or highest protocol-defined dose for each agent in the absence of exceeding the MTD) in a 2:1 ratio. The primary objective is to evaluate the antitumor activity as based on ORR of MEDI0680 in combination with durvalumab versus nivolumab monotherapy in immunotherapy-naïve subjects with advanced or metastatic ccRCC based on an application of RECIST v1.1 (Eisenhauer et al, 2009) to investigator-assessed tumor measurements. Assuming an ORR for

nivolumab monotherapy of 21.5%, the sample size is chosen to detect a difference in ORR of 26.0% (ie, ORR = 47.5%) with 76% power at a 1-sided significance level of 0.10. The 95% CI of a 47.5% ORR (19 responders / 40 subjects) based on the exact probability method is 31.5%, 63.9%. The assumption of a nivolumab monotherapy ORR of 21.5% is based on the data from the nivolumab package insert (see Section 1.5).

4.8.3 Safety Analyses

4.8.3.1 Maximum Tolerated Dose Evaluation (Every 2-week Dosing Schedule)

The MTD evaluation will be based on the DLT-evaluable Population which includes all subjects enrolled in the dose-escalation phase who receive 2 protocol-assigned doses of durvalumab and MEDI0680 and complete the safety follow-up through the end of the DLT-evaluation period, or experience a DLT during the DLT-evaluation period.

4.8.3.2 Analyses of Safety Endpoints

The safety evaluation will be based on the As-treated Population and will include AEs, SAEs, laboratory evaluations, vital signs, and physical examinations. Summary statistics will be provided for AEs, SAEs, and AE grade, and relationship to investigational product, reported from start of treatment with durvalumab and MEDI0680 or nivolumab alone. Adverse events will be graded according to the NCI CTCAE v4.03 and described by system organ class using the Medical Dictionary for Regulatory Activities preferred term. Laboratory abnormalities with toxicity grades according to the NCI CTCAE v4.03 will be derived and summarized. Safety analyses will be descriptive in nature and no formal statistical comparison will be made.

4.8.4 Efficacy Analyses

4.8.4.1 Analysis of Efficacy Endpoints

For the dose-escalation phase, efficacy analyses will be based on an application of modified RECIST v1.1 to investigator-assessed tumor measurements. RECIST v1.1 has been modified to require confirmation of PD. A confirmed PD will be a PD confirmed by a consecutive repeat assessment no fewer than 4 weeks later. A PD that occurs without follow-up scans to provide confirmation or only non-evaluable follow-up scans will also be considered a confirmed PD. The efficacy analysis will be based on the As-treated Population.

For the dose-expansion phase, efficacy analyses will be based on an application of RECIST v1.1 to investigator-assessed tumor measurements and blinded independent central review (BICR). The efficacy analysis will be based on the As-treated Population.

The following efficacy endpoints will be analyzed. More details will be provided in the statistical analysis plan.

ORR (primary endpoint) is defined as the proportion of subjects with a Best Overall Response (BOR) of confirmed CR or confirmed PR. ORR will be estimated with a 95% CI using the exact probability method. For the dose-expansion phase, comparison of arms will be obtained from Fisher's exact test.

DCR at 16 weeks (DCR16) is defined as the proportion of subjects with a BOR of confirmed CR, confirmed PR, or SD (maintained for ≥ 16 weeks). A similar definition applies to DCR24. DCR16 and DCR24 will be estimated with a 95% CI using the exact probability method.

Time to response (TTR) is defined as the time from the first dose of treatment until the first documentation of a subsequently confirmed OR. Only subjects who have achieved OR will be evaluated for TTR. The median TTR and its 95% CI will be assessed using the Kaplan-Meier method.

Duration of response (DR) is defined as the time from the first documentation of a subsequently confirmed OR until the first documentation of a disease progression (subsequently confirmed for dose escalation phase) or death due to any cause, whichever occurs first. Only subjects who have achieved OR will be evaluated for DR. The median DR and its 95% CI will be estimated using the Kaplan-Meier method.

Progression-free survival (PFS) is defined as the time from the first dose of treatment until the first documentation of a disease progression (subsequently confirmed for dose escalation phase) or death due to any cause, whichever occurs first. The median PFS and its 95% CI will be estimated using the Kaplan-Meier method. The Kaplan-Meier method will be used to estimate the PFS curve and the PFS rate at time points of interest.

Overall survival (OS) is defined as the time from the first dose of treatment with durvalumab and MEDI0680 or nivolumab until death due to any cause. The median OS and its 95% CI will be estimated using the Kaplan-Meier method. The Kaplan-Meier method will be used to estimate the OS curve and the OS rate at time points of interest.

4.8.5 Pharmacodynamic Analyses

Exploratory pharmacodynamic analyses may include but are not limited to:

1. Dose escalation only: Serum sPD-L1 levels will be measured to evaluate their association with drug exposure, and response to treatment with durvalumab and MEDI0680 or MEDI0680 alone
2. Dose escalation only: Levels of PD-1 expression and MEDI0680 receptor occupancy on peripheral blood T cells before and after treatment may be measured to evaluate associations with drug exposure, response to treatment with durvalumab and MEDI0680
3. Flow cytometric assessment of cell populations such as T cells, B cells, and myeloid-derived suppressor cell (MDSC) will be performed before and after treatment to evaluate its association with drug exposure and response to treatment with durvalumab and MEDI0680; analysis may include characterization of phenotype, expression of activation markers, proliferation, and production of cytokines and effector molecules
4. Levels of circulating soluble factors, which may include cytokines, chemokines, growth factors, soluble receptors, and antibodies against tumor and self-antigens, will be evaluated before and after treatment may be examined in relation to treatment with durvalumab and MEDI0680 compared with nivolumab monotherapy
5. Expression and localization of key molecules such as PD-L1, PD-L2, and PD-1 within the tumor microenvironment, as well as the frequency, localization, and phenotype of tumor-infiltrating lymphocytes, may be examined in biopsy specimens by IHC, IF, and/or flow cytometry and correlated with response to treatment
6. Expression of miRNA/mRNA in blood and/or tumor samples may be performed before and after treatment to examine gene expression patterns at baseline and changes in response to treatment and to try to identify a gene signature predictive of response to treatment
7. Genetic profiling of pre-treatment and posttreatment biopsy specimens may be performed to identify potential genetic predictors of response or resistance. This may include evaluation of key oncogenic mutations, and/or mutations in immune-related molecules.

4.8.6 Analyses of Immunogenicity and Pharmacokinetics

4.8.6.1 Immunogenicity

Only subjects who receive at least one dose of both durvalumab and MEDI0680 (if assigned), and provide at least one posttreatment sample will be evaluated. Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of subjects who develop detectable anti-durvalumab or anti-MEDI0680 antibodies. The immunogenicity titer will be reported for samples confirmed positive for the presence of anti-durvalumab or anti-MEDI0680 antibodies. The impact of ADAs on PK and pharmacodynamics will also be assessed if data allow. Samples will be collected and banked for evaluating neutralizing capacity of ADAs in the future.

4.8.6.2 Pharmacokinetics

Only subjects who receive at least one dose of durvalumab and MEDI0680 (if assigned) and provide at least one posttreatment sample will be evaluated. Individual durvalumab and MEDI0680 concentrations will be tabulated by dose cohort along with descriptive statistics. The PK of durvalumab and MEDI0680 will be assessed using parameters including C_{max} and minimum concentration (C_{min}) after the first dose. Durvalumab and MEDI0680 steady-state PK parameters including concentrations at peak concentration at steady state ($C_{max,ss}$) and trough concentration at steady state ($C_{min,ss}$) will be estimated. Accumulation to steady state will be assessed as the ratio of $C_{max,ss}$:C_{max} and $C_{min,ss}$:C_{min}. All PK parameters will be estimated by non-compartmental analysis. Descriptive statistics of non-compartmental PK parameters will be provided.

4.8.7 Exploratory Analyses

Descriptive statistics will be the primary methods for the exploratory analyses. Depending on the nature of the data, geometric mean and other appropriate statistical summaries might be used as well.

4.8.7.1 Immune-related Response Criteria

In order to more fully assess the efficacy of these immunotherapies, efficacy analyses will also be based on an application of immune-related Response Evaluation Criteria in Solid Tumors (irRECIST) (modified from Nishino et al, 2013) to investigator-assessed tumor measurements. Endpoints to be summarized include: BOR, OR, DC, TTR, DR, and PFS.Tumor response by irRECIST will be compared with that by RECIST v1.1. The irRECIST is similar to RECIST v1.1 (Appendix 5) except for the following:

- The measurements of the new lesions are included in the sum of the measurements of all target lesions and do not automatically constitute PD under irRECIST, whereas new lesions are not measured and automatically constitute PD under RECIST v1.1.

4.8.8 Interim Analyses

An interim futility analyses will be performed for the MEDI0680/durvalumab combination therapy arm in the dose-expansion phase after 20 subjects have been randomized and have reached their second post-baseline disease assessment or have completed study. Subject accrual may be paused in both cohorts to evaluate the MEDI0680/durvalumab combination therapy arm for futility. However, an accrual pause may not be necessary if existing data upon randomization of 20 subjects suggests futility criteria have not been triggered as per the

predefined futility stopping criteria. The purpose of the interim futility analysis will be for evaluation of key efficacy data for internal program decision as to whether to continue randomization of subjects. Continued randomization of subjects in both arms will be terminated if 2 (10%) or fewer responses within the MEDI0680/durvalumab combination arm are observed. For the futility analysis, a response is defined as either a confirmed or unconfirmed CR or PR as per RECIST v1.1.

Futility stopping criteria is defined as having a non-small probability (10%) to be greater than or equal to a target response rate of 25.1%. If the true response rate is ≥ 25.1% there is a 9.0% probability that the study will be stopped early erroneously (false negative). The target response rate was set so as to demonstrate an ORR at least as large as that of nivolumab based on investigator assessments, in a similar RCC population (ORR = 25.1 [95% CI: 21.0%, 29.6%]; Motzer et al, 2015).

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, medically significant 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 cells increased). Abnormal laboratory values that are not, in the investigator's opinion, medically significant and do not require intervention should not be reported as AEs.

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

Elective 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. Death clearly resulting from disease progression should not be reported as an SAE (see reporting guidelines in Section 5.4.3).

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. New metastatic lesion(s) of the subject's known cancer should not be reported as a new cancer.

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.

5.3.1 Immune-mediated Adverse Events

Adverse events of special interest for durvalumab or MEDI0680 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 also being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An imAE is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.

If the investigator has any questions in regards to an AE being an imAE, the investigator should promptly contact the study physician.

Potential imAEs include the following:

- Colitis, enterocolitis, and other corresponding gastrointestinal disorders
- Pneumonitis
- Hepatitis and hepatotoxicity, including ALT/AST increases

- Neuropathy and neuromuscular toxicity (ie, events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (ie, events of hypophysitis, hypopituitarism (including diabetes insipidus), adrenal insufficiency, hyper- and hypothyroidism, type 1 diabetes mellitus)
- Rash including dermatitis
- Nephritis and increased creatinine
- Pancreatitis (or laboratory tests suggestive of pancreatitis - increased serum lipase , increased serum amylase)

Further information on these risks (eg, presenting symptoms) can be found in the current version of the durvalumab and MEDI0680 Investigator's Brochures. More specific guidelines for evaluation and treatment of these risks are described in detail in Appendix 6.

5.3.2 Hepatic Function Abnormality (Hy's Law)

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. See Appendix 6 for the definition and reporting of AESIs of hepatic function abnormality

5.3.3 Infusion Reactions

Adverse events of infusion reactions (also termed infusion-related reactions) are of special interest to the sponsor and are defined, for the purpose of this protocol, as all AEs occurring from the start of the study treatment infusion up to 48 hours after the infusion start time. Guidelines for management of subjects with infusion-related reactions are outlined in Appendix 6. For all infusion reactions, the eCRF should be completed as instructed in Section 5.4, and all SAEs should be reported to MedImmune Patient Safety as described in Section 5.5.

5.3.4 Hypersensitivity (Including Anaphylaxis) Reactions

Hypersensitivity reactions (including anaphylaxis) 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 (immunoglobulin E-mediated) and anaphylactoid reactions against the mAb, and serum sickness, etc. 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

Adverse events will be recorded on the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to MedImmune Patient Safety. See Section 5.2 for the definition of SAEs and Appendix 2 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 monoclonal antibodies 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 MEDI0680 and durvalumab or nivolumab, 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 3.

5.4.1 Time Period for Collection of Adverse Events

Adverse events will be collected from time of signature of informed consent throughout the treatment period and including the follow-up period of 90 days after the last dose of durvalumab and MEDI0680 or nivolumab. Serious adverse events will be recorded from the

time of informed consent signature through 90 days after the last dose of durvalumab and MEDI0680 or nivolumab.

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 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 (autopsy) 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:

Patient Safety
MedImmune
One MedImmune Way
Gaithersburg, MD 20878, USA
[redacted]
Global Fax: [redacted]
North America Fax number: [redacted]

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 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to the sponsor.

5.6.2.1 Maternal Exposure

If a subject becomes pregnant during the course of the study investigational product should be discontinued immediately.

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

If any pregnancy occurs during the course of the study, then the investigator or other site personnel will inform the appropriate sponsor representatives within 1 day, ie, immediately but no later than 24 hours after becoming aware of the event.

The designated sponsor representative works with the investigator to ensure that all relevant information is provided to the sponsor's patient safety data entry site within 1 or 5 calendar days for SAEs (see Section 5.5) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The pregnancy reporting module in the eCRF is used to report the pregnancy and the pregnancy outcome module is used to report the outcome of the pregnancy.

5.6.2.2 Paternal Exposure

Pregnancy of the subject's partner(s) is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth or congenital abnormality), occurring from the date of the first dose until 120 days after the final dose of MEDI0680 or durvalumab or 150 days after the subject's last dose of nivolumab should, if possible, be followed up and documented.

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 study 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 (or designee) 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 met the minimum criteria for study completion if the subject was followed through the DLT-evaluation period or experienced a DLT during the DLT-evaluation period (for subjects in the dose-escalation phase) or the subject completed at least 1 on-treatment disease evaluation (for subjects in dose-expansion phase) regardless of the number of doses of investigational product that was received. Subjects should continue treatment with investigational product beyond these minimum completion criteria unless criteria for discontinuation are met (Section 4.1.6), and all subsequent protocol-specified assessments will be performed as detailed in Section 4.2.2 and Section 4.2.3.

The end of the study (“study completion”) is defined as the date of the last protocol-specified visit/assessment (including telephone contact) for the last subject in the study, 2 years after the last subject is enrolled, or the date the study is closed by the sponsor, whichever occurs first. Subjects may receive study drug(s) for a maximum of 2 years. At the conclusion of the study, subjects who continue to demonstrate clinical benefit will be eligible to receive study drug. Study drug will be provided via an extension of the study, a rollover study requiring approval by responsible health authority and ethics committee or through another mechanism at the discretion of the sponsor. The sponsor reserves the right to terminate access to study drug if any of the following occur: a) the study is terminated due to safety concerns; b) the subject can obtain medication from a government sponsored or private health program; or c) therapeutic alternatives become available in the local market.

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 enrolment 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 products. 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 CHANGES TO THE PROTOCOL

9.1 Protocol Amendment 5, 29Mar2017

The purpose of this amendment was to remove the MEDI0680 monotherapy arm from the dose-expansion phase and replace with a nivolumab monotherapy arm. Nivolumab monotherapy was added as a comparator arm in the dose expansion phase as it is the current standard of care in the metastatic RCC setting in some markets. The investigational product MEDI4736 has been renamed durvalumab throughout the document. Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 5. Major changes to the protocol are summarized below.

1. Title page: The following changes were made:
   - Updated title to remove MEDI0680 monotherapy arm, add nivolumab monotherapy arm and replace MEDI4736 by durvalumab.
   - Added nivolumab as a comparator product
   - Added the NCT number
   - Corrected the Primary Medical Monitor's phone number
   - Changed the Secondary Medical Monitor.
2. Protocol synopsis: The synopsis was updated to align with the body of the protocol.
3. Section 1.2 (MEDI0680 and Durvalumab [MEDI4736] Background), Section 1.3.2 (Durvalumab Nonclinical Experience), and Section 1.4 (Summary of Clinical Experience): Updated to align with information in the current MEDI0680 and durvalumab Investigator's Brochures.
4. Section 1.5 (Rationale for Conducting the Study): Clarified that the ORR value was based on independent review.
5. Section 1.5 (Rationale for Conducting the Study) and Section 3.2.2 (Rationale for Study Population): Included the rationale for addition of the nivolumab monotherapy arm as a comparator.
6. Section 1.5 (Rationale for Conducting the Study), Section 3.1.3.3 (Dose-limiting Toxicity), Section 3.1.5.1 (Dose Modification of Durvalumab and MEDI0680), Section 3.2.3 (Rationale for Endpoints), Section 4.1.3 (Exclusion Criteria) and Table A6-1 (Immune Mediated Reactions): Replaced the abbreviation irAE with imAE to align with updated information on patient safety guidelines.
7. Section 1.5 (Rationale for Conducting the Study): Changed the wording of this section to clarify that imAEs are considered AESIs but the terms imAE and AESI are not interchangeable. Updated to align with information in the current MEDI0680 Investigator's Brochures.
8. Section 1.6, Section 2.1 and Section 2.3: Revised safety and efficacy hypotheses and objectives to replace MEDI0680 monotherapy with nivolumab monotherapy. Removed MEDI0680 monotherapy from PK, immunogenicity and biomarker objectives.

9. Section 2.1 and 2.2: Presented objectives and endpoints together to enable clearer mapping. Clarified endpoint for primary objective in dose escalation
10. Section 2.1, Section 2.2 and Section 4.8.4: Clarified that OR is the primary endpoint in dose expansion and clarified OS as a secondary endpoint.
11. Section 2.1 and Section 2.2: Clarified safety endpoint and immunogenicity endpoint.
12. Section 2.3.2 (Exploratory Endpoints): The following changes were made to this section:
    - This section was updated to account for the removed of the MEDI0680 monotherapy arm and addition of the nivolumab monotherapy arm.
    - Removed the potential for analysis of total mutational load, gene conformational changes or epigenetics and T-cell reception (TCR) diversity
    - Removed the specification that biopsies were to be pre-treatment and posttreatment for IHC, IF and/or flow cytometry analysis for expression and localization of key molecules to reduce the burden for patients.
    - Clarified that sPD-L1 levels and receptor occupancy will only be measured in the dose-escalation phase as the data previously collected in the study are sufficient for analysis.
13. Section 3.1.1 (Overview) and Section 4.1.1 (Number of Subjects): Changed the number of study centers from 80 to 50 as fewer subjects are required following the change in study design.
14. Section 3.1.1 (Overview), Figure 3.1.1-1 (Study Flow Diagram), Figure 3.1.2.2-1 (Study Flow for Primary MEDI0680 Schedule (Every 2-week Dosing), Section 3.1.4 (Dose-expansion Phase), Section 3.2.3 (Rationale for Endpoints), Section 4.3.7 (Biomarker Evaluation and Methods), Section 4.6.1 (Methods for Assigning Treatment Groups), Section 4.8.2 (Sample Size and Power Calculations), Section 4.8.3.2 (Analyses of Safety Endpoints), and Appendix 5 (Solid Tumor Efficacy): Removed the MEDI0680 monotherapy arm and replaced with nivolumab monotherapy arm.
15. Section 3.1.1.1 (Dose escalation Phase), Section 3.1.2.3 (Alternative MEDI0680 Schedule [Every 4-week Dosing]), Figure 3.1.3.1-1 (Primary [Every 2-week Dosing of MEDI0680] Dose escalation Design), Figure 3.1.3.1-2 (Alternative [Every 4-week Dosing of MEDI0680] Dose escalation Design), Figure 3.1.3.2-2 (Dose escalation [Zone based] for Alternative Q4W Schedule), Section 3.1.3.3 (Dose limiting Toxicity), Section 3.2.1.1 (Dose escalation Phase), Section 4.1.7 (Replacement of Subjects), Section 4.2.2 (Treatment Period), Section 4.8.3.2 (Maximum Tolerated Dose Evaluation [Every 4 week Dose Schedule), Appendix 6 (Alternate Q4W Dosing Schedule): Removed the alternative Q4W dosing schedule as dose-escalation has completed and this schedule has not been used in this study.
16. Section 3.1.1.2 (Dose-expansion Phase): The following changes were made to this section:
    - Added that an interim futility analyses will be performed for the MEDI0680/durvalumab combination therapy arm in the dose-expansion phase after 20 subjects have been randomized and have reached their second post-baseline disease assessment or have completed study.

17. Section 3.1.1.2 (Dose-expansion Phase), Section 4.1.1 (Number of Subjects), and Section 4.8.2 (Sample Size and Power Calculations): Changed the planned number of subjects as follows as fewer subjects are required following the change in study design:
    - From 156 to approximately 96 subjects for both dose escalation and dose expansion.
    - The number of subjects in the dose-expansion phase was changed from 120 to approximately 60.
18. Section 3.1.1 (Figure 3.1.1-1), Section 3.1.1.2 (Dose expansion Phase), Section 3.1.4 (Dose expansion Phase), Section 4.3.7 (Biomarker Evaluation and Methods), Section 4.6.1 (Methods for Assigning Treatment Groups, and Section 4.8.2 (Sample Size and Power Calculation): Changed the ratio for randomization of combination and monotherapy from 1:1 to 2:1.
19. Section 3.1.1.2 (Dose-expansion Phase), Section 3.1.4 (Dose-expansion Phase), Table 4.2.2-2 (Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 7 13 Following Protocol Amendment 5), Section 4.3.7 (Biomarker Evaluation and Methods), and Section 4.5.1.1 (Durvalumab): Clarified that subjects were randomized into the dose-expansion phase.
20. Section 3.1.2 (Treatment Regimen), Section 4.1.3 (Exclusion Criteria), Section 4.3.3 (Medical History and Physical Examination), Section 4.5.1.4 (Monitoring of Dose Administration), Section 4.7 (Restrictions During the Study and Concomitant Treatment[s]), Section 4.8.4.1 (Analysis of Efficacy Endpoints), Section 5.4 (Recording of Adverse Events) and Appendix 5 (Solid Tumor Efficacy): The nivolumab monotherapy arm was added to these sections.
21. Section 3.1.2 (Treatment Regimen):
    - Clarified that in the dose-escalation phase subjects may be re administered MEDI0680 and durvalumab if they have PD only during the first 12 months of follow up.
    - And in Section 4.5.1.1: The time between the durvalumab infusion and MEDI0680 infusion was reduced from 1 hour to 30 minutes for subject convenience because of increased experience with durvalumab
22. Section 3.1.2 (Treatment Regimen), Section 3.1.5.2 (Dose Modifications of Nivolumab), Section 4.5.1.3 (Nivolumab), Section 4.5.1.4 (Monitoring of Dose Administration), and Section 4.5.4 (Storage): Added that for dosing and storage of nivolumab, the investigator should refer to the local (country-specific) package insert) (or similar).
23. Section 3.1.2.1 (Treatment Beyond Progression): Clarified that the initial assessment of PD will be based on an application of RECIST v1.1 to investigator-assessed tumor measurements.
24. Section 3.1.2.2 (Dosing Schedule): Added the frequency of dosing for the nivolumab monotherapy arm.
25. Section 3.1.4 (Dose-expansion Phase): The following changes were made:
    - And in Section 4.2.2: Added that prior to this Protocol Amendment some subjects had been randomized to and began receiving treatment in the MEDI0680 monotherapy arm, which has now been removed. Outlined the dose of MEDI0680 monotherapy that these subjects should receive and that they are to follow the same study procedures as the combination therapy arm.

- Explained that the dose information for nivolumab is the recommended dose for treatment of patients with advanced RCC.

26. Section 3.1.5 (Management of Study Medication Related Toxicities): The following changes were made:
    - The title of Section 3.1.5.1 was updated to clarify this relates to durvalumab and MEDI0680 only.
    - Section 3.1.5.2 (Dose Modification of Nivolumab) was added.
27. Section 3.1.5.1 (Dose Modifications of Durvalumab and MEDI0680): Reduced the information about treatment modifications for AEs clearly not related to MEDI0680/durvalumab as the previous information was repetitive.
28. Section 3.2.1.2 (Dose-expansion Phase) and Section 4.8.6 (Analyses of Immunogenicity and Pharmacokinetics): References to the MEDI0680 monotherapy arm were removed as this will no longer be performed.
29. Section 3.2.3 (Rationale for Endpoints): The following changes were made as the data previously collected in the study are sufficient for analysis:
    - Clarified that PBMC would no longer be collected in the dose-expansion phase after Protocol Amendment 5.
    - Clarified that biopsies are optional.
    - Added that sPD-L1 and PD-1 analysis would no longer be collected in the dose-expansion phase after Protocol Amendment 5.
    - Removed the specification that immune response will be assessed using paired pre-treatment and posttreatment biopsies.
    - Removed the assessment of TCR usage
30. Section 4.1.2 (Inclusion Criteria): The following changes were made
    - Inclusion criterion 4b – Changed the number of prior systemic treatment regimens from only 1 to at least 1 and no more than 2 prior anti-angiogenic therapy regimens (including, but not limited to, sunitinib, sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab) in the advanced or metastatic setting. This resulted in the addition of Criterion 4c, and thus re-lettering of subsequent criteria. Added that subjects must have received no more than 3 total prior systemic treatment regimens in the advanced or metastatic setting, and must have evidence of radiographic progression on or after the last treatment regimen received and within 6 months prior to study enrollment.
    - Inclusion criterion 5cii – Clarified that on-treatment biopsies are optional.
    - Inclusion criterion 5ciii – Removed this criterion as biopsies are now optional. “Once the initial 50 subjects have been enrolled and the futility analysis is completed, up to 15 subjects enrolled subsequently into each treatment arm must consent to and provide both pre-treatment and on treatment tumor biopsies. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions.”
    - Inclusion Criterion 6avi – Replaced serum creatinine cut-off with 24-hour urine creatinine clearance to align with clinical practice.
    - Inclusion Criterion 6b – Removed the inclusion of subjects with central nervous system metastases to enable clearer assessment of efficacy.

- Inclusion Criterion 8 – Updated this criterion relating to female subjects of childbearing potential to align with current protocol template language and guidance for nivolumab. This included adding that it is strongly recommended for the male partner of a female subject to also use male condom plus spermicide from screening until 120 days after the subject's last dose of MEDI0680 or durvalumab or 150 days after the subject's last dose of nivolumab and that female subjects should refrain from egg cell donation throughout this period.
- Inclusion Criterion 9 – Increased the time period that nonsterilized males who are sexually active with a female partner of childbearing potential should use male condoms plus spermicide from 90 to 120 days after the last dose of MEDI0680 or durvalumab or 150 days after the subject's last dose of nivolumab. The time period that they must refrain from fathering a child or donating sperm was also increased from 90 to 120 days to align with MEDI0680 requirements and the protocol schedule, and to 150 days for nivolumab.
- Table 4.1.2 (Effective Methods of Contraception): The title was reworded to clarify that not all methods in the table are highly effective. The methods listed in the table were also updated to align with current protocol template language.

31. Section 4.1.3 (Exclusion Criteria): The following change was made:
    - Exclusion Criterion 2 – Updated this criterion for clarity.
    - Removed Exclusion Criteria 5 about prior toxicities following immunotherapy as it is irrelevant in the population recruited as of Protocol Amendment 5.
    - Exclusion Criterion 15 – Clarified the time frame that second malignancies should not have occurred in and provided further examples of the second malignancies that are exempt from this criterion.
32. Section 4.1.5.2 (Withdrawal from Treatment): Removed text that stated 'Subjects who permanently discontinue treatment may either be considered to have completed the study or not to have completed the study' as it was not meaningful.
33. Table 4.2.1-1 (Schedule of Screening Procedures Following Protocol Amendment 5): The following changes were made to this table:
    - Added to the title "Following Protocol Amendment 5" to show that different screening procedures were carried out in earlier versions of the protocol.
    - Clarified that the physical examinations should be full physical examinations.
    - Removed receptor occupancy, sPD-L1, and PBMC as the data previously collected in the study are sufficient for analysis.
34. Section 4.2.2: (Treatment Period): The following changes were made:
    - Clarified that the study procedures in Table 4.2.2-1 and Table 4.2.2-2 are also to be followed in the dose-expansion phase as this was inadvertently omitted.
35. Table 4.2.2-1 (Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 1-6 Following Protocol Amendment 5) and Table 4.2.2-2 (Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 7 13 Following Protocol Amendment 5): The following changes were made:
    - Added to the title "Following Protocol Amendment 5" to show that different procedures were carried out in earlier versions of the protocol.

- Reduced the number of physical examinations, ECGs, hematology, serum chemistry, TSH, free T4, free T3, and urinalysis measurements as there is now more clinical experience with the investigational products.
- Changed some of the full physical examinations to abbreviated physical examinations as there is now more clinical experience with the investigational products.
- Reduced the number of vital sign and ECG measurements required as there is now more clinical experience with the investigational products.
- Clarified that MEDI0680 PK and MEDI0680 immunogenicity will be measured in the combination arm only as this information is not needed in the nivolumab monotherapy arm.
- Removed sPD-L1, receptor occupancy, and PBMC collection as the data previously collected in the study are sufficient for analysis.
- Clarified that disease assessments occur Q8W and should occur within 7 days prior to the planned administration of the scheduled treatment.
- Added nivolumab administration for the nivolumab monotherapy arm.
- Added a footnote to clarify that MEDI0680 will be administered in the combination arm and to those who were randomized and began receiving treatment with MEDI0680 monotherapy prior to Protocol Amendment 5.

36. Table 4.2.2-1 (Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 1-6 Following Protocol Amendment 5): The following changes were made:
    - Reduced the number of vital signs measurements and ECGs on dosing days and removed monitoring on non-dosing days as there is now more clinical experience with the investigational products.
    - Amended table to clarify when disease assessments should be performed (identified as prior to subsequent dosing rather than included as a separate visit day).
    - Clarified that biopsies are optional and removed “Once the initial 50 subjects have been enrolled and the futility analysis is completed, up to 15 subjects enrolled subsequently into each treatment arm must consent to and provide both pre-treatment and on treatment tumor biopsies” as biopsies are optional.
    - miRNA/mRNA assessments removed from Cycle 1 Days 2 and 8 and added to Cycle 1 Day 15.
37. Table 4.2.2-2 (Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 7 to13 Following Protocol Amendment 5):
    - Reduced the number of assessments for physical examinations and laboratory assessments following 1 year of treatment, unless clinically indicated.
    - Reduced the number of vital sign and ECG measurements required as there is now more clinical experience with the investigational products.
    - Revised Visit headers for clarity.
    - Removed flow cytometry, circulating soluble factors, miRNA/mRNA and tumor biopsies.
38. Section 4.2.3 (Follow-up Period): Changed the wording of this section to clarify that it is preferred but not mandatory that assessments are performed in a certain order. Clarified which physical examinations should be full or abbreviated.

39. Table 4.2.3-1 (Schedule of Study Procedures: End of Treatment and Posttreatment Laboratory Follow-Up Following Protocol Amendment 5): The following changes were made:
    - Added to the title "Following Protocol Amendment 5" to show that different procedures were carried out in earlier versions of the protocol.
    - Clarified that MEDI0680 PK, and immunogenicity will be measured in the combination arm only as this information is not needed in the nivolumab monotherapy arm and clarification of the timings.
    - Removed sPD-L1, flow cytometry, receptor occupancyand PBMC collection as the data previously collected in the study are sufficient for analysis.
    - Removed physical examinations, vital signs and AE assessments in long-term follow up as not required.
    - Clarified that disease assessments are only required for subject discontinued from treatment for a reason other than radiologic disease progression and these should continue on a Q8W schedule until radiologic disease progression is observed.
    - Added blood or urine pregnancy test in the long-term follow up to match new protocol template language.
    - Added that circulating soluble factors and miRNA/mRNA will be performed in all treatment arms and added a footnotes to clarify time points
    - Added that tumor biopsies are optional.
40. Section 4.3.2.2 (Tumor Biopsies): Clarified that posttreatment biopsies are optional and removed "Once the initial 50 subjects have been enrolled and the futility analysis is completed, up to 15 subjects enrolled subsequently into each treatment arm must consent to and provide both pre-treatment and on treatment tumor biopsies" as biopsies are now optional.
41. Section 4.3.3 (Medical History and Physical Examination): The following changes were made to this section:
    - Reduced the number of vital signs measurements on dosing days and removed monitoring on non-dosing days as there is now more clinical experience with the investigational products.
    - Stated the time points for measuring vital signs and ECGs in the nivolumab monotherapy arm.
    - Added that abbreviated symptom-directed examinations will be conducted post-screening, except for a full physical examination at the end of treatment.
42. Section 4.3.4 (Clinical Laboratory Tests): Clarified that only clinically significant abnormal laboratory results should be repeated.
43. Section 4.3.7 (Biomarker Evaluation and Methods): The following changes were made to this section as the data previously collected in the study are sufficient for analysis:
    - Removed the assessment of serum sPD-L1 levels.
    - Tumor DNA is referenced instead of nucleosomal DNA as a marker of apoptosis
    - Clarified that PBMC were only to be collected in the dose-escalation phase.

44. Section 4.3.7 (Biomarker Evaluation and Methods): Removed the specification that protein, nucleic acids and cellular biomarkers that are analyzed will be related to durvalumab or MEDI0680 to account for the addition of the nivolumab monotherapy arm.
45. Section 4.3.8 (Estimate of Blood Volume to be collected): Estimates reduced due to streamlining of assessments.
46. Section 4.5.1 (Identity of Investigational Products): The following changes were made to this section:
    - Added that nivolumab will be obtained from commercial supply and is formulated, administered and labelled according to locally approved prescribing information and guidance.
47. Section 4.5.1, 4.5.1.2, 4.5.4 and Appendix 8: Removed reference to the initial MEDI0680 60 mg/mL formulation and Amplimmune as the formulation is no longer in use.
48. Section 4.5.1.1 (Durvalumab): Clarified that the allowed storage time starts from needle puncture not reconstitution for the durvalumab dose preparation steps. Correction of infusion duration text.
49. Section 4.5.1.4 (Monitoring of Dose Administration): Removed time points for monitoring vital signs and added a cross reference to Section 4.3.3 where they are first presented.
50. Section 4.6.1 (Methods for Assigning Treatment Groups): text added to that the investigational products must be administered or dispensed within 2 days after randomization, to allow some flexibility in dosing from randomization.
51. Section 4.8.2 (Sample Size and Power Calculations): The following changes were made to this section to account for the removal of the MEDI0680 monotherapy arm and the addition of the nivolumab monotherapy arm:
    - Updated the ORR, power, sample size and 95%CI.
    - Added that subjects are randomized in a 2:1 ratio.
    - Updated the primary objective to be consistent with Section 2.1.
52. Section 4.8.4.1 (Analysis of Efficacy Endpoints): Clarified the definitions for duration of response and progression free survival.
53. Section 4.8.5 (Pharmacodynamic Analyses): The following changes were made to this section:
    - Added that serum sPD-L1 levels and levels of PD-1 expression will only be measured in the dose-escalation phase as the data previously collected in the study are sufficient for analysis.
    - Removed the specification that biopsies were to be pre-treatment and posttreatment for IHC, IF and/or flow cytometry analysis for expression and localization of key molecules.
54. Section 4.8.7.1 (Immune-related Response Criteria): Clarified the use of irRECIST and included the endpoints that will be summarized.
55. Section 4.8.8 (Interim Analysis): This section was replaced with detailed information about the conduct of the interim futility analysis.

56. Section 5.3 (Definition of Adverse Events of Special Interest): The following changes were made to this section to align with updated information on patient safety guidelines:
    - Replaced the abbreviation irAEs with imAEs.
    - Reworded the list of irAEs for clarity.
    - Removed neurotoxicity and autonomic neuropathy from the list of irAEs.
    - Removed Section 5.3.2 (pneumonitis) and Section 5.3.4 (Gastrointestinal Disorders).
57. Section 5.5: FAX numbers for reporting of SAEs were updated to be current.
58. Section 5.6.2.2 (Paternal Exposure): Changed that the outcome of all pregnancies should be followed-up from 90 days after the final dose of combination or monotherapy to 120 days.
59. Section 6.3 and Appendix 5: One of the criteria for the definition of the end of study was revised from 3 years to 2 years after the last subject was enrolled. Possible treatment options for subjects still receiving treatment at the end of study added.
60. Appendix 6 (Durvalumab and MEDI0680 Dose Modifications for Toxicity Management): The guidelines for durvalumab and MEDI0680 toxicity management were updated according to the 31Aug2016 version.

9.2 Protocol Amendment 4, 27May2016

Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 4. Major changes to the protocol are summarized below.

1. Title page: Added Protocol Administrative Change 1, 05Feb2015, which was inadvertently omitted.
2. Section 1.5 (Rationale for Conducting the Study): Updated to align with information in the current MEDI0680 Investigator's Brochure.
3. Section 2.2.3 (Exploratory Endpoints): Clarified exploratory endpoint 5 to align with the treatment arms.
4. Section 3.2.3 (Rationale for Endpoints), Predictive Markers: Included CD80 among the candidate biomarkers for evaluation.
5. Section 4.1.2 (Inclusion Criteria): Inclusion criterion 9 - Revised requirement for a female partner of childbearing potential of a male subject to use a highly effective method of contraception from mandatory to highly recommended, to align with current protocol template language. The clarification encourages safe contraceptive practices for individuals who are not study participants.
6. Section 4.1.3 (Exclusion Criteria): Added exception to permit enrollment of subjects with prior endocrine toxicities who are stable on replacement therapy since TKI-induced thyroid dysfunction is common, however, exact mechanisms are unclear. Symptomatic treatment of TKI-induced hypothyroidism improves the patient's quality of life and allows continuation of the anti-cancer therapy. Per original protocol, endocrine function tests will be monitored throughout study participation and guidelines for management of endocrinopathy are also included.

7. Table 4.2.1-1 (Schedule of Screening Procedures): Clarified that procedure for TSH includes assessment for TSH, free T4, and free T3, consistent with presentation in Table 4.2.2-1 and Table 4.2.2-2.
8. Table 4.2.2-1 (Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 1-6): Revised visits for disease assessment to begin on Day 56 and occur every 8 weeks (Q8W; ie, Days 50, 106, and 162 were revised to Days 56, 112, and 168); and added footnote "k" to clarify that results must be available prior to the planned administration of the scheduled investigational treatment.
9. Table 4.2.2-2 (Schedule of Study Procedures for Primary Q2W Treatment Period: Cycles 7-13): (1) Revised visits for disease assessment to continue on the Q8W schedule (ie, Day 218, Day 274, and Q8W starting on Day 330 were revised to Day 224, Day 280, and Q8W starting on Day 336), and added footnote "a" to clarify that results must be available prior to the planned administration of the scheduled investigational treatment; and (2) footnote "f" – clarified to indicate that MEDI0680 and durvalumab will be administered on a Q2W schedule. Consistent with edits in Protocol Amendment 3, assessments beginning in Cycle 12 Day 330 through end of treatment will be conducted Q8W, however, MEDI0680 and durvalumab will continue on a Q2W treatment schedule.
10. Section 9.3 (Protocol Amendment 3): Items 38 and 39 - Clarified changes to the appendices resulting from Protocol Amendment 3.
11. Section 9.4 (Protocol Administrative Change 1): Added this protocol administrative change, which was inadvertently omitted, to provide a complete history of protocol changes.

9.3 Protocol Amendment 3, 11Feb2016

The purpose of this amendment was to update the dose-expansion phase of the study to enroll PD-L1 positive immunotherapy naïve subjects who have RCC to either receive MEDI0680 monotherapy or in combination with durvalumab.

1. Title page: The title of the study was changed to "A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) Monotherapy and in Combination with MEDI4736 in Subjects with Select Advanced Malignancies"
   a. The EudraCT number was added
   b. The Primary Medical Monitor was changed to [redacted] and the Secondary Medical monitor was changed to [redacted].
2. Protocol Synopsis: The synopsis was updated to align with the body of the protocol.
3. Section 1.2 (Durvalumab [MEDI4736] and MEDI0680 Background): The background for durvalumab and MEDI0680 was updated, the sections were reorganized for clarity.
4. Section 1.3 (Summary of Nonclinical Experience): This section was updated to provide a more concise summary of the relevant studies.
5. Section 1.4 (Summary of Clinical experience): This section was updated and reorganized. The safety and efficacy information for studies in the MEDI0680 and durvalumab development program were updated based on current data.

6. Section 1.5 (Rationale for conduct of the study) was updated with rationale for including subjects with RCC.
7. Section 1.6 (Research Hypotheses): This section was updated to include primary and secondary hypotheses for the dose-expansion phase.
8. Section 2.1.1 (Primary Objectives): The objective for the dose expansion phase was changed to "To evaluate the antitumor activity of MEDI0680 monotherapy and in combination with durvalumab in immunotherapy-naïve subjects with advanced or metastatic ccRCC as based on investigator assessed response using RECIST v1.1," in order to provide a measure of efficacy for dose-expansion phase.
9. Section 2.1.2 (Secondary Objectives): The following changes were made.
    a. A secondary objective for the dose-expansion phase, "To describe the safety and tolerability of MEDI0680 monotherapy and in combination with durvalumab in immunotherapy-naïve subjects with advanced or metastatic ccRCC" was updated according to the new study design.
    b. A secondary objective for the dose expansion phase, "To evaluate the antitumor activity of MEDI0680 monotherapy and in combination with durvalumab in immunotherapy-naïve subjects with advanced or metastatic ccRCC as based on BICR assessed response using RECIST v1.1" was added.
    c. The wording for objectives applicable to both the dose-escalation and dose-expansion phase was updated for clarity.
10. Section 2.1.3 (Exploratory Objectives)
    a. The exploratory objective on patient-reported outcomes was removed.
11. Section 2.2.1 (Primary Endpoints):
    a. The primary endpoint "The primary endpoint is determination of the MTD, which is the highest dose within a cohort where no more than 1 out of 6 subjects experience DLTs, or the highest protocol-defined dose for each agent in the absence of exceeding the MTD" was removed.
    b. The primary endpoint for the dose-expansion phase "The primary endpoints to assess antitumor activity include best overall response (BOR), DC, time to response (TTR), duration of response (DR), progression-free survival (PFS) and change from baseline in tumor size as based on investigator assessed response using RECIST v1.1" was added to correspond with the updated study design.
12. Section 2.2.2 (Study Endpoints):
    a. The endpoint specific for the dose-escalation phase was updated to "the endpoints for assessment of antitumor activity include BOR, OR, DC, TTR, DR, PFS, OS, and change from baseline in tumor size. Antitumor activity analyses will be as determined by the investigator based on modified RECIST v1.1" in order to match the new study design
    b. In the dose-expansion phase the endpoint was updated to "The endpoints for assessment of safety include the presence of AEs, SAEs, laboratory parameters, vital signs, physical examination, and ECG results" in order to match the study design.
    c. The endpoint specifically for the dose-expansion phase was updated to "The endpoints for assessment of antitumor activity include BOR, DC, TTR, DR, PFS, and

change from baseline in tumor size as based on BICR assessed response using RECIST v1.1; and OS" in order to match the study design.

d. The endpoint "PD-L1 expression / localization on tumor membrane and tumor-infiltrating immune cells within the tumor microenvironment" was added to support the updated study design.

13. Section 2.2.3 (Exploratory Endpoints):
    a. The order of the endpoints was changed to match the order presented for the exploratory objectives
    b. The endpoint to measure quality of life was removed.
14. Section 3.1.1 (Overview) was updated. The dose-expansion phases for MDS subjects and immunotherapy pretreated subjects was removed. The dose-expansion phase for immunotherapy naïve RCC subjects was added.
15. Section 3.1.2.1 (Treatment Beyond Progression): This section was updated to correspond with new language applicable to MedImmune protocols.
16. Section 3.1.4 (Dose-expansion phase): An overview of the study design for the dose-expansion phase was added.
17. Section 3.1.5 (Management of Study Medication Related Toxicities): This section was updated to correspond with Medimmune Patient Safety guidelines
    a. The Dose modification table was replaced with toxicity management guidelines in Appendix 7 in order to correspond with MedImmune Patient Safety guidelines.
18. Section 3.2.1 (Dose Rationale [MEDI0680 and Durvalumab]): The dose rationale for MEDI0680 monotherapy and combination therapy with durvalumab was updated based on current study information.
19. Section 3.2.2 (Rationale for Study Population): The rationale for including the RCC subjects in the study population was added to support the new study design
20. Section 3.2.3 (Rationale for endpoints): The following sentence was updated "The EOT biopsy specimens will be evaluated to understand potential mechanisms of resistance in tumors that remain following 9 months of treatment." The text "9 months" of treatment was removed from the sentence in order to avoid language that restricts when tumor samples will be evaluated.
21. Section 4.1.1 (Number of Subjects): The total number of subjects was updated to 156 and the number of study centers was increased to 80.
22. Section 4.1.2 (Inclusion criteria): This following changes were included in this section:
    a. Inclusion criteria specific for MDS subjects (previously criterion 4 in Amendment 2) in the dose-expansion phase was removed because subjects with MDS will not be included in the dose-expansion phase.
    b. The following inclusion criteria for the RCC subjects to be included in the dose-expansion phase were added.
        i. Histological confirmation of advanced or metastatic RCC with a clear-cell component
        ii. Must have received only 1 total prior systemic treatment regimen in the solid tumor groups (advanced or metastatic setting and the prior treatment must be an approved anti-angiogenic therapy regimen (including, but not limited to, sunitinib,

sorafenib, pazopanib, axitinib, tivozanib, and bevacizumab), and must have evidence of progression

iii. No prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CD137, or anti CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co stimulation or checkpoint pathways

iv. No prior treatment with an mammalian target of rapamycin (mTOR) inhibitor (including, but not limited to everolimus, temsirolimus, sirolimus, and ridaforolimus)

v. Prior cytokine therapy (eg, IL-2, IFN-α) or treatment with cytotoxics is allowed.

vi. Subjects must have at least 1 measurable lesion according to RECIST v1.1. A previously irradiated lesion cannot be considered a target lesion. Radiographic disease assessment can be performed up to 28 days prior to the first dose

c. Contraception language (criteria 8 and 9) was updated according to current MedImmune patient safety guidelines.

i. Male condom with spermicide was removed from the list of highly effective contraceptive methods in order to align with health authority feedback.

ii. The list of highly effective hormonal methods of contraception was updated to align with recent health authority feedback.

d. The following biopsy requirements were added to support the new study design:

For dose-escalation

i. Subjects must consent to provide archival tumor tissue (initial and subsequent tumor biopsy samples, if possible) for correlative biomarker studies if available

ii. Able and willing to give valid written consent for fresh tumor samples if required. 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 and dose-expansion). Sites are encouraged to confirm adequacy of tumor biopsy material at the time of the procedure. Fine-needle aspirate specimens are not acceptable.

For dose-expansion:

iii. Tumor tissue (formalin fixed paraffin embedded [FFPE] archival or fresh tumor tissue) must be received by the central vendor (block or unstained slides) and evaluable for PD-L1 expression status in order to randomize a subject to study treatment.

iv. All subjects are encouraged to consent to and provide both pretreatment and on-treatment fresh tumor biopsies

v. Once the initial 50 subjects have been enrolled and the futility analysis is completed, up to 15 subjects enrolled into each treatment arm must consent to and provide both pre-treatment and on treatment tumor biopsies. Tumor lesions used for biopsy should not be lesions used as RECIST target lesions

vi. For dose-escalation and dose-expansion: (If evaluations performed as part of standard of care for other purposes prior to obtaining informed consent are suitable for screening and occurred within 7 days prior to starting treatment, those evaluations do not need to be repeated if the subject consents to their use):

23. Exclusion criteria specific to MDS subjects were removed.
24. Exclusion Criteria 12 was updated such that patients should not receive live attenuated vaccination 90 days after administration of MEDI0680 monotherapy or combination therapy durvalumab.
25. Section 4.1.7 (Replacement of Subjects): The text was updated to indicate that no subjects will be replaced in the dose-expansion phase in order to match the new study design.
26. Section 4.1.8 (Withdrawal of Informed Consent for Data and Biological Samples): The sentence "A file linking this sample identification number with the SID number will be kept in a secure place at the sponsor with restricted access" was removed. It is not applicable to the study.
27. Schedule of screening procedures was updated to remove bone marrow biopsy, archival bone marrow sample and cytogenics from bone marrow sample. A screening for receptor occupancy was added to support endpoints for the new study design.
28. The following changes were made to Schedule of Study Procedure Primary Q2W Cycles 1-6 and 7-13:
    a. The pain questionnaire, quality of life questionnaire and FACT-Leu were removed.
    b. For Cycles 7-13 the Day 197 tumor biopsy was removed and replaced with EOT tumor biopsy.
29. The following changes were made to serum chemistry labs; measurement for total protein was added and measurements for beta 2 microglobulin was removed.
30. The following changes were made to the hematology labs; the lab test for mean corpuscular Hgb concentration was removed and the lab test for hematocrit was added.
31. Section 4.3.8 (Estimate of Blood Volume to Be Collected): The estimated amount of blood to be collected was increased to facilitate completion of planned analysis. "A total of approximately 75 mL will be required for all screening tests, which may be conducted over 1 to 28 days during screening. No more than 90 mL of blood will be drawn on any visit day after screening. Approximately 90 mL of blood will be collected at all visits related to the first dose."
32. Section 4.5 (Investigational Product): The following information was updated.
    a. Details for preparation of MEDI680 60 mg/mL was moved to Appendix 8.
    b. Details for preparation of the MEDI0680 50 mg/mL drug product was added to the main body.
    c. For durvalumab dose preparation steps, the instruction for the duration to swirl the vail was removed and replaced with clear language.
    d. The following instructions for the time interval for between combination therapy with MEDI0680 and durvalumab was added "for subjects assigned to receive both products. MEDI0680 infusion will start approximately 1 hour after the end of durvalumab infusion."
    e. Section 4.5.1.2 (MEDI0680): Guidance that dose-escalation subjects receiving the 60 mg/ml drug product will be transitioned to the 50 mg/mL drug product was added.
    f. Section 4.5.4 (Storage): Information for storing the MEDI0680 (50 mg/mL) investigational product was added.

33. Section 4.7.1 (Prohibited Concomitant Medications): Biphosphonate and RANKL inhibitors was removed
34. Section 4.8 (Statistical Evaluation) was updated. The total amount of subjects to be enrolled was changed to 156.
35. Section 4.8.2 Sample Size and Power Calculations. The sample size and power calculations were updated to correspond with the new study design.
    a. For the dose expansion phase up to 120 subjects will be included (60 subjects per arm)
36. Section 4.8.8 (Interim analysis): A futility gate for the combination and monotherapy arm in the dose-expansion phase was added. The information will be used to support internal company decisions.
37. Section 5 Assessment of Safety was updated to correspond with MedImmune Safety guidelines
38. Appendices 5 (Pain Questionnaire), 6 (Patient-reported Outcome Questionnaire EORTC QLT-C30), and 7 (Patient-reported Outcome Questionnaire EORTC QLWQ-LC13): Deleted in alignment with removal of exploratory endpoint for patient-reported outcomes.
39. Appendices 7, 8, and 9 were added.
    a. Appendix 7 (Durvalumab and MEDI0680 Dose Modifications for Toxicity Management): Added to correspond with changes to Section 3.1.5 and to support the current MedImmune Patient Safety guidelines.
    b. Appendix 8 (Preparation of MEDI0680 60 mg/mL): Details for preparation of this dose level were removed from Section 4.5 and placed here since 50 mg/kg MEDI0680 is the new Drug Product presentation.
    c. Appendix 9 (Memorial Sloan Kettering Cancer Center Prognostic Score [Renal Cell Carcinoma]): Added to support inclusion of RCC patient population.

9.4 Protocol Administrative Change 1, 05Feb2015

The purpose of this administrative change was to correct typographical errors in Appendix 11, Schedule of Study Procedures for Alternative Q4W Treatment Period.

9.5 Protocol Amendment 2, 01Oct2014

The purpose of this amendment was to limit the tumor types in dose escalation to NCSLC, SCCHN, MSI-high CRC, bladder cancer, ovarian cancer, esophageal cancer, gastric cancer, and RCC, and to add a 20 mg/kg MEDI0680 (AMP-514) cohort to the Q2W dose-escalation schedule. Text revisions resulting from this amendment are incorporated in the body of Protocol Amendment 2. 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 1.4 (Summary of Clinical Experience): Updated this section with more recent clinical data for both durvalumab (Section 1.4.1) and MEDI0680 (AMP-514; Section 1.4.2).
3. Section 3.1.1 (Overview): The following changes were made to this section:
   - Limited the tumor types in dose escalation to NCSLC, SCCHN, MSI-high CRC, bladder cancer, ovarian cancer, esophageal cancer, gastric cancer, and RCC.
   - Increased the number of subjects in dose escalation from 30 to 36.
   - Allowed for any dose-escalation cohort that has not exceeded the MTD to be expanded by up to a maximum of 18 subjects for further evaluation of safety, PK, pharmacodynamics, and efficacy.
4. Section 3.1.1.1 (Dose-escalation Phase): Indicated that as of Amendment 2, only subjects with NCSLC, SCCHN, MSI-high CRC, bladder cancer, ovarian cancer, esophageal cancer, gastric cancer, or RCC will be enrolled in the dose-escalation phase.
5. Section 3.1.2 (Treatment Regimen): Revised the MEDI0680 (AMP-514) administration duration for doses > 2.5 mg to the following: MEDI0680 (AMP-514) will be administered over a minimum of 60 minutes at doses > 2.5 mg/kg up to a total dose of 1200 mg, and over a minimum of 90 minutes at total doses > 1200 mg.
6. Section 3.1.3.1 (Dose Escalation): The following changes were made:
   - Allowed for any dose-escalation cohort that has not exceeded the MTD to be expanded by up to a maximum of 18 subjects for further evaluation of safety, PK, pharmacodynamics, and efficacy.
   - Figure 3.1.3.1-1 (Primary [Every 2-week Dosing of MEDI0680 (AMP-514)] Dose-escalation Design): Added a 20 mg/kg MEDI0680 (AMP-514) plus 10 mg/kg durvalumab cohort (Cohort 6) to the Q2W dose-escalation schedule.
7. Section 3.1.3.2 (Modified Zone-based Design): Modified the zone-based design (Figure 3.1.3.2-1) to reflect the addition of dose-escalation Cohort 6.
8. Section 3.2.1.2 (MEDI0680 [AMP-514]): Revised the dosing information for Study D6020C00002 (AMP-514-01) to be consistent with the most recent amendment (Amendment 3).
9. Section 4.1.2 (Inclusion Criteria): The following changes were made:
   - Criterion #2: Revised to reflect the solid tumors types that will be allowed in the dose-escalation phase (NSCLC, SCCHN, MSI-high CRC, bladder cancer, ovarian cancer, esophageal cancer, gastric cancer, and RCC). In addition, indicated that no more than 3 prior lines of systemic therapy will be allowed in the recurrent or metastatic setting.
   - Criterion #2f: Added the following specific inclusion criteria for NSCLC subjects in dose escalation and dose expansion:
     - NSCLC subjects must have received no more than 3 prior lines of therapy, or either failed to respond, relapsed or were unable to tolerate standard treatment.
     - Subjects with EGFR-activating mutations must have received an EGFR TKI and subjects with ALK rearrangement positive tumors must have received an ALK TKI.

        - Subjects with wild-type EGFR and ALK mutation must have failed a platinum-based regimen. NOTE: Maintenance therapy following platinum doublet-based chemotherapy is not considered a separate line of therapy. Prior platinum-containing adjuvant, neoadjuvant, or definitive chemoradiation therapy given for locally advanced disease is considered first line therapy only if recurrent (local or metastatic) disease developed within 6 months of completing therapy. Subjects with recurrent disease > 6 months must also have progressed after a subsequent platinum-based chemotherapy regimen given to treat the recurrence.
    - Criterion #3b: Added that subjects with previously treated CNS metastases must be radiographically and neurologically stable for at least 6 weeks.
10. Section 4.1.3 (Exclusion Criteria): The following changes were made:
    - Criterion #13: Added that subjects, if enrolled, should not receive live vaccine during the study and 30 days after the last dose of durvalumab and MEDI0680.
    - Criterion #20: Revised to indicate that subjects who have been on bisphosphonates or RANKL inhibitors within the past 28 days prior to the first dose of both agents will be excluded.
11. Section 4.2.2 (Treatment Period): The following changes were made:
    - Indicated that ECGs will be obtained in triplicate for the first dose only and single ECGs will be obtained prior to infusion of investigational products at all other timepoints and as clinically indicated.
    - Added a cross-reference to the study procedures for the alternative Q4W dose-escalation treatment period in Appendix 11.
12. Section 4.3.2.2 (Tumor Biopsies): Indicated that fresh tumor biopsies will be obtained at baseline from subjects who are in the expanded dose-escalation cohorts or dose-expansion cohorts for the malignancies specified.
13. Section 4.3.4 (Medical History and Physical Examination): Indicated that ECGs will be obtained in triplicate for screening and the first dose only and single ECGs will be obtained prior to infusion of investigational products at all other timepoints and as clinically indicated.
14. Section 4.5.1.1 (Investigational Product Dose Preparation): The following changes were made:
    - In Table 4.5.1.1-1 (MEDI0680 [AMP-514] Total Deliverable Volume), a row was added to show that the total deliverable volume for the 20 mg/kg dose level is 60 mL.
    - Revised the MEDI0680 (AMP-514) administration duration for doses > 2.5 mg to the following: MEDI0680 (AMP-514) will be administered over a minimum of 60 minutes at doses > 2.5 mg/kg up to a total dose of 1200 mg, and over a minimum of 90 minutes at total doses > 1200 mg.
15. Section 4.5.1.2 (Treatment Administration): Revised the MEDI0680 (AMP-514) administration duration for doses > 2.5 mg to the following: MEDI0680 (AMP-514) will be administered over a minimum of 60 minutes at doses > 2.5 mg/kg up to a total dose of 1200 mg, and over a minimum of 90 minutes at total doses > 1200 mg.
16. Section 4.7.2 (Prohibited Concomitant Medications): Replaced “denosumab” with “bisphosphonates and RANKL inhibitors.”

17. Section 4.8.2 (Sample Size and Power Calculations): Changed the planned number of subjects as follows:
    - From 190 to 196 subjects for both dose escalation and dose expansion.
    - The maximum number of subjects that could be enrolled was increased from 510 to 516.
    - The number of subjects in the dose-escalation phase was changed from 30 to 36.
    - The number of dose cohorts to be evaluated in the dose-escalation phase was changed from 5 to 6.
18. Section 5.3 (Definition of Adverse Events of Special Interest): To be consistent with other MedImmune immunotherapy protocols, revised the language for Section 5.3.1 (Hepatic Function Abnormality) and Section 5.3.2 (Pneumonitis), and added language to Section 5.3.3 (Infusion Reactions), Section 5.3.4 (Hypersensitivity Reactions), and Section 5.3.5 (Gastrointestinal Disorders).

9.6 Protocol Amendment 1, 16Apr2014

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

1. All relevant sections: Given regulatory approval of the new drug name, “AMP-514” was replaced with “MEDI0680.”
2. Title page and headers: The protocol number “D.6020.C00001” was changed to “D6020C00001.”
3. Synopsis: The synopsis was updated to align with the body of the protocol.
4. Section 2.2.2 (Secondary Endpoints): A reference (Cheson et al, 2006) was added for the IWG 2006 MDS response criteria.
5. Section 3.1.1 (Overview) and Section 3.1.1.2 (Dose-expansion Phase): Text was added to clarify that immunotherapy-naïve subjects will be enrolled in up to 8 hematologic and solid tumor cohorts, and to indicate that the immunotherapy-naïve cohort could enroll an additional 60 subjects based on emerging efficacy and safety data from the current study and ongoing studies. In addition, text was added to specify that each hematologic cohort, including MDS, will only be expanded after submission of a formal protocol amendment. Identical language was added for the immunotherapy-pretreated cohort.
6. Section 4.1.2 (Inclusion Criteria): The following sub-bullet “b” was added under inclusion criterion #4: “Must have failed to respond or relapsed following platinum-containing doublet chemotherapy.”
7. Section 4.2.1 (Enrollment/Screening Period): In Table 4.2.1-1, the cross-reference to the Smoking Questionnaire was corrected (changed from “Appendix 5” to “Appendix 4”).
8. Section 4.3.3.1 (Pain Questionnaire): The cross-reference to the Pain Questionnaire was corrected (changed from “Appendix 4” to “Appendix 5”).
9. Section 4.7.2 (Prohibited Concomitant Medications): The following statement was removed from the exclusionary medications list: “If steroids are permitted, there must be

a 14 days delay between stopping of steroids and the next dose of durvalumab and AMP-514."

10. Section 8 (References): The Cheson et al, 2006 reference was added to the list.
11. Appendix 4 (Smoking Questionnaire): The questionnaire was revised to correct typos, number the questions, and add notes to indicate that questions can be skipped as needed.

APPENDICES

Appendix 1 Signatures

Sponsor Signature(s)

A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination with Durvalumab versus Nivolumab Monotherapy in Subjects with Select Advanced Malignancies

I agree to the terms of this protocol.

Signature and date: Electronic signature appended

[redacted], MD, [redacted], [redacted], [redacted]

One MedImmune Way, Gaithersburg MD, 20878, USA

Telephone number: [redacted]

Signature of Principal Investigator

A Phase 1/2, Open-label Study to Evaluate the Safety and Antitumor Activity of MEDI0680 (AMP-514) in Combination with Durvalumab versus Nivolumab Monotherapy in Subjects with Select Advanced Malignancies. 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 Conference 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): _____

Appendix 2 Additional Safety Guidance

Assessment of Severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.03 as provided below. The determination of severity for all other events not listed in the NCI CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

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

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 5.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of Relationship

Relationship to Investigational Product

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

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

- An unreasonable temporal relationship between administration of the investigational product and the onset of the event (eg, the event occurred either before, or too long after, administration of the investigational product for it to be considered product-related)
- A causal relationship between the investigational product and the event is biologically implausible (eg, death as a passenger in an automobile accident)
- A clearly more likely alternative explanation for the event is present (eg, typical adverse reaction to a concomitant drug and/or typical disease-related event)

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

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

Relationship to Protocol Procedures

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

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

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

Appendix 3 National Institute of Allergy and Infectious Diseases and Food Allergy and Anaphylaxis Network Guidance for Anaphylaxis Diagnosis

Sampson HA, Muñoz-Furlong A, Campbell RL, Adkinson FN Jr, Bock SA, Branum A, et al. Second symposium on the definition and management of anaphylaxis: Summary report -- Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. J Allergy Clin Immunol. 2006;117:391-7.

The NIAID and FAAN define anaphylaxis as a serious allergic reaction that is rapid in onset and may cause death. They recognize 3 categories of anaphylaxis, with criteria designated to capture from 80% of cases (category 1) to > 95% of all cases of anaphylaxis (for all 3 categories).

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula)
   AND AT LEAST ONE OF THE FOLLOWING
   a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow [PEF], hypoxemia)
   b. Reduced blood pressure (BP) or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
   a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue-uvula)
   b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
   c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
   d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
   a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP
   b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person’s baseline

Appendix 4 Smoking Questionnaire

Question	Answer
1. Have you ever smoked?	☐ Yes ☐ No (If no, skip to Question 9)
2. Do you currently smoke?	☐ Yes ☐ No (If yes, skip to Question 4)
3. If you do not currently smoke, specify number of years since cessation	_____ years (number)
4. Smoking duration	_____ years (number)
5. Average number of cigars/day	_____ per day (number)
6. Average number of pipes/day	_____ per day (number)
7. Average number of packs/day (20 cigarettes per pack)	_____ per day (number)
8. Number of pack-years	_____ years (number)
9. Have you ever used smokeless tobacco (chewing tobacco or snuff)	☐ Yes ☐ No (If no, skip the questions below)
10. Do you currently use smokeless tobacco?	☐ Yes ☐ No (If yes, skip to Question 12)
11. If you do not currently use smokeless tobacco, specify the number of years since cessation	_____ years (number)
12. Smokeless tobacco duration	_____ years (number)
13. Average packages (cans or pouches) of smokeless tobacco per day	_____ per day (number)

Appendix 5 Solid Tumor 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 images will be collected and stored for possible future central re-analysis. All subjects will be followed for survival every 3 months (± 1 week) until 12 months post last dose, and then every 6 months (± 2 weeks) until the end of the study (defined as 2 years after the last subject is enrolled or the sponsor stops the study).

In the dose-escalation phase, RECIST will be modified so that PD must be confirmed at least 4 weeks after the initial assessment of PD in the absence of clinical deterioration (ie, rapid disease progression or threat to vital organs/critical anatomical sites requiring urgent alternative medical intervention, decline in ECOG performance status, or symptoms or signs indicating clinically significant progressive disease). Treatment with investigational products (MEDI0680 and durvalumab) will continue between the initial assessment of progression and confirmation of progression (see Section 3.1.2.1 for treatment beyond progression). In the absence of clinical deterioration, RECIST with this modification may discourage the early discontinuation of the investigational products and provide a more complete evaluation of its antitumor activity than would be seen with conventional response criteria.

Tumor assessments should include the following evaluations: physical examination (with photograph and measurement of skin lesions as applicable) and CT or magnetic resonance imaging (MRI) scans. Computed tomography or MRI scan of the chest, abdomen, and pelvis will be performed at screening and for response assessment in all subjects. Computed tomography or MRI scan of the head and neck is only required for subjects with SCCHN or for subjects with metastatic disease in the head or neck not involving the CNS. Computed tomography or MRI scan of the brain will be performed at screening for subjects with known CNS metastatic disease or if the subject is neurologically symptomatic during the course of the study. 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.

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

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

MRI scan

- MRI scan should use the same anatomical plane for serial assessments.
- 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)
    - For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm)
- **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 are not measurable by reproducible imaging techniques.
- **Target Lesions** – At baseline, 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 case report form (eg, “multiple enlarged pelvic lymph nodes” or “multiple liver metastases”).
- **New Lesions -** If measurable, new lesions will be measured and included as target lesions in order to facilitate the exploratory irRECIST analysis. Using irRECIST, up to

5 additional new lesions (maximum of 2 additional lesions per organ) may be included in the tumor burden at each post-baseline assessment. Other new lesions will be followed as non-target lesions.

RECIST v1.1 Response Criteria

Evaluation of Target Lesions

- **Complete Response -** Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm (the sum may not be "0" if there are target nodes).
- **Partial Response -** At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- **Progressive Disease -** At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: The appearance of one or more new lesions is also considered progression.)
- **Stable Disease -** Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum of diameters while on study.

Evaluation of Non-target Lesions

- **Complete Response -** Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm in short axis).
- **Non-complete Response/Non-progressive Disease -** Persistence of 1 or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.
- **Progressive Disease -** Unequivocal progression of existing non-target lesions will be defined as the overall level of substantial worsening in non-target disease such that, even in presence of SD or PR in target disease, the overall tumor burden has increased sufficiently to merit discontinuation of therapy. In the absence of measurable disease, change in 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," or 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 MEDI0680/durvalumab combination therapy or nivolumab monotherapy if investigators consider that subjects continue to benefit from treatment (see Section 3.1.2.1).

Evaluation of Overall Response

Confirmation of CR, PR is required by a repeat assessment no fewer than 4 weeks from the date of first documentation.

For the dose-escalation phase, efficacy analyses will be based on an application of modified RECIST v1.1 to investigator-assessed tumor measurements. RECIST v1.1 has been modified to require confirmation of PD. A confirmed PD will be a PD confirmed by a consecutive repeat assessment no fewer than 4 weeks later. A PD that occurs without follow-up scans to provide confirmation or only non-evaluable follow-up scans will also be considered a confirmed PD. The efficacy analysis will be based on the As-treated Population.

For the dose-expansion phase, efficacy analyses will be based on an application of RECIST v1.1 to investigator-assessed tumor measurements and BICR. The efficacy analysis will be based on the As-treated Population.

Overall responses for all possible combinations of tumor responses in target and non-target lesions with or without the appearance of new lesions are shown below.

Table A5-1 Evaluation of Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
Complete response	Complete response or No non-target lesion	No	Complete response
Complete response	Non-complete response / Non-progressive disease or Non-evaluable [b]	No (or NE)	Partial response
Partial response	Complete response or Non-complete response / Non-progressive disease or Non-evaluable [b]	No (or NE)	Partial response
Stable disease	Complete response or Non-complete response / Non-progressive disease or Non-evaluable [b]	No (or NE)	Stable disease
Progressive disease	Any	Yes or No	Progressive disease
Any	Progressive disease	Yes or No	Progressive disease
Any	Any	Yes	Progressive disease
Non-evaluable	Complete response or Non-complete response /	No	Non-evaluable

Table A5-1 Evaluation of Overall Response

Target Lesions	Non-target Lesions	New Lesions	Overall Response
	Non-progressive disease or Non-evaluable [b]		
No target lesion [a]	Complete response	No	Complete response
No target lesion [a]	Non-complete response / Non-progressive disease	No	Non-complete response / Non-progressive disease
No target lesion [a]	Not all evaluated	No	Not evaluable
No target lesion [a]	Complete response or Non-complete response / Non-progressive disease	Yes	Non-complete response / Non-progressive disease

[a] Defined as no target or non-target lesion at baseline.

[b] Non-evaluable is defined as either when no or only a subset of lesion measurements are made at an assessment or when lesion intervention occurs that directly affects a target lesion. If progressive disease criteria is met despite these events, progressive disease should be defined.

Appendix 6 Durvalumab and MEDI0680 Dose Modifications for Toxicity Management

Table A6-1 Immune-mediated reactions

Table A6-2 Infusion-related reactions

Table A6-3 Non-immune mediated reactions

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Immune-mediated adverse events (overall management for toxicities not noted below)		Drug administration modifications of study drug/study regimen will be made to manage potential immune-mediated AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03. • In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below) , permanently discontinue study drug/study regimen for the following conditions: Inability to reduce corticosteroid to a dose of ≤ 10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.	It is recommended that management of imAEs follow the guidelines presented in this table – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, concomitant medications, infections, etc) – In the absence of a clear alternative etiology, all events should be considered potentially immune mediated. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events – For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥ 3) events promptly start prednisone PO 1-2 mg/kg/day or IV equivalent – If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [eg, up to 2-4 mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper) – More potent immunosuppressives such as TNF inhibitors (eg, infliximab) – (also refer to the individual sections of the immune mediated adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. – Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (eg, inflammatory reaction at sites of metastatic disease, lymph nodes etc). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that subject.
	Grade 1	No dose modification	

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 2	Hold study drug/study regimen dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to Grade ≤ 1 and 5-7 days have passed after completion of steroid taper Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10 mg/day or equivalent.	
	Grade 3	Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below	
	Grade 4	Permanently discontinue study drug/study regimen	
	Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen		

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/ILD	Grade of pneumonitis (CTCAE version 4.03)	Any Grade	– Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only, intervention not indicated)	No dose modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	• For Grade 1 (radiographic changes only) - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult
	Grade 2 (symptomatic, medical intervention indicated, limiting instrumental ADL)	• Hold study drug/study regimen dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • Study drug/study treatment can be resumed based upon treating physician's clinical judgment at the next scheduled dose once event stabilizes to Grade ≤ 1 or baseline and 5-7 days have passed after completion of steroid taper	• For Grade 2 (mild to moderate new symptoms) – Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (eg, prednisone 1-2 mg/kg/day or IV equivalent) – Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started – If still no improvement within 3-5 days despite IV methylprednisone at 2-4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			– Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[1] – Consider pulmonary and infectious disease consult – Consider as necessary discussing with study physician
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention indicated [eg, tracheostomy or intubation])	Permanently discontinue study drug/study regimen	• For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain pulmonary and infectious disease consult – Hospitalize the subject – Supportive Care (oxygen, etc) – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (eg, infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation) [2]
Diarrhea/ enterocolitis	Grade of diarrhea (CTCAE version 4.03)	Any grade	– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or

[1] ASCO Educational Book 2015. Michael Postow MD. “Managing Immune Checkpoint Blocking Antibody Side Effects”
[2] ASCO Educational Book 2015. Michael Postow MD. “Managing Immune Checkpoint Blocking Antibody Side Effects”

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, other medications, infections including testing for clostridium difficile toxin, etc) – Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event – Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 diarrhea (stool frequency of < 4 over baseline per day)	No dose modification	• For Grade 1 diarrhea : - Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
	Grade 2 diarrhea (stool frequency of 4-6 over baseline per day)	Hold study drug/study regimen until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date will be based upon treating physician's clinical judgment. • Study drug/study treatment can be resumed based upon treating physician's clinical judgment at the next scheduled dose once	• For Grade 2 diarrhea: – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (eg, American Dietetic Association colitis diet), and loperamide and/or budesonide – Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. If still no improvement within 3-5 days despite 2-4 mg/kg IV

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		event stabilizes to Grade ≤ 1 or baseline and 5-7 days have passed after completion of steroid taper	methylprednisolone, promptly start immunosuppressives - such as (infliximab at 5 mg/kg once every 2 weeks[3]). **Caution**: important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab – Consult study physician if no resolution to ≤ Grade 1 in 3-4 days – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥ 7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen	• For Grade 3 or 4 diarrhea: – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent – Monitor stool frequency and volume and maintain hydration – Urgent GI consult and imaging and/or colonoscopy as appropriate – If still no improvement within 3-5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (eg, infliximab at 5 mg/kg once every 2 weeks). – Caution: ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for

[3] ASCO Educational Book 2015 Michael Postow MD "Managing Immune Checkpoint Blocking Antibody Side Effects

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			treatment of cancer-related infections [Category 2B recommendation])
Hepatitis (elevated LFTs) **Infliximab should not be used for management of immune mediated hepatitis**	Grade of liver function test elevation (CTCAE version 4.03) Any grade Grade 1 (AST or ALT > ULN to 3 times ULN and/or TB > ULN to 1.5 times ULN)	No dose modification If it worsens, treat as Grade 2 event	– Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin – Evaluate for alternative etiologies (eg, viral hepatitis, disease progression, concomitant medications) • For Grade 1 AST or ALT and/or TB elevation • - Continue LFT monitoring per protocol
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or TB > 1.5-3.0 times ULN)	• Hold Study drug/study regimen dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • Study drug/study treatment can be resumed based upon treating physician's clinical judgment at the next scheduled dose once event stabilizes to Grade ≤ 1 or baseline and 5-7 days have passed after completion of steroid taper	• For Grade 2 AST or ALT and or TB elevation : – Regular and frequent checking of LFTs (eg, every 1-2 days) until elevations of these are improving or resolved. – If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2 mg/kg/day or IV equivalent. – If still no improvement within 3-5 days despite 1-2 mg/kg/day of prednisone or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – If still no improvement within 3-5 days despite 2-4 mg/kg/day of IV methylprednisolone, promptly start

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			immunosuppressives (mycophenolate mofetil-)[4] . Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 (AST or ALT > 5-20 times ULN and/or TB > 3.0-10 times ULN	• For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN • Hold study drug/study regimen dose until resolution to ≤ Grade 1 or baseline • Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline • Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 • For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue study drug/study regimen • Permanently discontinue study drug/study regimen for any case	• For Grade 3 or 4 AST or ALT and/or TB elevation: – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent – If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Hepatology consult, abdominal workup, and imaging as appropriate. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])

[4] ASCO Educational Book 2015 “Managing Immune Checkpoint Blocking Antibody Side Effects” , by Michael Postow MD

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		meeting Hy's law criteria (ALT > 3 × ULN + bilirubin > 2 × ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause[5]	
	Grade 4 (AST or ALT > 20 times ULN and/or TB > 10 times ULN)	Permanently discontinue study drug/study regimen	
Nephritis or renal dysfunction (elevated serum creatinine)	Grade of elevated serum creatinine (CTCAE version 4.03) Any grade	--	– Consult with nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (eg, routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc) – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression, infections etc.) – Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event
	Grade 1 [serum creatinine > 1-1.5 × baseline; > ULN to 1.5 × ULN]	No dose modification	• For Grade 1 elevated creatinine: • Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity , treat as

[5] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
			Grade 2 or Grade 3 or 4 • Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.
	Grade 2 [serum creatinine > 1.5-3.0 × baseline; > 1.5 × 3.0 × ULN]	• Hold study drug/study regimen until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • Study drug/study treatment can be resumed based upon treating physician's clinical judgment at the next scheduled dose once event stabilizes to Grade ≤ 1 or baseline and 5-7 days have passed after completion of steroid taper	• For Grade 2 elevated creatinine: – Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc. – Carefully monitor serum creatinine every 2-3 days and as clinically warranted – Consult nephrologist and consider renal biopsy if clinically indicated – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2-4 mg/kg/day started. – Once improving gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
	Grade 3 or 4 (Grade 3: serum creatinine > 3.0 × baseline; > 3.0-6.0 × ULN	Permanently discontinue study drug/study regimen	– Carefully monitor serum creatinine on daily basis – Consult Nephrologist and consider renal biopsy if clinically indicated – Promptly start prednisone 1 to 2 mg/kg/day or IV equivalent

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 4: serum creatinine > 6.0 × ULN)		– If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]
Rash (excluding bullous skin formations)	Grade of skin rash (please refer to NCI CTCAE version 4.03 for definition of severity/grade depending on type of skin rash)	Any grade	• Monitor for signs and symptoms of dermatitis (rash and pruritus) • **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****
	Grade 1	No dose modification	• For Grade 1: – Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream)
	Grade 2	• For persistent (> 1-2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline – If toxicity worsens then treat as Grade 3 – If toxicity improves then resume administration at next scheduled	• For Grade 2: – Obtain dermatology consult – Consider symptomatic treatment including oral antipruritics (eg, diphenhydramine or hydroxyzine) and topical therapy (eg, urea cream) – Consider moderate-strength topical steroid – If no improvement of rash/skin lesions occurs within 3-5 days or is worsening despite symptomatic treatment and/or use of

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		dose – Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to Grade ≤ 1 or baseline and 5-7 days have passed after completion of steroid taper	moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent – Consider skin biopsy if persistent for > 1-2 weeks or recurs
	Grade 3	• Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline • Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline	• For Grade 3 or 4: – Consult dermatology – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Consider hospitalization – Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – Discuss with study physician
	Grade 4	Permanently discontinue study drug/study regimen	

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Endocrinopathy (eg, hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc)	Any grade (depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)		– Consult Endocrinologist – Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. – Subjects should be thoroughly evaluated to rule out any alternative etiology (eg, disease progression including brain metastases, infections, etc.) – Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a subject experiences an AE that is thought to be possibly of autoimmune nature (eg, thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
	Grade 1 (depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade 1)	No dose modification	• For Grade 1: (including those with asymptomatic TSH elevation) – Monitor subject with appropriate endocrine function tests – If TSH < 0.5 × LLN, or TSH > 2 × ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2 (depending on the type of endocrinopathy, refer to NCI CTCAE version	• For Grade 2 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until subject is clinically stable • If toxicity worsens then treat as Grade 3 or Grade 4	• For Grade 2: (including those with symptomatic endocrinopathy) – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	4.03 for defining the CTC grade/severity 2)	• If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to Grade ≤ 1 and 5-7 days have passed after completion of steroid taper • Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per Investigator or treating physician's clinical judgement, and 3) doses of prednisone are at less than or equal to 10 mg/day or equivalent.	– Initiate hormone replacement as needed for management – Evaluate endocrine function, and as clinically indicated, consider pituitary scan – For subjects with abnormal endocrine work up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (eg, 1-2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (eg, Levothyroxine, hydrocortisone, or sex hormones). – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – For subjects with normal endocrine work up (lab or MRI scans), repeat labs/MRI as clinically indicated.
	Grade 3 or 4 (depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 3 or 4)	• For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled • Resume study drug/study regimen administration if controlled at the next scheduled dose • Study drug/study treatment can be resumed based upon treating physician's clinical judgment at the next scheduled dose once event stabilizes to Grade ≤ 1 or baseline and	• For Grade 3 or 4: – Consult endocrinologist – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate IV corticosteroids with mineralocorticoid activity

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		5-7 days have passed after completion of steroid taper	– Once improving, gradually taper immunosuppressive steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – Discuss with study physician
Immune mediated neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding myasthenia gravis and Guillain-Barre)	Grade of neurotoxicity Depending on the type of neurotoxicity, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity		
	Any grade		– Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc) – Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (eg, electromyogram and nerve conduction investigations) – Symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	• See “Any Grade” recommendations above.
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold study drug/study	– Discuss with the study physician – Obtain Neurology Consult

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
		regimen dose until resolution to ≤ Grade 1 • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1. – If toxicity worsens then treat as Grade 3 or Grade 4 – If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to Grade ≤ 1 and 5-7 days have passed after completion of steroid taper	– Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc) – Promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent – If no improvement within 3-5 days despite 1-2 mg/kg/day prednisone or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (eg, IVIG)
	Grade 3	• Hold Study drug/study regimen dose until resolution to ≤ Grade 1 • Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline.	• For Grade 3 or 4: – Discuss with study physician – Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (eg, IVIG) – Once stable, gradually taper steroids over ≥ 4 weeks
	Grade 4	• Permanently discontinue study drug/study regimen	
Immune-mediated peripheral		Any Grade	– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations which

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
neuromotor syndromes, such as Guillain-Barre and myasthenia gravis			can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Subjects should be evaluated to rule out any alternative etiology (eg, disease progression, infections, metabolic syndromes and medications, etc). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in subjects with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult – Neurophysiologic diagnostic testing (eg, electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation • Important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 1	No dose modification	– Discuss with the study physician – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above – Obtain a neurology consult unless the symptoms are very minor and stable

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 2	• Hold study drug/study regimen dose until resolution to ≤ Grade 1 • Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline	• Grade 2 – Discuss with the study physician – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above – Obtain a Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (eg, gabapentin, duloxetine, etc) ◦ *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each subject. o If Myasthenia Gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ◦ *GUILLAIN-BARRE:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.

Table A6-1 Immune-mediated reactions

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
	Grade 3	• Hold study drug/study regimen dose until resolution to ≤ Grade 1 • Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline	• For severe or life threatening (Grade 3 or 4) events: – Discuss with study physician – Recommend hospitalization – Monitor symptoms and obtain neurological consult ◦ *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. o If Myasthenia Gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ◦ *GUILLAIN-BARRE*: ◦ Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 4	Permanently discontinue study drug/study regimen	

AChE = acetylcholine esterase; ADL = activities of daily living; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CT = computed tomography; CTC = Common Terminology Criteria; FT4 = free thyroxine; GI = gastrointestinal; ILD = interstitial lung disease; imAE = immune-mediated adverse event; IV = intravenous; IVIG = intravenous immunoglobulin; LFT = liver function test; LLN = lower limit of normal; MRI = magnetic resonance imaging; NCCN = National Comprehensive Cancer Network; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PCP = pneumocystis pneumonia; PO = oral; TB = total bilirubin; TNF = tumor necrosis factor; TSH = thyroid-stimulating hormone; ULN = upper limit of normal.

Table A6-2 Infusion-related reactions

Severity Grade	Dose Modifications	Toxicity Management
Any grade		– Management per institutional standard at the discretion of investigator – Monitor subjects for signs and symptoms of infusion-related reactions (eg, fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, skin rashes etc) and anaphylaxis (eg, generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator – Consider premedication per institutional standard prior to subsequent doses
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

IM = intramuscular; IV = intravenous.

Table A6-3 Non-immune-mediated reactions

CTC Grade/Severity	Dose Modification	Toxicity Management
Any grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline, resume study drug/study regimen administration at next scheduled dose based upon treating physician's clinical judgment . Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the sponsor)	Treat accordingly as per institutional standard

AE = adverse event; CTC = Common Terminology Criteria.

Appendix 7 Memorial Sloan Kettering Cancer Center Prognostic Score (Renal Cell Carcinoma)

Table A7-1 Determination of MSKCC Prognostic Score in Previously Treated Subjects

Parameter	Risk Factor	Criteria Value	Subject Value	If subject value meets criteria value, enter 1
KPS	Low KPS	< 80%		
Corrected calcium[a]	High corrected calcium	≥ 10 mg/dL		
Hemoglobin	Low hemoglobin	Males: ≤ 13 g/dL Females: ≤ 11.5 g/dL		
				Sum total of above = MSKCC Prognostic Score

Adapted from Motzer et al, 2015

KPS = Karnofsky performance score; MSKCC = Memorial Sloan Kettering Cancer Center.

[a] Corrected calcium = ([4 - serum albumin in g/dL] × 0.8) + serum calcium

Table A7-2 Risk Group Based on MSKCC Prognostic Score

Risk Group	MSKCC Prognostic Score
Favorable-risk	0
Intermediate-risk	1 or 2
Poor-risk	3

MSKCC = Memorial Sloan Kettering Cancer Center.

Prognostic risk groups are based on the presence of 0 (favorable), 1 or 2 (intermediate), or 3 (poor) of the following prognostic factors: anemia, hypercalcemia, and poor Karnofsky performance status