MedImmune

Clinical Study Protocol

Drug Substance	MEDI0457 (INO-3112) Durvalumab (MEDI4736)
Study Code	D8860C00005
Version	8.0
Date	17 March 2021

A Phase 1b/2a, Multi-Center Open-Label Study to Evaluate the Safety and Efficacy of Combination Treatment with MEDI0457 (INO-3112) and Durvalumab (MEDI4736) in Patients with Recurrent / Metastatic Human Papilloma Virus Associated Head and Neck Squamous Cancer

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

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VERSION HISTORY

Version 8.0, 17 March 2021
The following changes were incorporated into Version 8.0 of the Clinical Study Protocol: • Section 4 (Table 3): Addition of COVID-19 vaccine footnote "p". Aligned footnote "d" with Section 7.2. • Section 4.4: Addition of an option to allow Investigators to remove patients from the Continued Treatment Period after 2 years of treatment. Update to remove collection of non-serious AEs from the Continued Treatment Period. • Section 5.5.2: Addition of COVID-19 vaccine guidance.

Version 7.0, 01 September 2020
The following changes were incorporated into Version 7.0 of the Clinical Study Protocol: • Title Page: Secondary Medical Monitor information removed. • Synopsis: Updated estimated date of last patient completed. • Section 4: Discontinuation of tests for HPV-16/HPV-18 E6/E7 antibody, HPV-16/HPV-18 E6/E7 ELISPOT and flow cytometry-based assay, as well as Tumor cell and tumor cell HPV DNA or RNA. Edit to vital signs footnote for clarification in Table 3. • Section 4.4: Addition of Continued Treatment Period • Section 5.8.1.1: Clarification that tumor biopsies collected as part of clinical care can be submitted for further analysis unless AZ determines to end sample collection/analysis. • Appendix H: Removed the link to the Durvalumab Dosing Modification and Toxicity Management Guidelines (https://tmg.azirae.com), as the web portal has been decommissioned. • Other minor formatting edits were made throughout the document.

Version 6.0, 27 January 2020
The following changes were incorporated into Version 6.0 of the Clinical Study Protocol: • Title Page: Primary and Secondary Medical Monitors and contact information updated. • Section 6.12.1: Addition of a reference to the latest Durvalumab Investigator's Brochure. Text detailing dose modifications for durvalumab infusion-related reactions was removed and a reference to Appendix H was added. • Section 11: Updated references to Durvalumab and MEDI0457 Investigator's Brochures. • Appendix H: Durvalumab Treatment Modification and Toxicity Management Guidelines tables in Appendix H removed and are to be maintained as a stand-alone document within the Site Master File and are available through the following link: https://tmg.azirae.com. • Other minor edits were made throughout the document for clarification.

Version 5.0, 12 July 2017
The following changes were incorporated into Version 5.0 of the Clinical Study Protocol: • CCI [redacted] • Clarification between the Safety Analysis Run-in patients and the Safety Analysis patients. • Update with Durvalumab Investigator Brochure details to reflect the more recent version for the Introduction and Adverse events of special interest sections. • Changes to the collection of screening biopsies. • Changes made to Inclusion criterion #9. • The reason for the screen failures will be recorded.

- Details of the Safety Data Monitoring Committee have been revised / clarified based on the discussions during the preparation of the Safety Data Monitoring Committee Charter.
- Corrections and clarifications made to the footnotes of Tables 3 and 4.
- Visit Windows: modifications of the visit windows for the treatment period (Table 3).
- Pregnancy tests: The frequency of pregnancy testing has been reduced to once every 4 weeks. The removal of the wording that a pregnancy test must be performed before every tumor biopsy or study drug administration since the frequency of pregnancy testing has been reduced to every 4 weeks.
- Addition of new creatine phosphokinase sampling times during the treatment period (at Weeks 7, 8 and 12 and then every 8 weeks) and at the Follow-up visit.
- Inclusion of white blood cell count and absolute eospinophil count to hematology assessments (Table 5).
- CCI [redacted]
- Replacement of the fluorescence activated cell sorting assay with the flow cytometry-based assay.
- Removal of the method of measurement of serum HPV-specific antibody levels with a multiplexed serology assay.
- Amendment of TS Biorepository to MedImmune Biorepository.
- Inclusion of the independent central review of all scans used in the assessment of tumors by RECIST version 1.1 and/or irRECIST.
- Clarification of administration site reactions as adverse events of special interest.
- Removal of the dose-limiting toxicity criterion: Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care is a dose-limiting toxicity.
- Correction made for study drug accountability. Study drug accountability will be captured using Interactive Voice and Web Response.
- Removal of the duplicate Safety Design table from the Safety Analysis run-in section.

- The definition of the Response-evaluable Population has reworded for clarification.
- The definition of the Pharmacokinetic Analysis Set has been updated to reflect the definition provided in the Statistical Analysis Plan.
- Clarifications made to the reporting of serious adverse events if the Web based Data Capture system is not available.
- Removal of the follow-up and documentation of pregnancy outcome for the partners of the male patients.
- Update made to the study timetable.
- Addition of abbreviations due to the introduction of new text.
- Removal of the signature pages from the protocol.
- Other minor edits were made throughout the document for clarification.

Version 4.4, 09 December 2016
Initial creation

CCI [redacted]

This Clinical Study Protocol has been subject to a peer review according to AstraZeneca Standard procedures. The Clinical Study Protocol is publicly registered and the results are disclosed and / or published according to the AstraZeneca Global Policy on Bioethics and in compliance with prevailing laws and regulations.

MedImmune

PROTOCOL SYNOPSIS

A Phase 1b/2a, Multi-Center Open-Label Study to Evaluate the Safety and Efficacy of Combination Treatment with MEDI0457 (INO-3112) and Durvalumab (MEDI4736) in Patients with Recurrent / Metastatic Human Papilloma Virus Associated Head and Neck Squamous Cancer

Study site(s) and number of patients planned

This will be a multi-center study with the participation of sites in the United States of America. Approximately eight centers will participate in the study. Approximately 50 patients will be enrolled to obtain 40 evaluable patients.

Study period		Phase of development
Estimated date of first patient enrolled	Q4 2016	1
Estimated date of last patient completed	Q1 2021	1

Study design

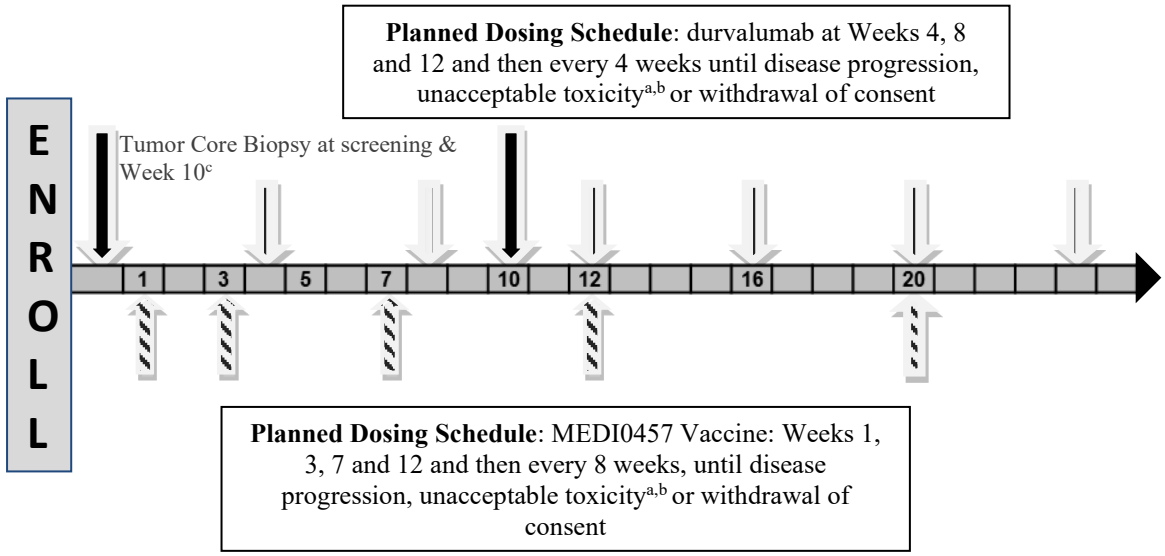
This is a Phase 1b/2a, open-label, multi-center study to evaluate the safety and tolerability, anti-tumor activity, and immunogenicity of MEDI0457 (also known as INO-3112) in combination with durvalumab (also known as MEDI4736). Approximately 50 patients with human papilloma virus associated recurrent / metastatic head and neck squamous cell cancer will be enrolled in this study. Approximately three to 12 patients (Safety Analysis Run-in patients) will be enrolled and assessed for safety before additional patients are enrolled at a recommended dose and schedule for the combination. Because this study is the first time MEDI0457 has been combined with durvalumab, the study will start with enrollment of a minimum of three patients who will receive four doses of MEDI0457 (**Limited Schedule**) in combination with durvalumab. Only if the safety analysis of the initial patients who complete the 7-week dose-limiting toxicity evaluation period, is deemed acceptable (i.e., none of the initial patients experience a dose-limiting toxicity), the vaccination schedule will switch from the limited four doses (**Limited Schedule**) to the **Indefinite Schedule** (also known as the **Planned Dosing Schedule,** i.e. vaccinations will continue until disease progression). This **Indefinite Schedule** will be implemented for all subsequent patients following the Safety Analysis Run-in. Otherwise, if a third of the initial patients experience a dose-limiting toxicity, a minimum of three additional patients (i.e., a minimum total of six patients for the Safety Analysis Run-in) will be enrolled and the initial minimum six patients in the Safety Analysis Run-in cohort will be limited to a total of four doses of MEDI0457 (**Limited Schedule**) before considering a switch to the **Indefinite Schedule**, provided the safety data was supportive and if only no more than a third of these patients experience a dose-limiting toxicity during their 7-week dose-limiting toxicity evaluation period. If at any time during the

enrollment of these patients, more than a third of the patients experience dose-limiting toxicity, then this regimen has exceeded the maximum tolerated dose and the regimen will be modified. The choice of modifications in the **Revised Dosing Schedule** during the Safety Analysis Run-in include the following: (1) decrease the dose of durvalumab to 750 mg every four weeks or decrease the total number of durvalumab doses, (2) increase the interval between MEDI0457 doses from every 8 weeks to intervals such as 12 or 16 weeks following the Week 12 dose or decrease the total number of MEDI0547 doses administered from a total of three to either one or two during the dose-limiting toxicity period. At least a minimum of three patients with no dose-limiting toxicity and up to approximately six patients with no more than a third with a dose-limiting toxicity must be evaluated using either the **Planned Dosing Schedule** or **Revised Dosing Schedule** before study enrollment will continue with a recommended dose and schedule for the combination. In the **Planned Dosing Schedule** both MEDI0457 and durvalumab treatment will continue until confirmed disease progression, unacceptable toxicity or withdrawal of consent. Either treatment may be stopped by the Investigator while the other treatment continues. See flowchart and Design for Safety Analysis Run-in table below.

Design for Safety Analysis Run-in

Rules
• A minimum of three patients will be enrolled and if none of the initial patients experience a dose-limiting toxicity, then the vaccination schedule will switch from the limited four doses (**Limited Schedule**) to the **Indefinite Schedule** (also known as the **Planned Dosing Schedule**, i.e. vaccinations will continue until disease progression). The **Indefinite Schedule** will be implemented for all subsequent patients following the Safety Analysis Run-in. • If a third of the initial patients experience a dose-limiting toxicity, then a minimum of three additional patients (i.e., a minimum total of six patients) will be enrolled into the Safety Analysis Run-in. These patients will be given the **Limited Schedule** (four doses) of MEDI0457 before considering a switch to the **Indefinite Schedule** provided the safety data was supportive and if no more than a third of these patients experience a dose-limiting toxicity during their 7-week dose-limiting toxicity evaluation period. • If at any time during the enrollment of these patients, more than a third of the patients experience a dose-limiting toxicity, then this regimen has exceeded the maximum tolerated dose and the regimen will be modified: **Revised Dosing Schedule** (per Safety Data Monitoring Committee). • At least a minimum of three patients with no dose-limiting toxicity and up to approximately six patients with no more than a third with a dose-limiting toxicity must be evaluated using either the **Planned Dosing Schedule** or **Revised Dosing Schedule** before study enrollment will continue with a recommended dose and schedule for the combination.

Overall Study Design Flow Chart



[a] **Planned Dosing Schedule:** Minimum time between Week 3 MEDI0457 dose and the Week 4 first durvalumab dose, and the Week 7 MEDI0457 dose and the Week 8 durvalumab dose is 7 days. Starting at Week 12, the administration of MEDI0457 and durvalumab treatments can be given on the same day. Safety Analysis run-in patients will initially receive a total of four doses of MEDI0457 (**Limited Schedule**) as per schedule above. Based on the rules shown in the Design for Safety Analysis Run-in table, the **Limited Schedule** (four doses) will be switched to the **Indefinite Schedule** (also known as the **Planned Schedule**).

[b] A **Revised Dosing Schedule** will be evaluated in up to six patients if two or more patients during the Safety Analysis Run-in period experience a dose-limiting toxicity.

[c] All patients should consent to pre-treatment biopsy of the tumor if it can be done safely (as judged by the Investigator) during screening, otherwise archival tissue within 3 years prior to study entry in all patients will be allowed except for a minimum 10 of the first 20 patients who will be required to provide a paired biopsy (a fresh biopsy at screening and at Week 10). After 10 paired biopsies have been obtained then Week 10 on-treatment biopsy will be made optional but will be encouraged.

Objectives

Primary Objectives:	Outcome Measures:
To determine the safety profile of MEDI0457 in combination with durvalumab in patients with recurrent / metastatic head and neck cancer.	Adverse events / serious adverse events Collection of hematology, serum chemistry, urinalysis, creatine phosphokinase, thyroid function testing and pregnancy test Electrocardiograms. The following parameters will be recorded for each electrocardiogram: date and time of electrocardiogram, heart rate (beats/min), PR interval (ms), QRS interval (ms), RR interval (ms), QT interval (ms), QTcB interval (ms), QTcF interval (ms), sinus rhythm (yes / no), and overall evaluation (normal / abnormal) Vital signs Physical examinations Concomitant medications World Health Organization / Eastern Cooperative Oncology Group performance status
To evaluate the anti-tumor activity of MEDI0457 in combination with durvalumab in patients with confirmed HPV-16 or HPV-18 associated recurrent / metastatic head and neck cancer.	Objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Response-evaluable Population)

Secondary Objectives:	Outcome Measures:
To evaluate the pharmacokinetics and anti-drug antibodies for durvalumab.	Serum concentrations of durvalumab Anti-drug antibodies for durvalumab

To evaluate the anti-tumor activity of MEDI0457 in combination with durvalumab.	Objective response rate by RECIST version 1.1 (As-treated population) and immune-related RECIST Disease control rate at 16 weeks by RECIST version 1.1 Overall survival Progression free survival as assessed by RECIST version 1.1

Exploratory Objectives:	**Outcome Measures:**
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]

Target patient population

Male or female patients 18 years of age or older with recurrent or metastatic human papilloma virus associated squamous cell carcinoma of the head and neck with persistent or progressive disease after treatment with a platinum based chemotherapy and lacking a curative treatment option. Patients who are platinum ineligible may be enrolled if they have received and failed an approved treatment and lack a treatment option with curative potential.

Eligible patients must have at least one "measurable target lesion" according to RECIST version 1.1 and one additional lesion that can be safely (as judged by the Investigator) biopsied at screening. Patients are required to provide their consent to have a screening biopsy; otherwise, archival tissue within 3 years prior to study entry in all patients will be allowed except for a minimum 10 of the first 20 patients who will be required to provide a paired biopsy (a fresh biopsy at screening and at Week 10).

Duration of treatment

Safety Analysis Run-in patients will initially receive a total of four initial doses of MEDI0457 as per schedule and will start durvalumab treatment at Week 4 and then every 4 weeks. Based on the rules shown in the Design for Safety Analysis Run-in table, the **Limited Schedule** (four doses) will be switched to the **Indefinite Schedule** (also known as the **Planned Schedule**). For the remaining patients, both MEDI0457 and durvalumab treatment will continue until confirmed disease progression, unacceptable toxicity or withdrawal of consent. Either treatment may be stopped by the Investigator while the other treatment continues.

Investigational product, dosage and mode of administration

All patients will receive combination treatment with MEDI0457 (also known as INO-3112) and durvalumab (also known as MEDI4736) as per the following **Planned Dosing Schedule**.

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Statistical methods

Sample size: CCI

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Statistical analyses: The safety evaluation will be based on the treated population, which includes all patients who receive any investigational product (defined as one dose of either study drug). Demographic and baseline characteristics will be summarized with means, medians, standard deviations, ranges or percentages. Safety will be summarized by the percentage of patients with adverse events, with grading according to Common Terminology Criteria for Adverse Event version 4.03 and attribution. The co-primary efficacy analysis of objective response rate via RECIST version 1.1 will be based on the Response-evaluable Population. Secondary analyses of objective response rate, disease control rate,

progression free survival and overall survival will be performed on both the As-treated and Response-evaluable populations. Immune responses will be analyzed in patients with available data by calculating the geometric mean and median antibody and T-cell levels and fold-increases along with associated 95% confidence intervals. Additional details will be provided in the Statistical Analysis Plan.

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LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

The following abbreviations and special terms are used in this study Clinical Study Protocol.

Abbreviation or special term	Explanation
AChE	Acetylcholinesterase
ADA	Anti-Drug Antibody
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALK	Anaplastic Lymphoma Kinase
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti PCP	Anti-Pneumocystis Pneumonia
Anti-PD-1	Anti-Programmed Cell Death Protein 1
Anti-PD-L1	Anti-Programmed Death Ligand 1
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
β-HCG	Beta-Human Chorionic Gonadotropin
COVID-19	Coronavirus disease of 2019
CPK	Creatine Phosphokinase
CR	Complete Response
CRF	Case Report Form (electronic)
CT	Computed Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Events
CV	Cardiovascular
DCR	Disease Control Rate
DCR-16w	Disease Control Rate at 16 weeks
DCR-24w	Disease Control Rate at 24 weeks
DILI	Drug Induced Liver Injury
DLT	Dose-Limiting Toxicity
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)

Abbreviation or special term	Explanation
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal Growth Factor Receptor
ELISPOT	Enzyme-Linked Immunosorbent Spot
EOS	End of Study
EOT	End of Treatment
EP	Electroporation
FDA	Food and Drug Administration
FDG	Fludeoxyglucose
FSH	Follicle-Stimulating Hormone
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
HBcAb	Hepatitis Virus B Core Antibody
HBsAg	Hepatitis Virus B Surface Antigen
HIV	Human Immunodeficiency Virus
HL	Hy's Law
HPV	Human Papilloma Virus
HPV-16	Human Papilloma Virus Type 16
HPV-18	Human Papilloma Virus Type 18
HR	Heart Rate
IATA	Airline Transportation Association
ICF	Informed Consent Form
ICH	International Council for Harmonisation
CCI	[redacted]
IHC	Immunohistochemistry
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
ILD	Interstitial Lung Disease
IM	Intramuscular
IND	Investigational New Drug
INR	International Normalized Ratio

Abbreviation or special term	Explanation
International Co-ordinating Investigator	If a study is conducted in several countries the International Co-ordinating Investigator is the Investigator co-ordinating the investigators and / or activities internationally.
IP	Investigational Product
irAE	Immune-Related Adverse Event
irRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
IV	Intravenous(ly)
IVIG	Intravenous Immunoglobulin
LD	Longest Diameter
LFT	Liver Function Test
LH	Luteinizing Hormone
LIMS	Laboratory Information Management System
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NSCLC	Non-Small Cell Lung Cancer
ORR	Objective Response Rate
OS	Overall Survival
CCI	[redacted]
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1
PET	Positron Emission Tomography
PFS	Progression Free Survival
PHL	Potential Hy's Law
PO	Oral(ly); by mouth
PR	Partial Response
PR interval	Interval on the electrocardiogram, from the start of the P wave to the start of the R wave
PRA	PRA Health Sciences

Abbreviation or special term	Explanation
Q4W	Every 4 weeks
QRS interval	Interval on the electrocardiogram from the start of the Q wave to the end of the of the S wave
QT interval	Interval on the electrocardiogram, from the beginning of the QRS complex to the end of the T wave
QTcB interval	QT interval corrected for heart rate based on the Bazett formula
QTcF interval	QT interval corrected for heart rate based on the Fridericia formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
SDMC	Safety Data Monitoring Committee
T_3	Triiodothyronine
T_4	Thyroxine
TBL	Total Bilirubin
CCI	[redacted]
TNF	Tumor Necrosis Factor
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBDC	Web Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

1.1 Background and rationale for conducting this study

Head and neck cancer accounts for about 3% of all cancers in the United States. In 2016, an estimated 61,760 people (45,330 men and 16,430 women) will develop head and neck cancer. It is estimated that 13,190 deaths (9,800 men and 3,390 women) will occur in 2016 from this disease.

There has been a remarkable shift in the epidemiology of head and neck cancer over the past 30 years. While exposure to chemical mutagens such as tobacco and alcohol remains the most common risk factor for squamous cell cancers of the aerodigestive tract, a rapidly expanding subset of head and neck cancers are acquired through human papilloma virus (HPV) infection. The oropharynx is uniquely susceptible to HPV, and now up to 70% of oropharyngeal cancers in the United States are HPV-related. The HPV viral oncoproteins, E6 and E7, are predominantly responsible for oncogenesis. E6 promotes degradation of p53, indirectly activates telomerase, and disrupts the function of the cellular phosphatase tumor suppressor PTPN13. E7 inactivates retinoblastoma protein and activates Mi2beta. Together, these oncogenic alterations result in the expression of p16, drive rapid cellular proliferation, suppress or down regulate key tumor suppressor proteins, and lead to cellular immortality. In addition, E6/E7 expression is required to maintain a malignant transformed phenotype (Scheffner et al 1990, Jabbar et al 2009).

While the currently available prophylactic HPV vaccines are highly effective in preventing infection by HPV types 16 and 18, these have no therapeutic effect, and therefore are of no value for patients already diagnosed with human papilloma virus type 16 (HPV-16) or human papilloma virus type 18 (HPV-18) positive head and neck cancer.

1.1.1 Summary of clinical experience

1.1.1.1 MEDI0457 with electroporation

MEDI0457, also known as INO-3112, is a combination of plasmids contained in the drug products called VGX-3100 and INO-9012.

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1.1.1.2 Durvalumab (investigational name MEDI4736)

Durvalumab is a human monoclonal antibody of immunoglobulin G1 (IgG1) kappa subclass that inhibits binding of programmed death ligand 1 (PD-L1). The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1, expressed on cancer cells and a subset of leukocytes, with the programmed cell death protein 1 (PD-1) molecules on antigen-presenting cells and T-cells. By binding to PD-L1 on tumor cells, the mechanism of action of durvalumab includes stimulation of the patient's anti-tumor immune response.

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1.2 Rationale for study design, doses and control groups

1.2.1 Rationale for the study

Although HPV associated head and neck cancers are generally associated with better prognosis than non-HPV cancer, approximately 20-25% of patients treated with curative intent for locoregional disease will have disease progression within 3 years (Ang et al 2010).

In addition, ~8-10% of patients will present with de novo incurable metastatic disease. Emerging data from anti-programmed cell death protein 1 (anti-PD-1) / anti-programmed death ligand 1 (anti-PD-L1) therapy in head and neck cancer as well as in other solid tumors are very promising with a subset of patients showing tumor regression and delayed progression and improvement in survival (Ferris et al 2016, Bauml et al 2016). However, a majority of patients do not respond to these novel treatments and thus are in need of additional therapies, including rational immunotherapy combinations.

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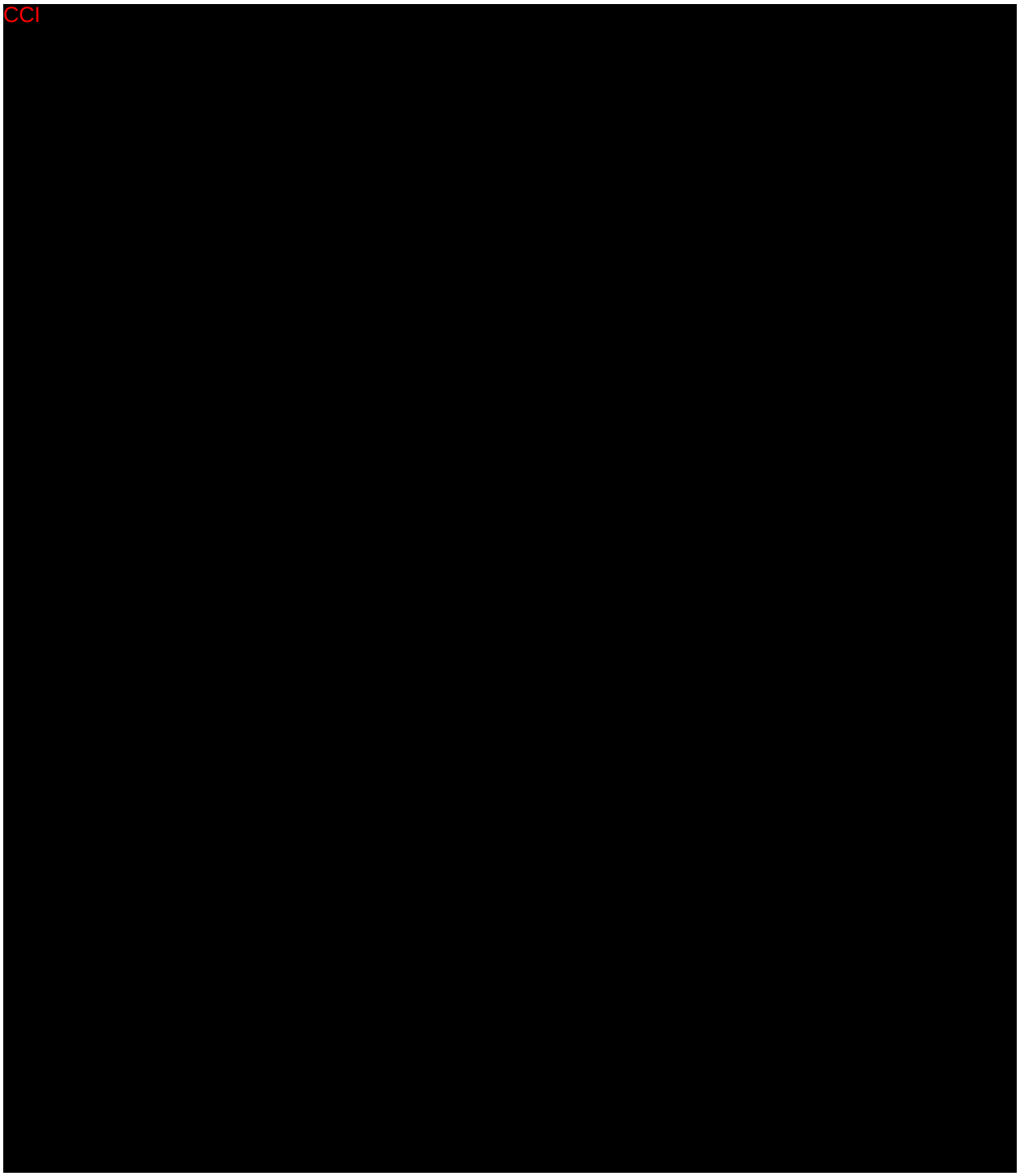

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1.2.2 Rationale for endpoints

In this first study of MEDI0457 and durvalumab in combination, safety and efficacy will be the primary endpoints. The secondary endpoints of immunogenicity, disease control rate (DCR), progression free survival (PFS) and overall survival (OS) will be used for deciding if further studies are warranted. In this study, there will be a Safety Analysis Run-in period because MEDI0457 and durvalumab have never been administered together. The Safety Analysis Run-in period patients will be included in the efficacy analysis. CCI [redacted]

1.2.3 Rationale for doses selected

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Durvalumab (also known as MEDI4736) has an acceptable safety profile. As of the data cut-off date of 12 July 2016, 5,225 patients 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 patients in open-label trials, and 2,347 patients as an estimate based on the randomization scheme in studies where the treatment arm is blinded. Additionally, > 1,700 patients have been exposed to one or more doses of durvalumab in externally-sponsored / investigator-initiated clinical trials. The data are not completely validated as all studies are ongoing and the databases have not been locked and fully cleaned. Please refer to the Durvalumab Investigator's Brochure for detailed data from ongoing studies. The 20 mg/kg (or its equivalent 1500 mg fixed dose) of durvalumab every 4 weeks has been tested in multiple studies and has been well tolerated.

1.2.4 Rationale for study population

The incidence of HPV associated head and neck cancers is rising and is expected to continue on this trajectory until at least 2030 (Zandberg et al 2013). The oropharynx is uniquely susceptible to HPV with ~70% of patients with cancer in this site are positive for oncogenic

HPV. A large majority (> 90%) of the cancers are positive for HPV-16 and / or HPV-18. The combination of HPV vaccine with anti-PD-L1 antibody is expected to enhance HPV-specific T-lymphocyte responses, resulting in improved outcome for these patients.

1.3 Benefit / risk and ethical assessment

1.3.1 Potential benefits - MEDI0457

The safety profile of MEDI0457 (INO-3112) with EP has been generally acceptable, although this is based on a limited number of patients who received MEDI0457 with EP. In addition to the safety, other benefits that already have been observed include (1) a generation of robust antigen-specific immune responses; (2) clinical benefits in patients with high grade cervical intraepithelial neoplasia, including viral clearance and improvement in pathological grade in the lesion area including viral clearance and improvement in pathological grade in the lesion area (Trimble et al 2015).

We expect to observe both immune response to MEDI0457 and clinical benefits in most patients in this study.

1.3.2 Potential benefits - Durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first-time-in-human, single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. Safety data are described in the current Durvalumab Investigator's Brochure. Efficacy data are available for three monotherapy studies (CD-ON-MEDI4736-1108, D4190C00007 and D4191C00003 [ATLANTIC] and two combination therapy studies (CD-ON-MEDI4736-1161 and D4190C00006). Clinical activity has been observed across the five studies (Durvalumab Investigator's Brochure).

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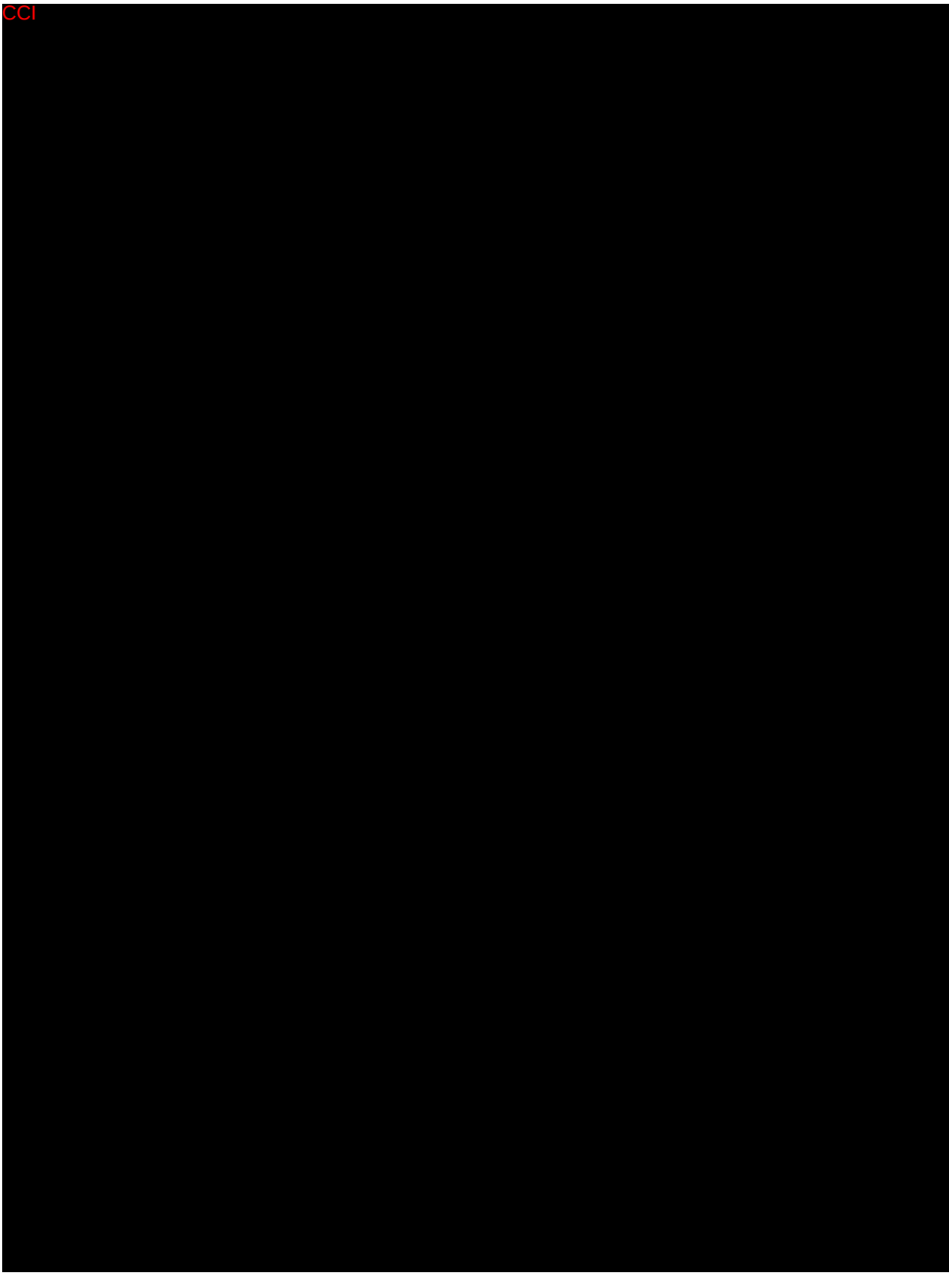

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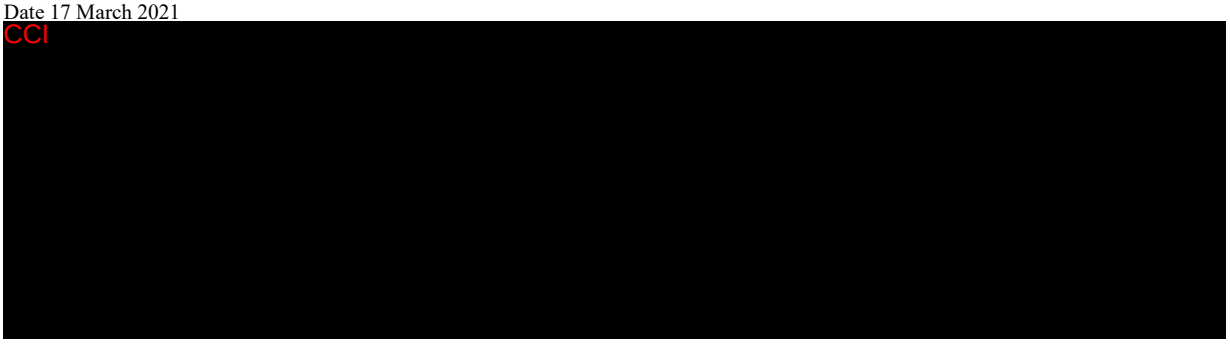

For further details, please refer to the Durvalumab Investigator's Brochure.

1.3.3 Potential benefits - DNA immunotherapy delivery with electroporation

DNA vaccines developed by Inovio have been delivered without EP (1 study) or with the Inovio EP devices (23 studies). Inovio EP devices have also been used to deliver DNA vaccines developed outside of Inovio in three different studies and two studies have evaluated the tolerability of Inovio EP devices with normal saline. None of these studies have shown any safety concern related to the use of an EP device. Electroporation indeed significantly enhances DNA transfer to host cells, resulting in robust immune responses (Sardesai and Weiner 2011).

1.3.4 Possible risks - MEDI0457 with electroporation

DNA based vaccines in general are less risky based on their safety information compared to other forms of vaccines that utilize viral and bacterial vectors.

In two companion papers by Sheets et al (Sheets et al 2006a, Sheets et al 2006b), potential toxicities (both intrinsic and immunotoxicities) and biodistribution profiles were compared for 21 different plasmid DNA constructs, in nine separate Good Laboratory Practice (GLP)-compliant studies. Despite differing plasmid DNA backbones, promoters, and sequence inserts, toxicity and biodistribution profiles were similar for all plasmid DNA constructs. With respect to the toxicity assessments, the authors reported that toxicity was localized to the site of the injection for all 21 plasmid DNA constructs. Similarly, all plasmid DNA constructs evaluated showed evidence that they were localized to the injection site and surrounding tissue in all studies.

Further, four separate GLP toxicology and biodistribution studies have been performed for eight additional plasmid DNA vaccine candidates developed by Inovio with identical backbones delivered by EP yielding similar toxicity and biodistribution profiles.

Intramuscular (IM) co-administration of interleukin-12 plasmid was evaluated in nonclinical studies to support the studies of IM interleukin-12 plasmid in humans. INO-9012 has been used in combinations with other DNA vaccines, including VGX-3100 (i.e., MEDI0457), in several ongoing studies (HPV-004 Study, HPV-005 Study, HPV-006 Study, PCa-001 Study and TRT-001 Study). There was no safety issue reported from these studies (for further details refer to MEDI0457 Investigator's Brochure).

Interleukin-12 may cause autoimmune events. This is at least partially associated with its Th1-promoting activity, which could favor Th1-mediated immunopathology and, in particular, the induction of Th1-mediated autoimmune diseases. With our clinical experience in the HPV-005 Study, we have not observed any AEs that suggest autoimmune activity or autoimmune disorder in patients who have received a DNA vaccine treatment that contains INO-9012 (human interleukin-12 DNA plasmid). This may reflect the use of IL-12 as a local adjuvant in relatively low concentrations as opposed to the administration of systemic doses. The study team will continue to vigilantly monitor patients for any possible risk of autoimmune AEs during the trial.

The EP procedure with CELLECTRA®5P could cause patient discomfort, such as transient injection site edema, swelling, or pain. Adverse events of administration site reactions are of special interest to the Sponsor. These are defined, for the purpose of this protocol, as all AEs occurring as a result of the administration of the study treatment. Guidelines for the grading and management of administration site reactions are outlined in Appendix I. In order to regularly monitor possible muscle damage, creatine phosphokinase (CPK) testing is scheduled during the study treatment.

Although safety data are generally acceptable for clinical testing, MEDI0457 is an investigational agent, and the full safety profile is unknown. Additionally, it is unknown about the possible risk due to the proposed changes in MEDI0457 administration regimen in this study and its combination in this study with other investigational agent durvalumab. This study will provide additional information on the safety profiles of these study treatments alone and in combination.

1.3.5 Possible risks - Durvalumab

Clinically significant risks of interest include immune-mediated reactions and their associated signs and symptoms, risks due to immunogenicity, and other potential risks.

Immune-mediated reactions / immune-related AEs (irAEs) that are important risks include: dermatitis / rash / pruritus, ALT / AST increases / hepatitis / hepatotoxicity, endocrinopathy (i.e., events of hypophysitis / hypopituitarism, adrenal insufficiency, type 1 diabetes, hypothyroidism and hyperthyroidism), neuropathy / neuromuscular toxicity (i.e., events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis), nephritis and increases in serum creatinine, pancreatitis (or laboratory tests suggestive of pancreatitis - increased serum lipase / increased serum amylase), myocarditis / pericarditis / uveitis, pneumonitis / interstitial lung disease and diarrhea / colitis. Hypersensitivity and serious allergic reaction events include infusion-related reactions, anaphylaxis / serious allergic reactions, and immune complex disease. These events are managed based on established administration and toxicity management guidelines for this entire class of therapeutics (see Appendix H, Postow 2015).

For further details, please refer to the Durvalumab Investigator's Brochure.

1.3.6 Possible risks and mitigations - MEDI0457 with electroporation + Durvalumab

Risks observed (administration site reactions) and anticipated (CPK elevations and autoimmune AEs [immunogenicity]) with the administration of MEDI0457 with EP are described in Section 1.3.4. Mitigations in place to reduce the adverse effects of MEDI0457 with EP administration include: rotation of injection sites, patients are educated to promptly report potential skin reactions and obtain visual assessment; protocol guidelines are in place for management and reporting of injection / administration site reactions; administration of MEDI0457 with EP will not occur in an extremity that contains a metal prosthesis or skin which is obscured with tattoos or having in the ipsilateral extremity of the chest an electronic defibrillator / pacemaker device; monitoring of possible muscle damage by measurement of CPK testing; clinical manifestation and laboratory monitoring for immunogenicity; and persistent CTCAE Grade 3 injection site reactions that persist for > 5 days will be considered a dose-limiting toxicity (DLT).

Clinically significant risks associated with immune oncology drugs (immune-mediated reactions and their associated signs / symptoms, and risks due to immunogenicity) have been briefly discussed in Section 1.3.5. It is reasonable to assume there is possible risk for additive or synergistic toxicity with this combination. Mitigations in place to detect and reduce the adverse effects of potential immune-mediated reactions include: eligibility criteria excluding certain autoimmune conditions present at baseline, baseline laboratory tests and monitoring per protocol; patients educated and instructed to notify the sites for any signs / symptoms that may represent an immune-mediated reaction; protocol guidelines for dose delay / withdrawal physical examinations at each site visit; and enlisting investigators familiar with the latest immune oncology toxicity management guidelines (Appendix H, Postow 2015).

Risks commonly associated with the administration of any foreign protein include: immune complex disease, infusion reactions (durvalumab), and anaphylaxis and serious allergic reactions. Mitigations to monitor, detect, and treat these potential adverse effects are: monitoring for the induction of anti-drug antibodies with signs / symptoms of immune complex disease; and monitoring of patients during and after administration of both investigational products (IPs) to detect and treat anaphylaxis / infusion reactions. Management criteria are in the protocol and in the appended immune oncology toxicity management guidelines (Appendix H, Postow 2015).

1.4 Study design

This is a Phase 1b/2a, open-label, multi-center study to evaluate the safety and tolerability, anti-tumor activity, and immunogenicity of MEDI0457 (also known as INO-3112) in combination with durvalumab (also known as MEDI4736). Approximately 50 patients with HPV associated recurrent / metastatic SCCHN will be enrolled in this study. Approximately three to 12 patients (Safety Analysis Run-in patients) will be enrolled and assessed for safety before additional patients are enrolled at a recommended dose and schedule for the combination. Because this study is the first time MEDI0457 has been combined with durvalumab, the study will start with enrollment of a minimum of three patients who will receive four doses of MEDI0457 (**Limited Schedule**) in combination with durvalumab. Only

if the safety analysis of the initial patients who complete the 7-week DLT evaluation period, is deemed acceptable (i.e., none of initial patients experience a DLT), the vaccination schedule will switch from the limited four doses (**Limited Schedule**) to the **Indefinite Schedule** (also known as the **Planned Dosing Schedule**, i.e. vaccinations will continue until disease progression). The **Indefinite Schedule** will be implemented for all subsequent patients following the Safety Analysis Run-in. Otherwise, if a third of the initial patients experience a DLT, a minimum of three additional patients (i.e., a minimum total of six patients for the Safety Analysis Run-in) will be enrolled and the initial minimum six patients in the Safety Analysis Run-in cohort will be limited to a total of four doses of MEDI0457 (**Limited Schedule**) before considering a switch to the **Indefinite Schedule**, provided the safety data was supportive and if only no more than a third of these patients experience a DLT during their 7-week DLT evaluation period. If at any time during the enrollment of these patients, more than a third of the patients experience a DLT, then this regimen has exceeded the MTD and the regimen will be modified. The choice of modifications in the **Revised Dosing Schedule** during the Safety Analysis Run-in include the following: (1) decrease the dose of durvalumab to 750 mg Q4W or decrease the total number of durvalumab doses (2) increase the interval between MEDI0457 doses from every 8 weeks to intervals such as 12 or 16 weeks following the Week 12 dose or decrease the total number of MEDI0457 doses administered from a total of three to either one or two during the DLT period. CCI [redacted] If the choice includes decreasing the number of vaccines doses administered during the DLT CCI [redacted] At least a minimum of three patients with no DLT and up to approximately six patients with no more than a third with a DLT must be evaluated using either the **Planned Dosing Schedule** or **Revised Dosing Schedule** before study enrollment will continue with a recommended dose and schedule for the combination. All dose and schedule decisions will be made after careful review of all available data by the SDMC which includes all enrolling investigators and the Sponsor Medical Monitor or designee. In the Planned Dosing Schedule (after the Safety Analysis is complete) both MEDI0457 and durvalumab treatment will continue until confirmed disease progression, unacceptable toxicity or withdrawal of consent. Either treatment may be stopped by the Investigator while the other treatment continues (refer to Figure 1). CCI [redacted] The choice of modifications include any of the following: (1) decrease the dose of durvalumab to 750 mg Q4W or decrease the total number of durvalumab doses, (2) increase the interval between MEDI0457 doses from every 8 weeks to intervals such as every 12 or 16 weeks following the Week 12 dose or decrease the total number of MEDI0547 doses administered from a total of three to either one or two during the DLT period.

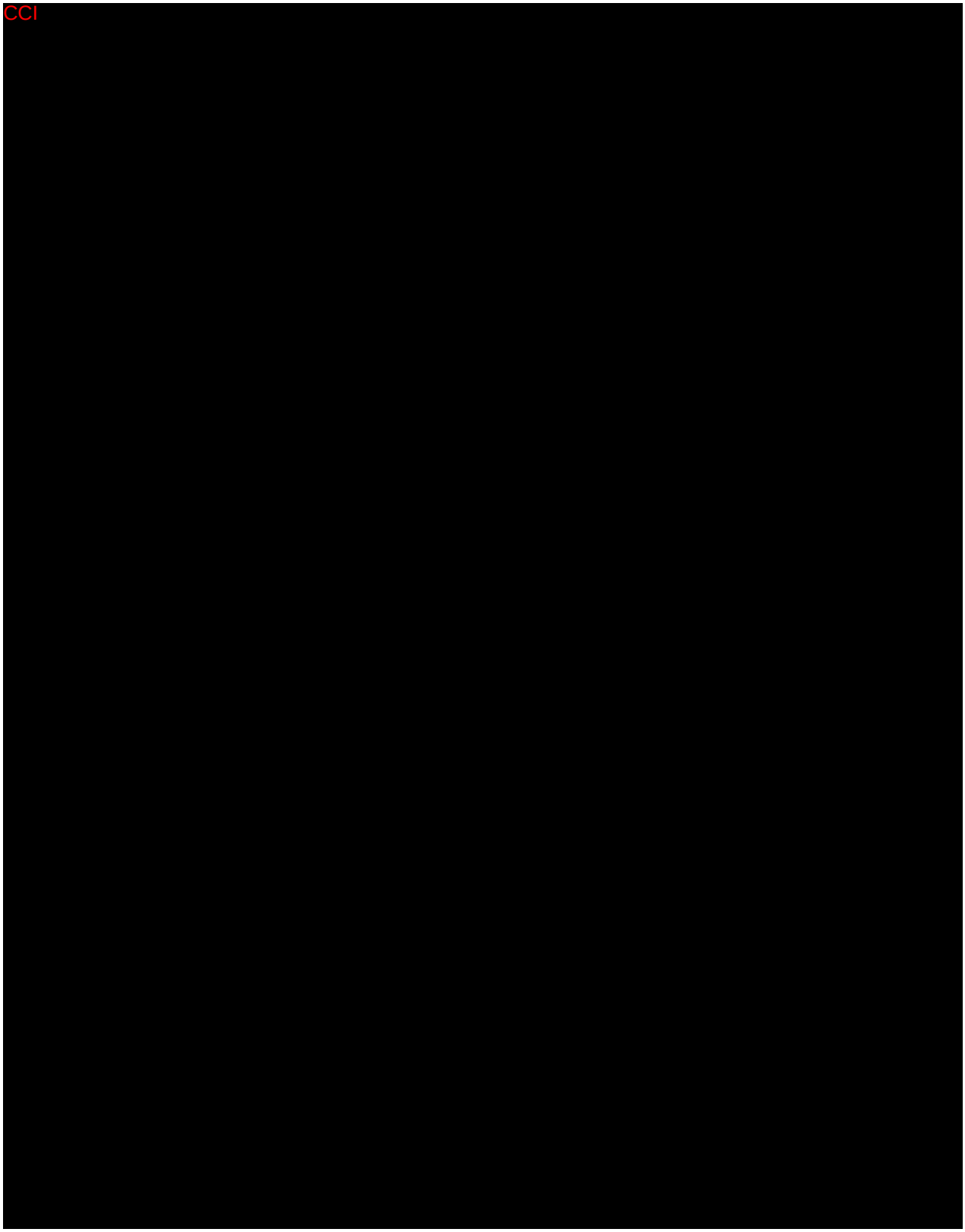
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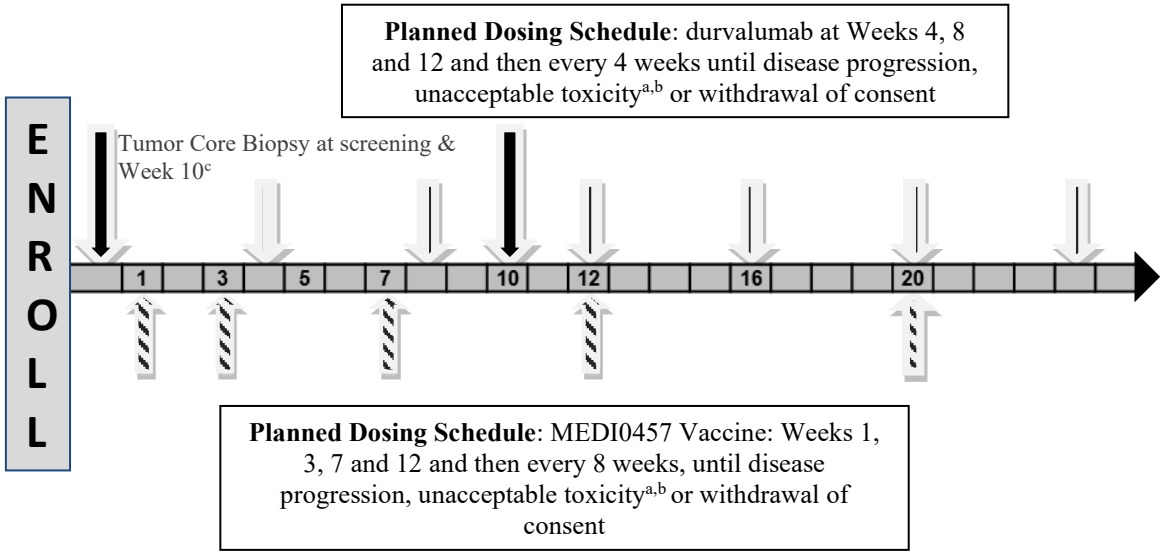
Figure 1 Overall Study Design Flow Chart



[a] **Planned Dosing Schedule:** Minimum time between Week 3 MEDI0457 dose and the Week 4 first durvalumab dose, and the Week 7 MEDI0457 dose and the Week 8 durvalumab dose is 7 days. Starting at Week 12, the administration of MEDI0457 and durvalumab treatments can be given on the same day. Safety Analysis Run-in patients will initially receive a total of four doses of MEDI0457 (**Limited Schedule**) as per schedule above. Based on the rules shown in the Design for Safety Analysis Run-in table, the **Limited Schedule** (four doses) will be switched to the **Indefinite Schedule** (also known as the **Planned Schedule**).

[b] A **Revised Dosing Schedule** will be evaluated in up to six patients if two or more patients during the Safety Analysis Run-in period experience a DLT.

[c] All patients should consent to pre-treatment biopsy of the tumor if it can be done safely (as judged by the Investigator) during screening, otherwise archival tissue within 3 years prior to study entry in all patients will be allowed except for a minimum 10 of the first 20 patients who will be required to provide a paired biopsy (a fresh biopsy at screening and at Week 10). After 10 paired biopsies have been obtained then Week 10 on-treatment biopsy will be made optional but will be encouraged.

2. HYPOTHESIS AND STUDY OBJECTIVES

2.1 Hypothesis

Primary Hypothesis: MEDI0457 treatment in combination with durvalumab will be safe in patients with recurrent / metastatic HPV associated head and neck cancer.

Secondary Hypothesis: MEDI0457 treatment in combination with durvalumab will be immunogenic in patients with recurrent / metastatic head and neck cancer associated with HPV-16 and / or HPV-18.

2.2 Primary objectives

Primary Objectives:	**Outcome Measures:**
To determine the safety profile of MEDI0457 in combination with durvalumab in patients with recurrent / metastatic head and neck cancer.	Adverse events / SAEs Collection of hematology, serum chemistry, urinalysis, CPK, thyroid function testing and pregnancy test Electrocardiograms (ECGs). The following parameters will be recorded for each ECG: date and time of ECG, heart rate (HR) (beats/min), PR interval (ms), QRS interval (ms), RR interval (ms), QT interval (ms), QTcB interval (ms), QTcF interval (ms), sinus rhythm (yes / no), and overall evaluation (normal / abnormal) Vital signs Physical examinations Concomitant medications World Health Organization (WHO) / ECOG performance status
To evaluate the anti-tumor activity of MEDI0457 in combination with durvalumab in patients with confirmed HPV-16 or HPV-18 associated recurrent / metastatic head and neck cancer	Objective response rate by Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 (Response-evaluable Population)

2.3 Secondary objectives

Secondary Objectives:	Outcome Measures:
To evaluate the pharmacokinetics and anti-drug antibodies (ADAs) for durvalumab.	Serum concentrations of durvalumab Anti-drug antibodies for durvalumab
To evaluate the anti-tumor activity of MEDI0457 in combination with durvalumab.	Objective response rate by RECIST version 1.1 (As-treated Population) and immune-related RECIST (irRECIST) Disease control rate at 16 weeks by RECIST version 1.1 Overall survival Progression free survival as assessed by RECIST version 1.1

2.4 Exploratory objectives

Exploratory Objectives:	Outcome Measures:
CCI [redacted]	CCI [redacted]
CCI [redacted]	CCI [redacted]

3. PATIENT SELECTION, ENROLLMENT, REGISTRATION, PATIENT INSTRUCTIONS, DISCONTINUATION AND WITHDRAWAL

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study. Under no circumstances can there be exceptions to this rule.

3.1 Inclusion criteria

For inclusion in the study patients should fulfill the following criteria:

1. Written informed consent in accordance with institutional guidelines. If required by

local law, candidates must also authorize the release and use of protected health information.

2. Male and female patients age 18 years or older, and be able and willing to comply with all study procedures.

3. Patient weight of > 30 kg. Patients who weigh< 30 kg can be enrolled but will need to receive durvalumab at 20 mg/kg at every 4 weeks and if their weight increases to ≥ 30 kg they can be switched to durvalumab at 1500 mg every 4 weeks. Only patients who weigh ≥ 30 kg can be included in the Safety Analysis Run-in period.

4. Histologically or cytologically confirmed diagnosis of SCCHN associated with HPV by a p16 immunohistochemistry (IHC) assay or HPV-16 or HPV-18 positive by nucleic acid testing.

5. Recurrent or metastatic disease that has been treated with at least one platinum-containing regimen and lacking a curative treatment option. Patients who are platinum ineligible may be enrolled if they have received and failed an approved treatment and lack a treatment option with curative potential.

6. Has measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10 mm by computed tomography (CT) scan, except lymph nodes which must have minimum short axis size of 15 mm (CT scan slice thickness no greater than 5 mm in both cases). Indicator lesions must not have been previously treated with surgery, radiation therapy, or radiofrequency ablation unless there is documented RECIST version 1.1 progression in the lesion after such therapy.

7. Has at least two SCCHN tumor lesions, one for biopsy and one for RECIST tracking. All patients should consent to pre-treatment biopsy of the tumor if it can be done safely (as judged by the Investigator) during screening, otherwise archival tissue within 3 years prior to study entry in all patients will be allowed except for a minimum 10 of the first 20 patients who will be required to provide a paired biopsy (a fresh biopsy at screening and at Week 10). After 10 paired biopsies have been obtained then Week 10 on-treatment biopsy will be made optional but will be encouraged. 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 5.8.1.1). Tumor lesions used for biopsy should not be lesions used as RECIST target lesions. Sites are encouraged to confirm adequacy of tumor material at the time of the procedure.

8. World Health Organization / ECOG performance status of 0 or 1.

9. Adequate organ and bone marrow function within 28 days of starting study treatment. Criteria "a" to "c" cannot be met in patients with ongoing or recent (within 14 days of screening test) transfusions or require ongoing growth factor support:

    a) Hemoglobin ≥ 8 g/dL **NOTE:** Subjects requiring ongoing transfusions or growth factor support to maintain hemoglobin ≥ 8 g/dL are not eligible.

    b) Absolute neutrophil count ≥ 1,000/mm^3.

    c) Platelet count ≥ 100,000/mm^3.

    d) Total bilirubin (TBL) ≤ 1.5 × upper limit of normal (ULN) except patients with documented Gilbert's syndrome (> 3 × ULN).

    e) Alanine aminotransferase and AST ≤ 3 × ULN.

    f) Serum creatinine ≤ 2.0 mg/dL or creatinine clearance ≥ 40 mL/min (measured or calculated according to the method of Cockcroft and Gault).

10. Adequate venous access for repeated blood sampling according to study schedule.

11. Evidence of post-menopausal status or negative serum pregnancy test for females of childbearing potential who are sexually active with a non-sterilized male partner. For women of childbearing potential, a negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit (Table 2) and a urine beta-human chorionic gonadotropin (β-HCG) pregnancy test during the treatment period (Table 3). Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply: women older than 50 years of age (i.e., ≥ 50 years) would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels in the post-menopausal range for the institution. Women younger than 50 years of age (i.e., ≤ 50 years) would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced oophorectomy with last menses > 1 year ago, had chemotherapy-induced menopause with > 1 year interval since last menses, or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

12. Female patients of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Table 1) from the time of screening and must agree to continue using such precautions for 90 days after the last dose of IP. Not all methods of

contraception are highly effective. Female patients must refrain from egg cell donation and breastfeeding while on study and for 90 days after the last dose of IP.

13. Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use a condom with spermicide from screening to 90 days after the final dose of IP. Not engaging in sexual activity for the duration of the study and drug washout period is an acceptable practice; however, periodic or occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. It is strongly recommended for the female partners of a male patient to also use at least one highly effective method of contraception throughout this period, as described in Table 1. In addition, male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of IP.

3.2 Exclusion criteria

Patients should not enter the study if any of the following exclusion criteria are fulfilled:

1. Patients with nasopharyngeal cancer as the primary site will not be included in the study.

2. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment; receipt of any investigational or approved anticancer therapy (chemotherapy, targeted therapy, biologic therapy, monoclonal antibodies, etc) within 21 days or 5 half-lives, whichever is shorter prior to the first dose of IP. In addition, local treatment (e.g. by local surgery or radiotherapy) of isolated lesions for palliative intent is acceptable beyond the DLT evaluation period with prior consultation and in agreement with the Medical Monitor.

3. Major surgical procedure or significant traumatic injury within 28 days before the first dose of study drug or anticipation of the need for major surgery during the course of study treatment.

4. Any unresolved toxicity National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE version 4.03) Grade 2 or greater from previous anticancer therapy with the exception of alopecia, and the laboratory values defined in the inclusion criterion 9. Hearing loss of Grade 3 or lower and peripheral neuropathy of Grade 2 or lower is allowed.

5. Current or prior use of immunosuppressive medication within 14 days prior to first study dose, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids at doses not to exceed 10 mg/day of prednisone or equivalent. Steroids as premedication for hypersensitivity reactions due to radiographic contrast agents are allowed.

6. Patients requiring therapeutic anticoagulation and irreversible platelet inhibitors (e.g., clopidogrel, prasugrel, ticagrelor etc) are excluded. NOTE: Low dose aspirin for cardiac prophylaxis will be permitted.

7. No prior exposure to immune-mediated therapy defined as prior exposure to T-cell and natural killer cell directed therapy (e.g., anti-PD-1, anti-PD-L1, anti-CD137, and anti-CTLA4, etc).

8. History of allogeneic organ transplantation. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, sarcoidosis, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc]). The following are exceptions to this criterion:

   – Patients with vitiligo or alopecia.

   – Patients with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement.

   – Any chronic skin condition that does not require systemic therapy.

   – Patients without active disease in the last 5 years may be included but only after consultation with the Study Physician.

   – Patients with celiac disease controlled by diet alone.

9. Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, uncontrolled hypertension, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness / social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs or compromise the ability of the patient to give written informed consent.

10. Patients with spinal cord compression, or a history of leptomeningeal carcinomatosis. At the time of Day 1 of the study, patients with central nervous system metastases must have been treated and must be asymptomatic and meet the following:

(a) No concurrent treatment, inclusive of but not limited to surgery, radiation, and / or corticosteroids. **Note:** patients are allowed on systemic steroids at doses not to exceed the equivalent of 10 mg/day prednisone but not if these are being administered to manage central nervous system metastases.

(b) Neurologic stability (lack of signs or symptoms greater than baseline prior to radiotherapy) until the time of dosing of MEDI0457.

(c) For radiation treatment:

- At least 14 days between last day of stereotactic radiosurgery or gamma-knife treatment and Day 1 of protocol treatment.
- At least 28 days between last day of whole brain radiation therapy and Day 1 of protocol treatment.
- At least 14 days since last dose of corticosteroids and Day 1 of protocol treatment.

11. Patients with cardiovascular (CV) disease conditions including New York Heart Association Class 3 or 4 congestive heart failure, unstable angina pectoris or clinically important cardiac arrhythmias, a recent (< 3 months) CV event including myocardial infarction, unstable angina pectoris, stroke.

12. Mean QT interval corrected for heart rate (QTc) > or = 470 ms calculated from the triplicate ECGs using Frederichia's Correction by manual read.

13. History of active primary immunodeficiency.

14. Active tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice) or Mycobacterium avium intracellulare infection.

15. Presence of acute or chronic hepatitis B or active hepatitis C or immunodeficiency virus (HIV) infection. Patients with a past or resolved hepatitis B virus infection (defined as the presence of hepatitis B core antibody [HBcAb] and absence of hepatitis B surface antigen [HBsAg]) are eligible provided the hepatitis virus DNA test is negative. Patients positive for hepatitis C antibody are eligible only if polymerase chain reaction (PCR) is negative for hepatitis C virus RNA. Testing for HIV is only required if clinically indicated and is not mandatory for this study.

16. History of another primary malignancy except for:

- Malignancy treated with curative intent and with no known active disease ≥ 2 years before the first dose of IP and of low potential risk for recurrence.
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease.
- Adequately treated carcinoma in situ without evidence of disease.

17. Receipt of live, attenuated vaccine within 30 days prior to the first dose of MEDI0457. Note: Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of IP.

18. Pregnant or breastfeeding female patients.

19. Known allergy or hypersensitivity to study treatment or any of the study drug excipients.

20. Any medical condition that, in the opinion of the Investigator, would interfere with evaluation of the study treatment or interpretation of patient safety or study results.

21. Fewer than two acceptable sites exist for IM injection and EP between the deltoid and lateral quadriceps muscles. Note: A site for injection / EP is not acceptable if there are tattoos or scars within 2 cm of the proposed injection / EP site or if there is implanted metal within the same limb. Any device implanted in the chest (e.g., cardiac pacemaker or defibrillator excludes the use of the deltoid muscle on the same side of the body).

22. Patients who are unable to provide informed consent, are incarcerated or unable to follow protocol requirements.

Procedures for withdrawal of incorrectly enrolled patients see Section 3.4.

3.3 Patient enrollment and registration

Investigator(s) should keep a record, the patient screening log, of patients who entered pre-study screening.

The investigator(s) will:

1. Obtain signed informed consent from the potential patient before any study specific procedures are performed.

2. Assign potential patient a unique enrollment number, beginning with ‘E#’.

3. Determine patient eligibility. See Section 3.

If a patient withdraws from participation in the study, then his / her enrollment code cannot be reused.

Study personnel will screen patients and assign unique patient identification number. Information regarding patient’s screening number and screen date must be documented on a screening log.

3.4 Procedures for handling incorrectly enrolled patients

Patients who fail to meet the eligibility criteria should not under any circumstances be enrolled or receive study medication. There can be no exceptions to this rule.

Where a patient does not meet all the eligibility criteria but is incorrectly started on-treatment, the Investigator should inform the MedImmune Study Physician immediately, and a

discussion should occur between the MedImmune Study Physician and the Investigator regarding whether to continue or discontinue the patient from treatment. The MedImmune Study Physician must ensure all decisions are appropriately documented.

3.5 Methods for assigning treatment groups

Not applicable for this study. All patients will receive combination treatment with MEDI0457 and durvalumab.

3.6 Methods for ensuring blinding

Not applicable for this study. The study is an open-label study.

3.7 Methods for unblinding

Not applicable for this study. The study is an open-label study.

3.8 Patient instructions

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

Patients will be offered medications to manage anxiety and pain due to the EP procedure by the Investigator (see Section 5.4.9.1).

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

1. Any concurrent chemotherapy, IP, biologic, radiotherapy (except palliative radiotherapy after consultation with the Medical Monitor) or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. Concurrent use of adjuvant hormonal therapy for a history of breast and prostate cancer is allowed if the cancer for which the subject is being enrolled on this study has been histologically proven NOT to be breast or prostate cancer (Refer to Exclusion Criterion 16).

2. MEDI0457 or durvalumab cannot be administered when the subject is taking immunosuppressive medications, including corticosteroids with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids at doses not to exceed 10 mg/day of prednisone or equivalent. Treatment with corticosteroids to prevent or treat hypersensitivity reactions to radiographic contrast agents is allowed. A temporary period of steroids will be allowed for different indications after discussion with the Medical Monitor (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc). Use of immunosuppressive medications for the management of IP-related AEs or in patients with contrast allergies is acceptable. Immunosuppressive medications also include drugs like methotrexate, azathioprine and tumor necrosis factor-alpha blockers.

3. Use of anticoagulants and irreversible platelet inhibitors (e.g. clopidogrel, prasugrel, ticagrelor etc) are not allowed. Low dose aspirin for cardiac prophylaxis is allowed.

4. Females of childbearing potential (defined as those who are not surgically sterile [i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy] or post-menopausal) who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Table 1) from the time of screening and must agree to continue using such precautions from 90 days after the last dose of IP; cessation of birth control after this point should be discussed with a responsible physician.

   Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

   – Women < 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have LH and FSH levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).

   – Women ≥ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses > 1 year ago, had chemotherapy-induced menopause with last menses > 1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

   A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Highly effective methods of contraception presented in Table 1 include copper T intrauterine device, levonorgestrel-releasing intrauterine system (e.g., Mirena®), implants, hormone shot or injection, combined pill and patch.

Table 1 Effective Methods of Contraception

Barrier Methods	Intrauterine Methods	Hormonal Methods
Male condom plus spermicide[a,b,c]	e.g., Copper T intrauterine device[e]	e.g., Implants[e]
Cap plus spermicide[a,b,c]	Progesterone T intrauterine device[d]	Hormone shot or injection[e]
Diaphragm plus spermicide[a,b,c]	Levonorgesterel-releasing intrauterine system (e.g., Mirena®[d,e]	Combined pill[e]
		Minipill[b]
		Patch[e]

[a] Female partners of male patients should use an effective method of birth control
[b] Not highly effective (failure rate of = 1% per year)
[c] A male condom plus cap, diaphragm, or sponge with spermicide (double barrier methods) are also considered acceptable, but not highly effective, birth control methods
[d] Also considered a hormonal method
[e] Highly effective (failure rate of < 1% per year)

3.9 Discontinuation of investigational product

An individual patient will not receive any further IP if any of the following occur:

1. Initiation of subsequent anticancer therapy including another investigational agent

2. Confirmed PD: the initial assessment of PD by RECIST version 1.1 (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 tumor assessment time point (beyond the first PD assessment) 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 patient would be deemed as having confirmed PD and must be discontinued. Patients will need to sign an additional informed consent form (ICF) to continue treatment beyond the initial (unconfirmed) PD assessment.

3. An AE that, in the opinion of the Investigator or the Sponsor, contraindicates further dosing.

4. Patient experienced a DLT as defined in Section 6.12.2.1.

5. Withdrawal of consent from further treatment with investigational product or lost to follow-up.

6. Patient is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation and continuing to receive investigational product might constitute a safety risk.

7. Pregnancy or intent to become pregnant.

8. Non-compliance with the study protocol that, in the opinion of the Investigator or Sponsor, warrants withdrawal from treatment with IP (e.g., refusal to adhere to scheduled visits).

9. The treating Physician determines it is not in the best interest of the patient to continue on-treatment.

3.9.1 Procedures for discontinuation of a patient from investigational product

At any time, patients are free to discontinue IP or withdraw from the study (i.e., IP and assessments – see Section 3.10), without prejudice to further treatment. A patient that decides to discontinue investigational therapy 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(s). Adverse events will be followed up (see Section 6) and all study drugs should be returned.

If a patient is withdrawn from study, see Section 3.10.

3.10 Criteria for withdrawal

A patient will be considered to have completed the study when he / she completes all protocol specified scheduled study assessments. The Follow-up visit will be the last study visit.

If a patient discontinues or is withdrawn at any time after initiation of study treatment, the Investigator should make every effort to have the patient complete all assessments designated for the Follow-up visit. The Investigator will make every effort to have all scheduled assessment blood samples collected as indicated in Table 3. Any AEs present at the time of discontinuation / withdrawal should be followed in accordance with the safety requirements outlined in Section 6.

All patients will be followed for survival and subsequent anticancer therapy until the end of the study. Patients refusing to return to the site should be contacted by phone to assess for survival and subsequent anticancer therapy unless consent is withdrawn every 3 months for the first year and every 6 months thereafter until the end of study. Patients who leave the study because of a serious or significant safety issues should be followed closely until the AEs are fully and permanently resolved or stabilized (if complete resolution is not anticipated), with the follow-up data recorded in the Case Report Form (CRF) (see Section 6.7.3 for further details regarding the follow-up of unresolved AEs). Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, with follow-up data recording in the CRF.6.7.3).

If a patient discontinues from treatment for reasons other than disease progression, and therefore continues to have tumor assessments, drug or procedure-related SAEs must be captured until the patient is considered to have confirmed PD and will have no further tumor assessments.

Investigator should discuss the reason for any discontinuation of study treatment with the Sponsor's Medical Monitor prior to any action or within 24 hours when information becomes available.

The primary reason for the patient discontinuing study treatments or withdrawal from the study should be among the following standard categories:

- Death.
- Withdrawal of Consent: The patient desired to withdraw from further participation in the study in the absence of an Investigator-determined medical need to withdraw. If the patient gave a reason for withdrawal, it should be recorded on CRF. This reason does not allow for further data collection and should not be selected if follow-up data collection of this patient is anticipated by the patient.
- Protocol Deviation: The patient's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., treatment non-compliance, failure to return for defined number of visits). The violation should be discussed with the Sponsor's Medical Monitor prior to discontinuation of study treatments or study withdrawal.
- Lost to Follow-up: The patient fails to attend study visits and study personnel are unable to contact the patient after repeated attempts including letter sent by certified mail or equivalent.
- Physician Decision: The patient was terminated for a reason other than those listed above by the physician caring for the patient.
- Other: The patient was terminated for a reason other than those listed above, such as termination of study by the Sponsor.

3.10.1 Screen failures

Screening failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be enrolled into the study. The reason for the screen failure will be recorded.

3.10.2 Withdrawal of the informed consent

Patients are free to withdraw from the study at any time (IP and assessments), without prejudice to further treatment.

A patient who withdraws consent should always be asked about the reason(s) and the presence of any AE. The Investigator should follow-up AEs outside of the clinical study.

If a patient withdraws from participation in the study, then his / her enrollment code cannot be reused.

3.11 Safety analysis run-in patients

Approximately three to 12 patients will be enrolled and assessed for safety before additional patients are enrolled at a recommended dose and schedule for the combination. Because this study is the first time MEDI0457 has been combined with durvalumab, the study will start with enrollment of a minimum of three patients who will receive four doses of MEDI0457 (**Limited Schedule**) in combination with durvalumab. Only if the safety analysis of the initial patients, who complete the 7-week DLT evaluation period, is deemed acceptable (i.e., none of the initial patients experience a DLT), the vaccination schedule will switch from the limited four doses (**Limited Schedule**) to the **Indefinite Schedule** (also known as the **Planned Dosing Schedule**, i.e. vaccinations will continue until disease progression). This **Indefinite Schedule** will be implemented for all subsequent patients following the Safety Analysis Run-in. Otherwise, if a third of the initial patients experience a DLT, a minimum of three additional patients (i.e., a minimum total of six patients for the Safety Analysis Run-in) will be enrolled and the initial minimum six patients in the Safety Analysis Run-in cohort will be limited to a total of four doses of MEDI0457 (**Limited Schedule**) before considering a switch to the **Indefinite Schedule**, provided the safety data was supportive and if only no more than a third of these patients experienced a DLT during their 7-week DLT evaluation period. If at any time during the enrollment of these patients, more than a third of the patients experience a DLT, then this regimen has exceeded the MTD and the regimen will be modified. The choice of modifications in the **Revised Dosing Schedule** during the Safety Analysis Run-in include the following: (1) decrease the dose of durvalumab to 750 mg Q4W or decrease the total number of durvalumab doses (2) increase the interval between MEDI0457 doses from every 8 weeks to intervals such as 12 or 16 weeks following the Week 12 dose or decrease the total number of MEDI0547 doses administered from a total of three to either one or two during the DLT period. CCI [redacted] If the choice includes decreasing the number of vaccines doses administered during the DLT CCI [redacted]. At least a minimum of three patients with no DLT and up to approximately six patients with no more than a third with a DLT must be evaluated using either the **Planned Dosing Schedule** or **Revised Dosing Schedule** before study enrollment will continue with a recommended dose and schedule for the combination.

In order to adequately monitor the safety of patients in Study D8860C00005, there will be two levels of ongoing monitoring of safety data for this study.

- CCI [redacted]

CCI [redacted]

- CCI [redacted]

An analysis of the following data will be performed:

- Adverse events
- Safety laboratory tests (ECG data, hematology, chemistry and urinalysis)
- Vital signs
- Physical examinations

CCI [redacted]

CCI [redacted]

CCI [redacted]

- CCI [redacted]
- CCI [redacted]
- CCI [redacted]

Regardless of the reason for termination, all data available for the patient at the time of discontinuation of follow-up must be recorded in the CRF. All reasons for discontinuation of treatment must be documented.

In terminating the study, the Sponsor will ensure that adequate consideration is given to the protection of the patients' interests.

4. STUDY PLAN AND TIMING OF PROCEDURES

Table 2 Study Plan - Screen Procedures

Tests	Screen (Days -28 to -1)
Informed consent	X
Demographics	X
Medical history	X
History of prior cancer treatment	X
Inclusion / exclusion criteria	X
Complete physical examination	X
WHO / ECOG performance status	X
Adverse event assessment	X
Concomitant medications	X
History of procedures	X
Disease status[a]	X
Vital signs[b]	X
12-lead ECG[c]	X
Laboratory assessments[d]	
p16 IHC[e]	X
Hematology	X
Serum chemistry	X
Urinalysis	X
Creatine phosphokinase	X
Thyroid function testing (T_3, T_4, and TSH)[f]	X
Coagulation (APTT and either INR or prothrombin time)	X
Pregnancy test[g]	X
Hepatitis B, hepatitis C and HIV serology[h]	X
Luteinizing hormone and follicle-stimulating hormone[i]	X
Other laboratory assessments and assays[j]	
HPV-16/HPV-18 E6/E7 antibody	X
Tumor cell and tumor cell HPV DNA or RNA	X
HPV-16/HPV-18 E6/E7 ELISPOT and flow cytometry-based assay	X
Tumor biopsy[k]	X

[a] Magnetic resonance imaging scan of the brain will be performed at screening and also at each assessment if there are abnormalities at baseline.

[b] Vital signs at the screening visit include temperature, respiratory rate, pulse oximetry, blood pressure, HR, weight and height.

[c] 12-lead ECGs will be performed in triplicate (all three ECG assessments within a 5 minute time period)

[d] Samples will be analyzed at local laboratories.

[e] Historical tissue samples may be used; there is no need for additional samples / test for histological HPV assessment (p16) to be collected just for this protocol.

[f] Free triiodothyronine (T_3) and free thyroxine (T_4) will only be measured if thyroid stimulating hormone (TSH) is abnormal. They should also be measured if there is clinical suspicion of an AE related to the endocrine system.

[g] Serum pregnancy test will be performed for women of childbearing potential.

[h] Hepatitis B and C testing is mandatory, while HIV serology is only required if clinically indicated.

[i] Only for women of child bearing potential who may be post-menopausal.

[j] Samples will be analyzed at central laboratories.

[k] At least three core samples are required if samples are collected are via a core needle of 18 gauge or larger or are collected as an excisional tumor biopsy sample. When a smaller gauge needle is used, the number of required cores rises to four. Note: a new baseline biopsy is required for all patients. All patients should consent to pre-treatment biopsy of tumor if it can be done safely (as judged by the Investigator) during screening, otherwise archival tissue up to 3 years to study entry in all patients will be allowed except for a minimum 10 of the first 20 patients who will be required to provide a paired biopsy (a fresh biopsy at screening and at Week 10).

Abbreviations are on the next page.

Abbreviations:
AE=adverse event; APTT=activated partial thromboplastin time; CPK=creatine phosphokinase; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ELISPOT=enzyme-linked immunospot; HIV=human immunodeficiency virus; HPV=human papilloma virus; IHC=immunohistochemistry; INR=International Normalized Ratio; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid stimulating hormone; WHO=World Health Organization

Table 3 Study Plan - Study Administration Procedures

Tests		Administration Visits							
		Week[o]							
Week	1	3	4	7	8	10	12	Every 4 Weeks	Every 8 Weeks
Day	1	1	1	1	1	1	1	1	1
Study Procedures									
Inclusion / exclusion criteria	X								
Physical examination[a]	X[n]	X	X	X	X	X	X	X	X
WHO / ECOG performance status	X[n]				X				X
Adverse events assessment	X	X	X	X	X	X	X	X	X
Concomitant medications / concomitant procedures [p]	X	X	X	X	X	X	X	X	X
Disease status[b,l]					X				X
Vital signs, pre-dose and post-dose[c,d]	X[n]	X	X	X	X	X	X	X	X
12-lead ECG[e]	X	X	X	X			X		X
Laboratory Procedures[m]									
Hematology	X[n]			X	X		X	X[k]	X[k]
Serum chemistry	X[n]			X	X		X	X[k]	X[k]
Creatine phosphokinase	X[n]			X	X		X		X
Thyroid function testing (T_3, T_4, and TSH)[f]	X[n]		X		X		X	X[k]	X[k]
Pregnancy test	X[n]		X		X		X	X	X
CCI [redacted]									
Study Treatment Procedures									
CCI [redacted]									
Durvalumab administration[h,l]			X		X		X	X	
Download EP data	X	X		X			X		X

Table 3 Study Plan - Study Administration Procedures

Tests		Administration Visits							
		Week[o]							
Week	1	3	4	7	8	10	12	Every 4 Weeks	Every 8 Weeks
Day	1	1	1	1	1	1	1	1	1
Tumor biopsy[j]						X			

[a] Targeted physical examination will be performed at all visits except at the Follow-up visit for which a complete physical examination will be performed.

[b] Patients discontinued from treatment for reasons other than PD will continue disease assessments until confirmed PD or start of subsequent anticancer therapy. Magnetic resonance imaging scan of the brain will be performed at screening and also at each assessment if there are abnormalities at baseline. The preferred method of disease assessment is CT with contrast except for brain metastasis where a magnetic resonance imaging (MRI) with contrast is preferred. The same method is preferred for all subsequent tumor assessments for the same patient.

[c] Temperature, respiratory rate, pulse oximetry, blood pressure, HR and weight.

[d] Vital signs will be measured within 30 minutes prior to the start of durvalumab administration, every 30 minutes (± 5 minutes) during durvalumab administration, at the end of durvalumab infusion (± 5 minutes), followed by a 1 hour (± 15 minutes) collection, and period of observation except for Week 10. A 1 hour observation period is required after the first infusion of durvalumab is administered.

[e] Electrocardiograms are to be collected in triplicate (all three ECG assessments within a 5 minute time period) within 30 minutes before dosing of MEDI0457 and 30-60 minutes after dosing at Weeks 1, 3, 7 and 12 and thereafter single ECGs at pre-dose at subsequent dosing visits. Triplicate (all three ECG assessments within a 5 minute time period) ECGs will be performed within 30 minutes before dosing of MEDI4736 at Week 4 and 30-60 minutes after dosing of MEDI4736 at Weeks 4 and 12. An ECG assessment can also be performed if clinically indicated and according to the Investigator.

[f] Free T_3 and free T_4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an AE related to the endocrine system.

CCI

[j] Core tumor biopsies will be collected. At least three core samples are required if samples are collected are via a core needle of 18 gauge or larger or are collected as an excisional tumor biopsy sample. When a smaller gauge needle is used, the number of required cores rises to four. Either fresh tissue or formalin-fixed paraffin-embedded samples may be used. Archival tissue within 3 years prior to study entry in all patients will be allowed except for a minimum 10 of the first 20 patients who will be required to provide a paired biopsy (a fresh biopsy at screening and at Week 10). After 10 paired biopsies have been obtained then Week 10 on-treatment biopsy will be made optional but will be encouraged.

[k] Serum chemistry and hematology will be performed on Day 1, Week 7, Week 8 and Week 12, then every 4 weeks for the first 12 months and every 3 months thereafter until study discharge. Thyroid function testing will be performed on Day 1, Week 4, Week 8 and Week 12, then every 4 weeks for the first 12 months and every 3 months thereafter until study discharge. Urinalysis will only be performed if clinically indicated.

[l] After scan and durvalumab administration are completed in Week 8. Disease status assessments should continue to be performed at every 8 weeks ± 5 days for 1 year if CR / PR / SD are achieved and then every 12 weeks ± 7 days until end of treatment (EOT).

[m] Additional baseline blood samples will be also collected in a 10 mL red top tube in order to have serum samples collected at baseline for future analysis which includes but is not limited to an autoimmune work-up (refer to the Laboratory Manual for the processing of this sample).

[n] If physical examination, ECOG, weight or safety laboratory tests (hematology, chemistry, creatine phosphokinase, thyroid function testing and pregnancy tests) are performed within 3 days prior to Day 1, they do not need to be repeated. Patients with a negative serum pregnancy test within 3 days prior to Day 1, do not require a Week 1 Day 1 pregnancy test to be performed.

[o] All visit windows will be ±3 days with the following exceptions: tumor biopsy assessments will have the visit window of ±7 days; disease status assessments every 8 weeks (± 5 days) (relative to the date of the first MEDI0457 administration) for 1 year. After the first year on treatment, if CR / PR / SD are achieved then disease status assessments can be performed every 12 weeks (± 7 days) until the EOT. Disease status assessments will be performed once at the end of treatment if PD is observed, otherwise at end of treatment and then at Day 90 ± 7 days, every 3 months after Day 90 up to Month 12 ± 7 days then every 6 months after Month 12 ± 14 days until the death of the patient, withdrawal of consent or loss to follow-up.

[p] Administration of the COVID-19 vaccine and MEDI0457 should be separated by 14 days.

Abbreviations are on the next page.

Abbreviations:
CCI AZ=AstraZeneca; COVID-19 = coronavirus disease of 2019; CR=complete response; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; CCI EP=electroporation; EOT=end of treatment; =human immunodeficiency virus; CCI IHC=immunohistochemistry; MRI=magnetic resonance imaging; PD=progressive disease; PR=partial response; SD=stable disease; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid stimulating hormone; WHO=World Health Organization

Table 4 Study Plan - Follow-up Visit Procedures

Tests	Follow-up visit 28 days after last dose (±7 days)
Complete physical examination	X
WHO / ECOG performance status	X
Adverse event assessment	X
Concomitant medications	X
Vital signs	X
12-lead ECG[a]	X
Disease assessment[b,f]	X
Laboratory assessments[c]	
Hematology	X
Serum chemistry	X
Creatine phosphokinase	X
Thyroid function test (free T_3, free T_4 and TSH)[d]	X
Other laboratory assessments and assays[e]	
HPV-16/HPV-18 E6/E7 antibody	Collected if the Follow Up Visit occurs, but not collected if AZ decides to stop collection
HPV-16/HPV-18 E6/E7 ELISPOT and flow cytometry-based assay	Collected if the Follow Up Visit occurs, but not collected if AZ decides to stop collection
Tumor cell and tumor cell HPV DNA or RNA	Collected if the Follow Up Visit occurs, but not collected if AZ decides to stop collection
Collection of survival data and subsequent anticancer therapy	X

[a] Electrocardiograms will be performed in triplicate (all three ECG assessments within a 5 minute time period).
[b] Disease assessment to be performed once at EOT if PD, otherwise at EOT and then at Day 90 ± 3 days, every 3 months after Day 90 up to Month 12 ± 7 days then every 6 months after Month 12 ± 14 days until the end of study (EOS).
[c] Samples will be analyzed at local laboratories.
[d] Free T_3 and free T_4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an AE related to the endocrine system.
[e] Samples will be analyzed at central laboratories.
[f] All patients will be followed for survival and subsequent anticancer therapy until the end of the study. Patients refusing to return to the site should be contacted by phone to assess for survival and subsequent anticancer therapy unless consent is withdrawn every 3 months for the first year and every 6 months thereafter until the EOS.

Abbreviations:
AE=adverse event; AZ=AstraZeneca; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; ELISPOT=enzyme-linked immunospot; EOS=end of study; EOT=end of treatment; HPV=human papilloma virus; PD=progressive disease; T_3=triiodothyronine; T_4=thyroxine; TSH=thyroid stimulating hormone, WHO=World Health Organization

4.1 Enrollment / screening period

Procedures will be performed according to Table 2.

At screening, consenting patients are assessed to ensure that they meet eligibility criteria. Patients who do not meet these criteria must not be enrolled in the study.

All patients will be required to provide consent to supply a sample of their blood and urine as well as a fresh tumor biopsy sample (at least three or four core samples, refer to Section 5.8.1.1 for further details) for entry into this study. This consent is included in the main patient ICF.

4.2 Treatment period

Descriptions of the procedures for this period are included in Table 3.

4.3 Follow-up period

Descriptions of the procedures for this period are included in Table 4.

4.4 Continued Treatment Period

The data cut-off for the primary endpoint will be in Q1 2021. Data analysis will be performed, and a Clinical Study Report will be written based on this data cut-off.

Any patients still receiving IP at the time of this data cut-off will be able to continue to receive MEDI0457 or durvalumab or both within the current study through a Continued Treatment Period. Patients are eligible for the Continued Treatment Period if the Investigator determines the patient is deriving clinical benefit from treatment and the patient has not fulfilled discontinuation criteria. Investigators also have the option to remove patients from the Continued Treatment Period after 2 years of treatment with MEDI0457 and durvalumab. Patients are often removed from immunotherapy treatment after 2 years because the necessity for further treatment is not clear, and disease control with immunotherapy can last for a year or more after the end of treatment. If Investigators decide to keep patients on treatment, these patients may continue until 30 April 2023, when the MEDI0457 drug supply expires and the study will end.

During the Continued Treatment Period, assessments will revert to the standard of care for each individual site. Data will not be entered into the clinical study database after the data cut-off date. Patients will continue to be monitored for all SAEs, overdoses, and pregnancies up to 28 days after the last dose of IP. Paper-based reporting will be used for any SAE, overdose, or pregnancy identified after the data cut-off. All reported events will be entered in to the AstraZeneca global safety database.

The Interactive Voice and Web Response System will be closed following the data cut-off, and sites will manually order IP. The IP dispensation and reconciliation will be handled by the study site at each patient's visit. Drug accountability information must still be collected until all patients have completed treatment.

After the data cut-off for the Clinical Study Report, individual study sites will be closed once their final patient completes the 28-day follow-up visit. The Continued Treatment Period will remain available to patients until the last patient discontinues treatment and has his or her

28-day safety follow-up visit. The Last Subject Last Visit in the Continued Treatment Period is defined as the date of the last patient's final visit.

5. STUDY ASSESSMENTS

The RAVE Web Based Data Capture (WBDC) system will be used for data collection and query handling. The Investigator will ensure that data are recorded on the electronic CRFs 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 electronic CRFs. A copy of the completed electronic CRFs will be archived at the study site.

5.1 Demographics

The demographics (date of birth, sex and race) details for each patient will be collected at the screening visit.

5.2 Medical history

The Investigator should document all relevant and clinically significant medical conditions and illnesses that the patient has experienced at time of screening as medical history. Medical history should include treatment detailed information on all therapy directed against recurrent / metastatic HPV associated SCCHN e.g., past surgical and / or radiation regimens. Any prior chemotherapy or immunotherapies, adjuvants, etc should be recorded on the CRFs.

Illnesses first occurring or detected after the signing of ICF or during the study and / or worsening of an existing illness in severity, frequency or nature after the signing of ICF are to be documented as AEs on the CRF.

5.3 Efficacy assessments

RECIST version 1.1 will be used to assess patient response to treatment by determining ORR, DCR-16w and PFS. Objective response rate will also be assessed using irRECIST. The RECIST version 1.1 guidelines for measurable, non-measurable, target and non-target lesions are presented in Appendix F. Overall survival will also be evaluated.

The methods of assessment of tumor burden used at baseline are CT and / or or magnetic resonance imaging (MRI) scans, preferably with IV contrast imaging, of the neck (including the base of skull) through chest and abdomen. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients. At the

discretion of the Sponsor, an independent central review of all scans used in the assessment of tumors by RECIST version 1.1 and/or irRECIST may be conducted. Guidelines for imaging collection and storage will be provided in a separate document. The management of the patients will be based solely upon the results of assessment conducted by the investigator based on RECIST version 1.1 per protocol.

The baseline assessment should be performed no more than 28 days before the start of MEDI0457 treatment and ideally as close as possible and not later than the start of the IP. Efficacy for all patients will be assessed by disease status assessments every 8 weeks (± 5 days) (relative to the date of the first MEDI0457 administration; Table 3) for 1 year. After the first year on treatment, if CR / partial response (PR) / SD are achieved then disease status assessments can be performed every 12 weeks (± 7 days) until the end of treatment. Disease status assessments will be performed once at the end of treatment if PD is observed, otherwise at end of treatment and then at Day 90 ± 7 days, every 3 months after Day 90 up to Month 12 ± 7 days then every 6 months after Month 12 ± 14 days until the death of the patient, withdrawal of consent or loss to follow-up. Disease assessment will also stop if patient is started on subsequent anticancer therapy. If an unscheduled assessment is performed, and the patient has not progressed, every attempt should be made to perform the subsequent assessments at their scheduled visits (± 14 days).

For patients who discontinue therapy due to toxicity in the absence of confirmed objective progression, disease status assessments should be continued until confirmed PD or start of subsequent anticancer therapy.

Patients who discontinued from treatment for reasons other than PD will continue disease assessments until confirmed PD or start of subsequent anticancer therapy.

Progression would be considered confirmed if the following criterion is met:

- Confirmed PD: the initial assessment of PD by RECIST version 1.1 (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 tumor assessment time point (beyond the first PD assessment) 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 patient would be deemed as having confirmed PD and must be discontinued from treatment. Patients will need to sign an additional ICF to continue treatment beyond the initial (unconfirmed) PD assessment.

In the absence of clinically significant deterioration, the Investigator should continue study treatment until progression is confirmed.

If progression is not confirmed, the patient should continue on study treatment and on-treatment assessments.

If a patient discontinues treatment prior to progression, the patient should still continue to be followed until confirmed objective disease progression or until subsequent anticancer treatment.

If the Investigator is in doubt as to whether progression has occurred, particularly with response to non-target lesion or the appearance of a new lesion, it is advisable to continue treatment until the next scheduled assessment or sooner if clinically indicated and reassess the patient's status. If repeat scans confirm progression, then the date of the initial scan should be declared as the date of progression.

Tumor assessments should include the following evaluations: physical examination (with photograph and measurement of skin lesions as applicable) and CT or MRI scan of the neck, chest, abdomen, and pelvis (pelvic scan is optional unless known pelvic disease is present at baseline). Magnetic resonance imaging scan of the brain will be performed at screening and also at each assessment if the patient is found to have abnormalities at baseline scan. The preferred method of disease assessment is CT with contrast except for brain metastasis where an MRI with contrast is preferred. If CT with contrast is contraindicated, CT without contrast is preferred over MRI. A CT with contrast may be substituted for an MRI with contrast if an MRI is contraindicated. The same method is preferred for all subsequent tumor assessments for the same patient. Note: if a patient receives a combined positron emission tomography (PET) / diagnostic quality CT scan at screening, a CT scan without PET later in the study is acceptable.

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following (Wolchok et al 2009, Nishino et al 2013):

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

Progression free survival measures progression by growth of the primary tumor, nodal spread metastases, death from the cancer, or death from other causes. Progression free survival will be assessed by the periodic tumor assessment using imaging per the institutional guidelines at the schedules according to Table 3.

All study evaluations for disease response must be based on RECIST version 1.1.

Immune-related RECIST (Appendix G)

Based on the above-described unique response to immunotherapy and based on guidelines from regulatory agencies, e.g., European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4) for immune modulating anticancer compounds, the study will implement the following in addition to standard RECIST version 1.1:

- RECIST will be modified so that PD must be confirmed at the next scheduled visit, preferably, and no earlier than 4 weeks after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with MEDI0457 and durvalumab would continue between the initial assessment of progression and confirmation for progression.

5.4 Safety assessments

5.4.1 Laboratory safety assessments

At screening, blood samples will be collected for hematology and serum chemistry. Blood samples will also be taken for LH and FSH (for select patients), CPK, thyroid function testing (if thyroid stimulating hormone [TSH] is abnormal then free triiodothyronine [T_3] and free thyroxine [T_4] will be required to be measured, if TSH is normal then free T_3 and free T_4 are not required to measured), coagulation tests (activated partial thromboplastin time [APTT] and either International Normalized Ratio [INR] or prothrombin time), hepatitis B and hepatitis C testing. Testing for HIV is only required if clinically indicated and is not mandatory for this study. A urine sample will also be obtained to determine eligibility (see Table 2).

A serum pregnancy test will be performed for women of childbearing potential at the screening visit. A urine pregnancy test will be performed during the treatment period.

A local laboratory will be used for the collection of blood and urine samples (see Laboratory Manual for further details).

Blood and urine samples will be collected during the IP administration period for determination of hematology, serum chemistry, CPK, thyroid function testing (TSH, free T_3 and free T_4), coagulation tests (prothrombin time, APTT and INR). A urine pregnancy test will be taken at the times indicated in Table 3. Urinalysis will be taken if clinically indicated as deemed by the Investigator (Table 3).

Additional baseline blood samples will be also collected in a 10 mL red top tube in order to have serum samples collected at baseline for future analysis which includes but is not limited to an autoimmune work-up (Table 3) (refer to the Laboratory Manual for the processing of this sample).

Blood samples will also be taken at the Follow-up visit (28 days after the last dose [± 7 days]) for determination of hematology, serum chemistry, CPK and thyroid function testing (TSH, free T_3 and free T_4), at the times indicated in Table 4.

Additional safety samples may be collected if clinically indicated at the discretion of the Investigator. The date, time of collection and results (values, units and reference ranges) will be recorded on the appropriate CRF.

The Investigator should make an assessment of the available results with regard to clinically relevant abnormalities. The laboratory results should be signed and dated and retained at the Investigator's site as source data for laboratory variables. For information on how AEs based on laboratory tests should be recorded and reported, see Section 6.7. Note: In case a patient shows an AST or ALT ≥ 3 x ULN or TBL ≥ 2 x ULN please refer to Appendix D for further instructions.

The hematology, serum chemistry and urinalysis will be performed at a local laboratory at or near to the Investigator site (see Table 5, Table 6 and Table 7, respectively). Sample tubes and sample sizes may vary depending on laboratory method used and routine practice at the site.

The following laboratory variables will be measured:

Hematology

Table 5 Laboratory Safety Variables - Hematology

Hematology (whole blood)
Hemoglobin
White blood cell count
Absolute eosinophil count
Absolute lymphocyte count
Absolute neutrophil count
Platelet count

Serum Chemistry

Table 6 Laboratory Safety Variables - Serum Chemistry

Clinical Chemistry (serum)	
Albumin	Glucose
ALP	Lactate dehydrogenase
ALT[a]	Lipase[b]
AST	Magnesium[c]
Amylase[b]	Potassium
Bicarbonate[c]	Sodium
Calcium	TBL[a]
Chloride[c]	Total protein
CPK	Urea or blood urea nitrogen, depending on local practice
Creatinine	Gamma glutamyltransferase

[a] Tests for ALT, AST, ALP and TBL must be conducted and assessed concurrently. If TBL is ≥ 2 × ULN (and evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.
[b] It is preferable that both amylase and lipase parameters are assessed. For sites where only one of these parameters is routinely measured then either lipase or amylase is acceptable.
[c] Bicarbonate (where available), chloride, gamma glutamyltransferase, magnesium, testing are to be performed at screening, on Day 0, and if clinically indicated.

Abbreviations:
ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; CPK=creatine phosphokinase; TBL=total bilirubin; ULN=upper limit of normal

Luteinizing Hormone and Follicle-Stimulating Hormone

Levels of LH and FSH will be measured at screening only in select patients.

Creatine Phosphokinase

Levels of CPK will be measured at screening, during the study treatment period and at the Follow-up visit.

Thyroid Hormone Function

Free T_3 or free T_4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.

Coagulation Tests

Coagulation parameters (APTT and either prothrombin time or INR) are to be assessed at baseline and as clinically indicated.

Serology

Antibodies to, hepatitis B and hepatitis C will be measured. Antibodies to HIV will only be measured if clinically indicated.

Patients positive for hepatitis C antibody are eligible only if polymerase chain reaction (PCR) is negative for hepatitis C virus RNA.

Patients with a positive HBsAg test at screening are not eligible for the study.

Patients who are HBsAg and HBcAb negative, but are positive for hepatitis virus B surface antibody may be included in the study provided that all other eligibility criteria are satisfied.

A hepatitis virus B DNA test will be performed if the patient is HBsAg negative but HBcAb positive (regardless of hepatitis virus B surface antibody status).

- If the hepatitis virus DNA test is positive, the patient will be excluded.
- If the hepatitis virus DNA test is negative, the patient may be included in the study.

Prophylactic antiviral therapy, in addition to the monitoring described above, may be initiated at the discretion of the Investigator.

If the patient becomes hepatitis virus DNA positive during the study, the Investigator will manage the clinical situation as per the standard of care of that institution and the Medical Monitor will be notified.

Urinalysis

Urinalysis must be done at baseline (screening) and then as clinically indicated. A urine pregnancy test will be performed for women of childbearing potential during the treatment period at the frequency shown in Table 3.

Table 7 Laboratory Safety Variables - Urinalysis

Urinalysis (dipstick)	
Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Color and appearance

5.4.2 Pregnancy testing

For women of reproductive potential, a negative result for serum pregnancy test (test must have a sensitivity of at least 25 mIU/mL) must be available at the screening visit and a urine β-HCG pregnancy test is required to be performed during the treatment period at the frequency shown in Table 3. If at any point, the β-HCG (pregnancy) test is positive, indicating that the patient is pregnant, no additional IP will be administered, but the patient will be followed for the duration of the study and beyond to determine the outcome of the pregnancy (with the patient's consent).

5.4.3 Physical examination

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, CV, abdomen, skin (for signs of injection site reactions due to MEDI0457 or EP), head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, abdomen, musculoskeletal (including spine and extremities) and neurological systems at screening and Follow-up visits. A targeted physical examination to document changes in any medical condition since the last visit will be performed at all other visits.

5.4.4 WHO / ECOG performance status

A WHO / ECOG performance status will be conducted at screening, during IP administration and at follow-up. A WHO / ECOG performance status will be performed at other visits as determined by Investigator or directed per patient complaints.

WHO / ECOG performance status (Oken et al 1982) will be assessed based on the following:

0=Fully active; able to carry out all pre-disease performance without restrictions.

1=Restricted in physically strenuous activity but ambulatory and able to carry out light work or work of a sedentary nature, e.g., light housework, office work.

2=Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.

3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.

4=Completely disabled. Unable to carry out any self-care and totally confined to bed or chair.

5=Dead

Any significant changes from baseline or screening must be reported as an AE.

5.4.5 Post-treatment reaction assessment

The Investigator will assess local and systemic reactions post-treatment (within 30-60 minutes after study treatment) and at post-treatment visits. Any reported MEDI0457 local

post-treatment reactions and systemic post-treatment reactions will be graded per NCI CTCAE version 4.03 and all must be recorded on the CRFs.

5.4.6 Vital signs

Vital signs including temperature, respiration rate, pulse oximetry, blood pressure, HR and weight will be measured at all the study visits.

On infusion days, patients receiving durvalumab treatment will be monitored during and after infusion of IP as present in the bulleted list below.

Supine blood pressure will be measured using a semi-automatic blood pressure recording device with an appropriate cuff size, after the patient has rested for at least 5 minutes. Blood pressure and pulse will be collected from patients receiving durvalumab before, during and after each infusion at the following times (based on a 60 minute infusion):

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the start of the infusion]).
- Approximately every 30 minutes (± 5 minutes) after start of the infusion (half way through the infusion).
- At the end of the infusion (approximately 60 minutes ± 5 minutes).
- A 1 hour (± 15 minutes) observation period is required after each infusion of durvalumab is administered if clinically significant infusion reactions are observed during or after the first dose and at Investigator discretion.

If no clinically significant infusion reactions are observed during or after the first dose, the length of subsequent infusion observation periods can occur at the Investigator's discretion (suggested 30 minutes after each durvalumab infusion). If the infusion duration exceeds 60 minutes, then blood pressure and pulse measurements should follow the principles as described above or be obtained more frequently if clinically indicated. The date and time of collection and measurement will be recorded on the appropriate CRF. Additional monitoring with assessment of vital signs is at the discretion of the Investigator per standard clinical practice or as clinically indicated.

Situations in which vital signs results should be reported as AEs are described in Section 6.7.9.

5.4.7 Weight and height

Height (cm) will be collected at the screening visit only. Weight (kg) will be collected at the screening visit, each additional visit from Week 1 to the Follow-up visit.

5.4.8 Electrocardiogram

An ECG will be performed at screening within 28 days of Day 0 for all patients to determine patient eligibility and as clinically indicated throughout the study. Three 12-lead ECG recordings are required in triplicate (all three ECG assessments within a 5 minute time period) at the screening visit.

The following parameters will be recorded for each ECG: date and time of ECG, HR (beats/min), PR interval (ms), RR interval (ms), QRS interval (ms), QT interval (ms), QTcF interval (for Fridericia's) (ms), QTcB interval (ms), sinus rhythm (yes / no), and overall evaluation (normal / abnormal).

Abnormal ECGs should be interpreted as clinically significant or not clinically significant.

In case of clinically significant ECG abnormalities, including a QTcF value > 470 ms, two additional 12-lead ECGs should be obtained over a brief period (e.g., 30 minutes) to confirm the finding.

Electrocardiograms should be obtained after the patient has been in a supine position for 5 minutes and recorded while the patient remains in that position. Electrocardiograms will be performed in triplicate. Electrocardiograms will be read and collected locally and held in digital format by core laboratory.

Electrocardiograms are to be collected in triplicate (all three ECG assessments within a 5 minute time period) within 30 minutes before dosing of MEDI0457 and 30-60 minutes after dosing at Weeks 1, 3, 7 and 12 and thereafter single ECGs at pre-dose at subsequent dosing visits. Triplicate (all three ECG assessments within a 5 minute time period) ECGs will be performed within 30 minutes before dosing of MEDI4736 at Week 4 and 30-60 minutes after dosing of MEDI4736 at Weeks 4 and 12. An ECG assessment can also be performed if clinically indicated and according to the Investigator.

5.4.9 Other safety assessments

5.4.9.1 Management of anxiety and pain due to electroporation procedure

Patients will be offered topical anesthetic (e.g., EMLA [lidocaine + prilocaine]), to prevent significant discomfort from the study treatment procedure. If EMLA (lidocaine 2.5% and prilocaine 2.5%) is used, an approximately 1.5 cm diameter amount will be applied with occlusion to the site of injection ~30 minutes prior to study treatment.

Patients may be offered a mild sedative (e.g., 0.5-1 mg lorazepam) for anxiety related to the EP procedure. Mild sedatives may be administered approximately 1 hour prior to EP. Patients who receive a mild sedative must not be allowed to operate a motor vehicle for 3-4 hours after receiving medication and must have arranged transportation to depart the study site.

Patients will be offered an analgesic (e.g., ibuprofen, ketorolac) after study treatment. Note: The use of any narcotic (including Tylenol® [acetaminophen] with codeine) for pain meets the

definition of severe pain (Grade 3) and therefore will not be offered to the patients unless clinically indicated.

Patients who are allergic to or have contraindications to ibuprofen, ketorolac or lorazepam will be offered a suitable alternative.

Medications administered to manage anxiety and pain due to the EP procedure will be captured as concomitant medications on the CRF.

5.4.9.2 Monitoring of durvalumab administration

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Note: Per Inclusion criterion 3, patients who weigh < 30 kg will receive durvalumab at 20 mg/kg at every 4 weeks and if their weight increases to ≥ 30 kg they can be switched to durvalumab at 1500 mg every 4 weeks. If in the course of the study after the Safety Analysis Run-in the dose is reduced to 750 mg of durvalumab, then patients who weigh ≤ 30 kg will receive durvalumab at 10 mg/kg at every 4 weeks and if their weight increases to ≥ 30 kg they can be switched to durvalumab at 750 mg every 4 weeks.

The following steps apply specifically to durvalumab. Each dose of durvalumab should be administered using the following guidelines:

- Investigational product must be administered at room temperature by controlled infusion into a peripheral vein or central line. Prior to the start of the infusion, ensure that the bag contents are at room temperature to avoid an infusion reaction due to the administration of the solution at low temperatures.

- A physician must be present at the site or immediately available to respond to emergencies during all administrations of IP. 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.

- Lines used for infusion during dose administration will need to be equipped with 0.22- or 0.2-µm in-line filters.

- Some IP may remain in the IV line after the infusion has completed. A volume of IV solution equal to the priming volume of the infusion set should be used to flush the lines. A separate flush bag may be used to clear the line or remaining IP. The infusion rate should not be changed. The infusion should be completed according to the institutional policy to ensure that the full dose of the IP is administered. It will be documented if the line was not flushed.

5.4.9.3 Management of infusion reactions due to durvalumab

Patients will be monitored during and after the infusion with assessment of vital signs at the times specified in the study protocol.

In the event of a ≤ Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event and re-initiated at 50% of the initial rate until completion of the infusion. For patients with a ≤ Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. If the patient tolerates subsequent infusions without reaction, the infusion rate may be increased again back to the initial infusion rate. Acetaminophen and / or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the Investigator. If the infusion-related reaction is ≥ Grade 3 or higher in severity, study drug will be discontinued.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

Note: Any infusion-related reaction is considered as an AESI. As soon an AE is entered into the Medidata RAVE system by the site and an AESI is selected, then the site must inform MedImmune within 24 hours post-infusion. In addition, all infusion-related reactions should be reported to MedImmune within 24 hours post-infusion. If in the opinion of the Investigator, the infusion-related reaction is considered to be an SAE, then the infusion-related reaction should be reported as an SAE.

5.4.9.4 Assessment of clinical adverse events

Patients will be questioned by the Investigator regarding the occurrence of any possible AEs, concomitant medications and new onset chronic disease during their clinic visits. Patients will be reminded to contact study personnel and immediately report any event that may happen for the duration of the study. These events will be recorded on the patient's CRF.

5.5 Other assessments

5.5.1 Downloading of electroporation data from CELLECTRA®5P device

Within 48 hours following each treatment with MEDI0457, data should be downloaded from the EP device and the data file that is created should be sent to the Sponsor or designee by e-mail to PPD. Instructions on how to download the data are provided separately. Training will be provided. Appendix E provides the CELLECTRA®5P device error reporting form.

5.5.2 Coronavirus disease of 2019 vaccine

Patients enrolled in the study can receive coronavirus disease of 2019 (COVID-19) vaccines, at the discretion of the Investigator, following a benefit/risk evaluation for the individual patient and in accordance with local rules and regulations and vaccination guidelines. Investigators should consider the potential impact of relevant labelling information (i.e. "Indications," "Contraindications," "Warnings and Precautions," "Adverse Reactions").

Except for the specific type of vaccine (e.g., live, attenuated virus vaccines) prohibited in the study (Section 3.2 Exclusion criteria), any type of COVID-19 vaccinations are acceptable. Alternative vaccines available in the investigator's area would need to be discussed, in the interest of the patient, as part of normal patient counselling and good clinical practice.

Administration of MEDI0457 and the COVID-19 vaccine should be separated by 14 days. Ensure the COVID-19 vaccination details (including brand name and manufacturer) are captured in the electronic CRF or patient chart as concomitant medication.

5.6 Pharmacokinetics

5.6.1 Collection of samples

Blood samples for determination of durvalumab levels in serum will be taken at the visits presented in the study plan (Table 3).

Pre-dose sampling (samples collected up to 60 minutes prior to durvalumab start of administration) for both ADA and pharmacokinetic sampling schemes of durvalumab.

Samples will be collected, labeled stored and shipped as detailed in the Laboratory Manual.

A central laboratory will be used for the collection of blood for pharmacokinetic analysis (see Laboratory Manual for further details).

5.6.2 Determination of drug concentration

Blood samples for determination of durvalumab concentration in serum will be obtained according to the assessment schedules (see Table 3).

Samples for determination of durvalumab concentration in serum will be analyzed by a designated third party on behalf of MedImmune, using an appropriate bioanalytical method. Full details of the analytical method used will be described in a separate Bioanalytical Report.

5.6.3 Storage and destruction of pharmacokinetic / anti-drug antibody samples

Pharmacokinetic and ADA samples will be disposed of 5 to 10 years after durvalumab is approved for marketing.

Pharmacokinetic and ADA samples may be disposed of or destroyed and anonymized by pooling. Additional analyses may be conducted on the anonymized, pooled pharmacokinetic

samples to further evaluate and validate the analytical method. Results from such analyses may be reported separately from the Clinical Study Report.

Incurred sample reproducibility analysis, if any, will be performed alongside the bioanalysis of the test samples. The results from the evaluation will not be reported in the Clinical Study Report but separately in a Bioanalytical Validation Report.

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5.6.4 Collection of samples to measure for the presence of anti-drug antibody

The presence of ADA will be assessed in serum samples taken according to the assessment schedules (see Table 3).

Samples will be measured for the presence of ADA using validated assays. Tiered analysis will be performed to include screening, confirmatory, and titer assay components, and positive negative cut points previously statistically determined from drug-naïve validation samples will be employed. Samples will be collected and stored for potential neutralizing ADA analysis in the future.

5.7 Pharmacogenetics

Refer to Appendix C for full details.

5.8 Biomarker analysis

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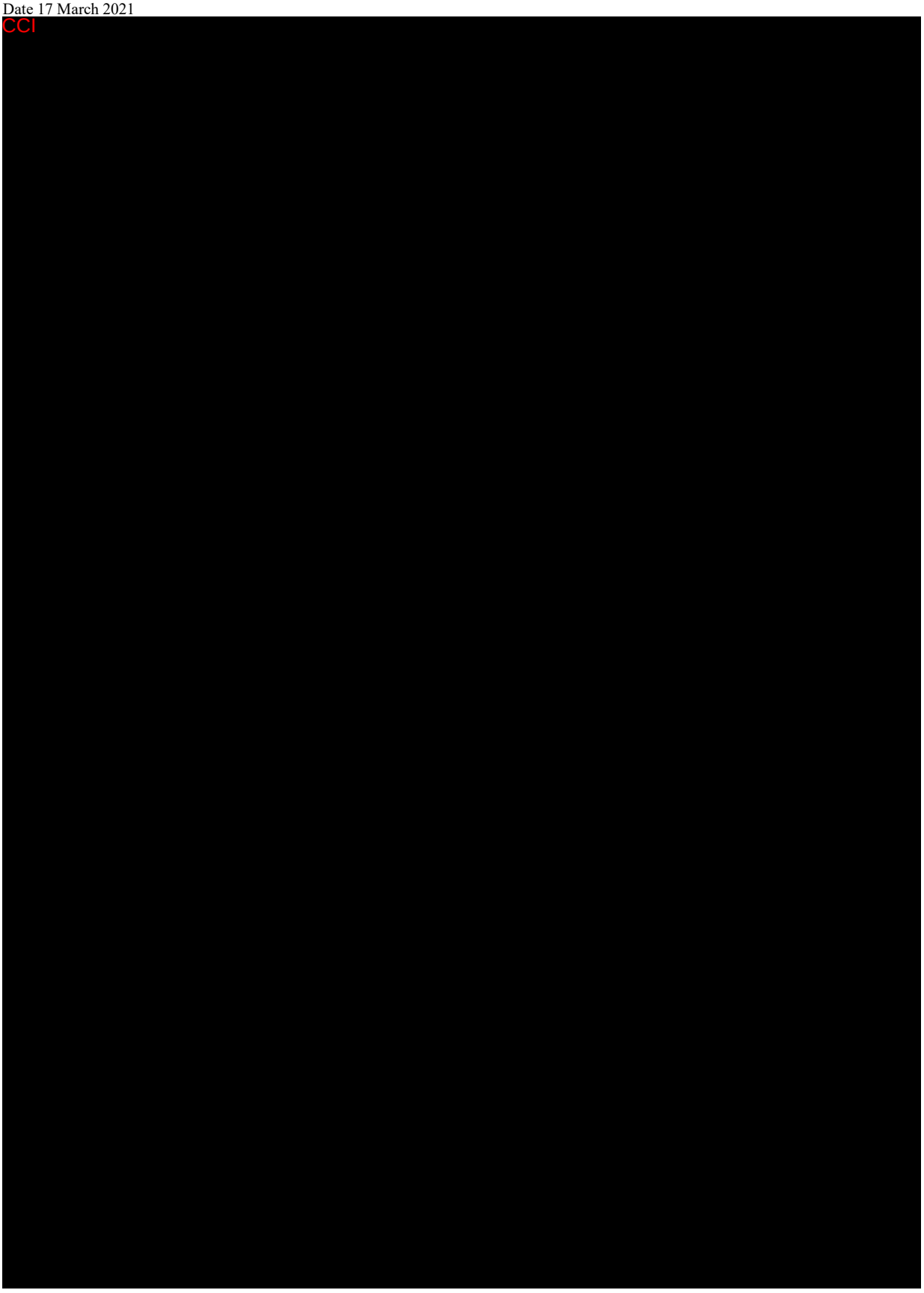


CCI

[redacted]

CCI

[redacted]

5.8.3 Storage, reuse and destruction of biological samples

Samples will be stored for a maximum of 15 years from the date of the Last Patient's Last Visit, after which they will be destroyed. CCI [redacted]

CCI [redacted]

5.8.4 Labeling and shipment of biological samples

The Principal Investigator ensures that samples are labeled and shipped in accordance with the Laboratory Manual and the Biological Substance, Category B Regulations (materials containing or suspected to contain infectious substances that do not meet Category A criteria), see Appendix B 'IATA 6.2 Guidance Document'.

Any samples identified as Infectious Category A materials are not shipped and no further samples will be taken from the patient unless agreed with MedImmune and appropriate labeling, shipment and containment provisions are approved.

5.8.5 Chain of custody of biological samples

A full chain of custody is maintained for all samples throughout their lifecycle.

The Principal Investigator at each center will keep full traceability of collected biological samples from the patients while in storage at the center until shipment or disposal (where appropriate) and keeps documentation of receipt of arrival.

The sample receiver keeps full traceability of the samples while in storage and during use until used or disposed of or until further shipment and keeps documentation of receipt of arrival.

MedImmune keeps oversight of the entire life cycle through internal procedures, monitoring of study sites and auditing of external laboratory providers.

Samples retained for further use are registered in the MedImmune Biorepository during the entire life cycle.

5.8.6 Withdrawal of informed consent for donated biological samples

If a patient withdraws consent to the use of donated biological samples, the samples will be disposed of / destroyed, and the action documented. If samples are already analyzed, MedImmune is not obliged to destroy the results of this research.

The Principal Investigator:

- Ensures patients' withdrawal of informed consent to the use of donated samples is notified immediately to MedImmune.
- Ensures that biological samples from that patient, if stored at the study site, are immediately identified, disposed of / destroyed, and the action documented.

- Ensures the laboratory(ies) holding the samples is / are informed about the withdrawn consent immediately and that samples are disposed of / destroyed, the action documented and the signed document returned to the study site.

- Ensures that the patient and MedImmune are informed about the sample disposal.

MedImmune ensures the central laboratory(ies) holding the samples is / are informed about the withdrawn consent immediately and that samples are disposed of / destroyed and the action documented and returned to the study site.

6. SAFETY REPORTING AND MEDICAL MANAGEMENT

The Principal Investigator is responsible for ensuring that all staff involved in the study are familiar with the content of this section.

6.1 Definition of adverse events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related (Guidance for Industry and Investigators).

In this study, such changes will be monitored, classified, and summarized, and as Clinical or Laboratory AEs, respectively. Medical condition / diseases present before starting the investigational drug will be considered AEs only if they worsen after starting study treatment.

An unexpected AE is one not identified in the Investigator's Brochures (MEDI0457 Investigator's Brochure and Durvalumab Investigator's Brochure) or otherwise not expected from the characteristics of the clinical material.

Adverse events include the following:

- Pre- or post-treatment complications that occur as a result of protocol-mandated procedure during or after the first screening visit (before the administration of study drug).

- Any pre-existing condition that increases in severity, or changes in nature during or as a consequence of the study drug phase of a human clinical trial, will also be considered an AE.

- Complications and termination of pregnancy; see Section 6.11 for additional information.

- All AEs that occur from the study screening visits onwards and throughout the duration of the study, including the follow-up off-study treatment period should be recorded as an AE.

Adverse events do not include the following:

- Medical or surgical procedures (e.g., surgery, endoscopy, tooth extraction, transfusion) performed; the condition that leads to the procedure is an AE.
- Pre-existing diseases or conditions or laboratory abnormalities present or detected before the screening visits that do not worsen.
- Situations where an untoward medical occurrence has not occurred (e.g., hospitalization for elective surgery, social and / or convenience admissions).
- Overdose without clinical sequelae.
- Any medical condition or clinically significant laboratory abnormality with an onset date before the consent form is signed and not related to a protocol associated procedure is not an AE. It is considered to be pre-existing and should be documented on the medical history CRF.
- Uncomplicated pregnancy (documented on a pregnancy CRF).
- An induced elective abortion to terminate a pregnancy without medical reason (documented on a pregnancy CRF).

The term AE is used to include both serious and non-serious AEs.

6.2 Definitions of serious adverse events

An AE or suspected adverse reaction is considered ‘‘serious’’ if, in the view of either the Investigator or Sponsor, it results in any of the following outcomes: death, a life-threatening AE, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly / birth defect. Important medical events that may not results in death, be life-threatening, or require hospitalization may be considered serious when based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (Guidance for Industry and Investigators).

<u>Clarification of Serious Adverse Events</u>

- Death is an outcome of an AE, and not an AE in itself. Note: death due to disease progression is not considered to be an SAE (see Section 6.7.13 for further details).

- The patient may not have been on IP at the occurrence of the event. Administration may have been given as treatment cycles or interrupted temporarily before the onset of the SAE, but may have contributed to the event.

- "Life-threatening" means that the patient was at immediate risk of death from the event as it occurred. This does not include an event that might have led to death if it had occurred with greater severity.

- Complications that occur during hospitalizations are AEs. If a complication prolongs the hospitalization, it is an SAE.

- Inpatient hospitalization means the patient has been formally admitted to a hospital for medical reasons, for any length of time. This may or may not be overnight. It does not include presentation and care within an emergency department.

The Investigator should attempt to establish a diagnosis of the event on the basis of signs, symptoms, and / or other clinical information. In such cases, the diagnosis should be documented as the AE and / or SAE and not the individual signs / symptoms.

Serious adverse events that are ongoing should be followed until resolution. The reporting period for SAEs is described in Section 6.8.

For further guidance on the definition of an SAE, see Appendix A to the Clinical Study Protocol.

6.3 Definition of adverse reactions

An adverse reaction means any AE caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event (Guidance for Industry and Investigators).

6.4 Definition of suspected adverse reactions

Suspected adverse reaction means any AE for which there is a reasonable possibility that the drug caused the AE. For the purposes of Investigational New Drug (IND) safety reporting, 'reasonable possibility' means there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any AE caused by a drug (Guidance for Industry and Investigators).

6.5 Definition of unexpected events / reactions

An AE or suspected adverse reaction is considered ''unexpected'' if it is not listed in the Investigator's Brochure or is not listed as the specificity or severity that has been observed; or if an Investigator's Brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be

unexpected (by virtue of greater severity) if the Investigator's Brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the Investigator Brochure listed only cerebral vascular accidents. ''Unexpected'' as used in this definition, also refers to AEs or suspected adverse reactions that are mentioned in the Investigator's Brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation (Guidance for Industry and Investigators).

6.6 Definition of life-threatening events / reactions

An AE or suspected adverse reaction is considered ''life-threatening'' if, in the view of either the Investigator or Sponsor, its occurrence places the patient or subject at immediate risk of death. It does not include an AE or suspected adverse reaction that, had it occurred in a more severe form, might have caused death (Guidance for Industry and Investigators).

6.7 Recording of adverse events

6.7.1 Time period for collection of adverse events

Adverse events and SAEs will be collected from time of signature of informed consent, through 90 days after the last dose of the last study treatment. Note: AEs / SAEs that occur post-signature but prior to IP administration are non-treatment-emergent AEs / SAEs. When a patient is defined as a screen failure, AE data will not be collected in the CRF. The site will document AE data and keep the data in their files at the site.

6.7.2 Methods and timing of the collection and recording of adverse events

After study treatment: Patients will be directly observed by study personnel for 30-60 minutes after each administration of MEDI0457 IM+EP for immediate reactions. Injection sites will also be assessed at the subsequent study visit.

The occurrence and severity of any AE during this period will be recorded on the appropriate CRF. Patients will be given an oral thermometer and instructed to take and record their temperature daily (at the same time each day).

Throughout the study: Patients will also be questioned by the Investigator regarding the occurrence of any possible AEs, concomitant medications and new onset chronic disease during their clinic visits. Patients will be reminded to contact study personnel and immediately report any event that may happen for the duration of the study. If events occur, these events will be recorded on the patient's CRF.

On study treatment visits, the assessments will be performed prior to administration. Study patients will be queried at each clinic visit regarding the occurrence of any AEs, including SAEs that may have occurred since the last visit. They will be reminded to contact study personnel and immediately report any such event that happens during the course of the study. These events will be recorded on the CRFs.

6.7.3 Follow-up of unresolved adverse events

During the course of the study, all AEs and SAEs should be proactively followed up for each patient. Every effort should be made to obtain a resolution for all events, even if the events continue after discontinuation or study completion.

Any AEs that are unresolved at the patient's last visit in the study are followed up by the Investigator for as long as medically indicated, with follow-up data recording in the CRF. MedImmune retains the right to request additional information for any patient with ongoing AE(s) / SAE(s) at the end of the study, if judged necessary.

6.7.4 Variables

The following variables will be collected for each AE:

- Adverse event (verbatim)
- The date and time when the AE started and stopped
- Each CTCAE grade for a repeated AE
- Whether the AE is serious or not
- Investigator causality rating against the IP (yes or no)
- Action taken with regard to IP
- Administration of treatment for the AE
- Whether the AE caused the patient's withdrawal from the study (yes or no)
- Outcome

In addition, the following variables will be collected for SAEs:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Seriousness criteria fulfilled
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death

- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s) and other medication(s)
- Description of AE

The grading scales found in the revised NCI CTCAE version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used.

It is important to distinguish between serious and severe AEs. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 6.2. An AE of severe intensity need not necessarily be considered serious. For example, nausea that persists for several hours may be considered severe nausea, but not an SAE unless it meets the criteria shown in Section 6.2. On the other hand, a stroke that results in only a limited degree of disability may be considered a mild stroke but would be an SAE when it satisfies the criteria shown in Section 6.2.

6.7.5 Severity codes for adverse events

Study personnel will grade laboratory AEs and clinical AEs (based on discussions with study participants) with respect to the following levels of severity as defined in NCI CTCAE version 4.03.

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

- Grade 1 (mild): An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living (ADL).
- Grade 2 (moderate): An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual ADL, causing discomfort but poses no significant or permanent risk of harm to the patient.
- Grade 3 (severe): An event that requires intensive therapeutic intervention. The event interrupts usual ADL, or significantly affects the clinical status of the patient.
- 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 patient to perform ADL (eating, ambulation, toileting, etc).
- Grade 5 (fatal): Death (loss of life) as a result of an event.

6.7.6 Causal relationship of investigational product to adverse events

A causally related AE is one judged to have a possible, probable or definite relationship to the administration of the IP and / or the investigational device. An AE may also be assessed as not related to the IP and / or the investigational device. Because the Investigator is knowledgeable about the patient (e.g., medical history, concomitant medications), administers the IP, and monitors the patient's response to the IP, the Investigator is responsible for reporting AEs and judging the relationship between the administration of the IP and EP and a subsequent AE. The Investigator is aware of the patient's clinical state and thus may be sensitive to distinctions between events due to the underlying disease process versus events that may be product related and may have observed the event. The Sponsor will assess the overall safety of the IP delivered by EP and determine whether to report expeditiously to the regulatory agencies.

Investigators should use their knowledge of the Study Patient, the circumstances surrounding the event, and an evaluation of any potential alternative causes to determine whether or not an AE is considered to be related to the IP and / or the investigational device indicating "yes" or "no" accordingly. Causality should be assessed by the Investigator as "yes, related" or "no, unrelated" by the following criteria:

- Yes – there is a reasonable possibility that administration of the Study Treatment contributed to the event.
- No – there is no reasonable possibility that administration of the Study Treatment contributed to the event and there are more likely causes.

The following guidance should also be taken into consideration:

- Temporal relationship of event to administration of IP and / or EP.
- Course of the event, considering especially the effects of dose reduction, discontinuation of IP, or reintroduction of IP (where applicable).
- Known association of the event with the IP, EP or with similar treatments.
- Known association of the event with the disease under study.
- Presence of risk factors in the Study Patient or use of concomitant medications known to increase the occurrence of the event.

The Investigator is also required to provide an assessment of relationship of SAEs to protocol procedures on the SAE Report Form. This includes non-treatment-emergent SAEs (i.e., SAEs that occur prior to the administration of IP) as well as treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., 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 patient'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 patient's medical record).

6.7.7 Relationship to protocol procedures

The Investigator is also required to provide an assessment of the relationship of SAEs to protocol procedures on the SAE Report Form. This includes both non-treatment-emergent (i.e., SAEs that occur prior to the administration of IP) and treatment-emergent SAEs. A protocol-related SAE may occur as a result of a procedure or intervention required during the study (e.g., blood collection). 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 or intervention that was described in the protocol for which there is no alternative etiology present in the patient's medical record.

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

6.7.8 Adverse events based on signs and symptoms

All AEs spontaneously reported by the patient or reported in response to the open question from the study personnel: "Have you had any health problems since the previous visit / you were last asked?" or revealed by observation will be collected and recorded in the CRF. When collecting AEs, the recording of diagnoses is preferred, when possible, to recording a list of signs and symptoms. However, if a diagnosis is known and there are other signs or symptoms that are not generally part of the diagnosis, the diagnosis and each sign or symptom will be recorded separately.

6.7.9 Adverse events based on examinations and tests

The results from protocol-mandated laboratory tests and vital signs will be summarized in the Clinical Study Report. Deterioration as compared to baseline in protocol-mandated laboratory values and vital signs should therefore only be reported as AEs if they fulfill any of the SAE criteria or are the reason for discontinuation of treatment with the IP.

If deterioration in a laboratory value / vital sign is associated with clinical signs and symptoms, the sign or symptom will be reported as an AE and the associated laboratory result / vital sign will be considered as additional information. Wherever possible the reporting Investigator uses the clinical, rather than the laboratory term (e.g., anemia versus low hemoglobin value). In the absence of clinical signs or symptoms, clinically relevant deteriorations in non-mandated parameters should be reported as AE(s).

Deterioration of a laboratory value, which is unequivocally due to disease progression, should not be reported as an AE / SAE.

Any new or aggravated clinically relevant abnormal medical finding at a physical examination as compared with the baseline assessment will be reported as an AE.

6.7.10 Abnormal laboratory value

Laboratory abnormalities are only to be reported as AEs, if the Investigator feels they are clinically significant. At the time of entry, the site physician will grade the laboratory abnormality that they feel is an AE. Other laboratory abnormalities will not be graded. In addition, laboratory or other abnormal assessments (e.g., ECG, x-rays, vital signs) that are associated with signs and / or symptoms must be recorded as an AE or SAE if they meet the definition of an AE (or SAE) as described in Sections 6.1 and 6.2. If the laboratory abnormality is part of a syndrome, record the syndrome or diagnosis (e.g., anemia) not the laboratory result (e.g., decreased hemoglobin).

Any laboratory abnormality that is new in onset or worsened in severity or frequency from the baseline condition and meets one of the following criteria will be recorded as an AE:

- Requires therapeutic intervention or diagnostic tests
- Leads to discontinuation of study treatment
- Has accompanying or inducing symptoms or signs
- Is judged by the Investigator as clinically significant

Grade is an essential element of these criteria. Each CTCAE grading term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term. Note: the most current version of MedDRA will be used.

Investigators are asked to take the CTCAE grading criteria into account when assessing if a laboratory abnormality qualifies as a laboratory AE. Their clinical judgment ultimately determines whether the abnormality in question is “clinically significant” or “not clinically significant” and the severity of the event. CTCAE grading can be used as a reference when making this determination. It is the responsibility of the investigators to ensure all AEs are accurately reported and graded.

6.7.11 New cancers

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

6.7.12 Disease progression

Disease progression can be considered as a worsening of a patient's condition attributable to the disease for which the IP 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 new, or progression of existing metastasis to the primary cancer under study should be considered as disease progression and not an AE. Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

6.7.13 Deaths

All deaths that occur during the study, or within the protocol-defined follow-up period after the administration of the last dose of study treatment, must be reported as follows:

- Death clearly resulting from disease progression should be reported to the Study Physician at the next monitoring visit and should be documented in the CRF. It should not be reported as an SAE.

- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to the Study Physician as an SAE within 24 hours. The report should contain a comment regarding the co-involvement of PD, 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 examination 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 Drug Safety or its representative within the usual timeframes.

6.8 Reporting of serious adverse events

All SAEs have to be reported, whether or not considered causally related to the IP, or to the study procedure(s). All SAEs will be recorded in the CRF.

If any SAE occurs in the course of the study, then investigators or other site personnel inform the appropriate MedImmune representatives within one day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

PRA works with the Investigator to ensure that all the necessary information is provided to the MedImmune Patient Safety Data Entry Site **within 1 calendar day** of initial receipt for fatal and life-threatening events **and within 5 calendar days** of initial receipt for all other SAEs.

For fatal or life-threatening AEs where important or relevant information is missing, active follow-up is undertaken immediately. Investigators or other site personnel inform MedImmune representatives of any follow-up information on a previously reported SAE within one calendar day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

Once the investigators or other site personnel indicate an AE is serious in the WBDC system, an automated e-mail alert is sent to the designated MedImmune representative.

If the WBDC system is not available, then the Investigator or other study site personnel reports an SAE to the appropriate MedImmune representative by telephone. The Principal Investigator must use the back-up paper SAE Report recognizing that the same reporting time frames still apply.

The MedImmune representative will advise the investigator / study site personnel how to proceed.

6.9 Reporting of serious and unexpected suspected adverse reactions

The Sponsor must report in an IND safety report any suspected adverse reaction to study treatment (i.e., including active comparators) that is both serious and unexpected. Before submitting an IND safety report, the Sponsor needs to ensure that the event meets all three of the definitions (Guidance for Industry and Investigators):

- Suspected adverse reaction
- Serious
- Unexpected

If the AE does not meet all three of the definitions, it should not be submitted as an IND safety report.

The timeframe for submitting an IND safety report, any serious unexpected suspected adverse reaction which is not fatal or life-threatening to the Food and Drug Administration (FDA) is **no later than 15 calendar days** after the Sponsor determines that the suspected adverse reaction or other information qualifies for reporting.

Unexpected fatal or life-threatening suspected adverse reactions shall be reported by the Sponsor to FDA is **no later than 7 calendar days** after the Sponsor's initial receipt of the information (in accordance with 21 CFR 312.32(c)(2)).

The day of initial receipt for cases that are interpretable as single cases and the day the Sponsor determines that multiple cases qualify for expedited reporting are considered day zero.

If FDA requests any additional data or information, the Sponsor shall submit it to FDA as soon as possible, but **no later than 15 calendar days** after receiving the request (in accordance with 21 CFR 312.32(c)(1)(v)).

6.10 Overdose

An overdose is defined as a patient receiving a dose of IP(s) in excess of that specified in the Investigator's Brochures (MEDI0457 Investigator's Brochure and Durvalumab Investigator's Brochure), unless otherwise specified in this protocol.

Any overdose of a study patient with IP, with or without associated AEs / SAEs, is required to be reported within 24 hours of knowledge of the event to the Sponsor designee. If the overdose results in an AE, the AE must also be recorded as an AE (see Section 6.7).

Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE (see Section 6.8). There is currently no specific treatment in the event of an overdose of either MEDI0457 or durvalumab (see MEDI0457 Investigator's Brochure and Durvalumab Investigator's Brochure).

The Investigator will use clinical judgment to treat any overdose.

- An overdose with associated AEs is recorded as the AE diagnosis / symptoms on the relevant AE modules in the CRF and on the Overdose CRF module.

- An overdose without associated symptoms is only reported on the Overdose CRF module.

If an overdose on a MedImmune study drug occurs in the course of the study, then the Investigator or other site personnel inform appropriate MedImmune representatives immediately, or **no later than 24 hours** of when he or she becomes aware of it.

PRA works with the Investigator to ensure that all relevant information is provided to the MedImmune Patient Safety Data Entry Site.

For overdoses associated with an SAE, the standard reporting timelines apply, see Section 6.8. For other overdoses, reporting must occur within 30 days.

6.11 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to MedImmune.

6.11.1 Maternal exposure

If a patient becomes pregnant during the course of the study the IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP 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 patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel informs the PRA within 1 day i.e., immediately but **no later than 24 hours** of when he or she becomes aware of it.

PRA works with the Investigator to ensure that all relevant information is provided to the MedImmune Patient Safety Data Entry Site within 1 or 5 calendar days for SAEs (see Section 6.8) and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

The PREGREP module in the CRF is used to report the pregnancy and the PREGOUT is used to report the outcome of the pregnancy.

6.11.2 Paternal exposure

Male patients must refrain from fathering a child or donating sperm during the study since the potential for chromosomal aberrations in male gametes, and possible teratogenic effects thereof, has not yet been thoroughly investigated. Male patients who are sexually active must use a barrier (condom with spermicide) method of contraception from the first dose until 90 days after the last dose of IP.

Pregnancy of the patients' partners is not considered to be an AE.

If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform PRA within 1 day i.e., immediately but no later than 24 hours of when he or she becomes aware of it.

PRA will work with the Investigator to ensure that all relevant information is provided to the MedImmune Patient Safety Data Entry Site within 1 or 5 days for SAEs, see Section 6.8 and within 30 days for all other pregnancies.

6.12 Management of investigational product related toxicities

6.12.1 Dose modifications

Either treatment may be stopped by the Investigator while the other treatment continues.

MEDI0457 and durvalumab dose should not be modified.

Durvalumab: For AEs that are considered at least partly due to administration of durvalumab the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding durvalumab).

- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab.

- All dose modifications should be documented with clear medical reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (Appendix H, Postow 2015).

Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed (Appendix H, Postow 2015). All toxicities will be graded according to NCI CTCAE version 4.03.

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study. Potential irAEs include immune-mediated dermatitis, hepatitis / hepatotoxicity, endocrinopathy (hypothyroidism, hyperthyroidism, hypophysitis, and adrenal insufficiency), neuropathy / neuromuscular toxicity, nephritis, pancreatitis (elevated lipase / amylase), pneumonitis, and colitis. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of dermatitis, hepatitis / hepatotoxicity, endocrinopathy (hypothyroidism, hyperthyroidism, hypophysitis, and adrenal insufficiency), neuropathy / neuromuscular toxicity, nephritis, pancreatitis (elevated lipase / amylase), pneumonitis, and colitis should be considered to be immune-related. Refer to the latest Durvalumab Investigator's Brochure for more information.

Dose modifications will not be required for AEs that are clearly not attributable to durvalumab (such as an accident) or for laboratory abnormalities that are not deemed to be clinically significant. Administration may continue despite concurrent vitiligo of any AE grade.

Acetaminophen and / or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered prior to infusion at the discretion of the Investigator for primary prophylaxis against infusion-related reactions. For more information on dose modification for immune-related reactions please refer to Appendix H.

As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit patients to an intensive care unit if necessary.

6.12.2 Toxicity management

The Sponsor's Medical Monitor or a designee will be responsible for the overall safety monitoring of the study.

6.12.2.1 Dose-limiting toxicity

Grading of DLTs will be according to the NCI CTCAE version 4.03.

For the Safety Analysis Run-in patients, the DLT period will be 4 weeks after their first durvalumab dose.

A DLT will be defined as any Grade 3 or higher treatment-related toxicity that occurs during the DLT evaluation period (i.e., 4 weeks after the first dose of durvalumab is administered for patients in the Safety Analysis Run-in), including the following treatment-related toxicities:

(a) Any Grade 4 irAE is a DLT.

(b) Any ≥ Grade 3 colitis is a DLT.

(c) Any ≥ Grade 3 non-infectious pneumonitis irrespective of duration is a DLT.

(d) Any ≥ Grade 3 neurotoxicity (to include but not limited to limbic encephalitis, autonomic neuropathy, including peripheral neuromotor syndromes such as myasthenia gravis and Guillain-Barré) irrespective of duration is a DLT.

(e) Any ≥ Grade 3 cardiotoxicity (to include but not limited to arrhythmias, myocarditis with cardiomyopathy, ventricular dysfunction) irrespective of duration is a DLT.

(f) Any ≥ Grade 3 ocular toxicity (including but not limited to iritis, uveitis, significant vision changes) irrespective of duration is a DLT.

(g) Any ≥ Grade 3 irAE, excluding colitis or pneumonitis or neurotoxicity or cardiotoxicity and ocular toxicity as mentioned above, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days.

(h) Alanine aminotransferase or ALT elevation > 8 × ULN or TBL > 5 × ULN.

(i) Any ≥ Grade 3 non-irAE, except for the exclusions listed below.

- Grade 3 or greater injection site reaction that is persistent beyond 5 days or does not downgrade to ≤ Grade 1 in 14 days.
- Grade 3 or greater fever, not associated with above listed events (a to f), assessed by Principal Investigator as related to study treatment.
- Grade 3 or greater systemic symptoms, not associated with above listed events (a to e), assessed by Principal Investigator as related to study treatment.
- Any Grade 3 or greater anaphylaxis related to study treatment.

The DLT definition excludes the following conditions:

- Grade 3 fatigue lasting ≤ 7 days.
- Grade 3 endocrine disorder (thyroid, pituitary, and / or adrenal insufficiency) that is managed with or without systemic corticosteroid therapy and / or hormone replacement therapy and the patient is asymptomatic.
- Grade 3 inflammatory reaction attributed to a local anti-tumor response (e.g., inflammatory reaction at sites of metastatic disease, lymph nodes, etc).
- Concurrent vitiligo or alopecia of any AE grade.
- Grade 3 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.
- Grade 3 or 4 neutropenia that is not associated with fever or systemic infection that improves by at least one grade within 3 days. Grade 3 or Grade 4 febrile neutropenia **will be a DLT** regardless of duration or reversibility.
- Grade 3 or 4 lymphopenia.
- Grade 3 thrombocytopenia that is not associated with clinically significant bleeding that requires medical intervention, and improves by at least one grade within 3 days.
- Isolated Grade 3 electrolyte abnormalities that are not associated with clinical signs or symptoms and are reversed with appropriate maximal medical intervention within 3 days.

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

6.12.2.2 Events requiring expedited reporting within 24 hours

Overdose

An overdose is defined as a patient receiving a dose of IP in excess of that specified in the Investigator's Brochures (MEDI0457 Investigator's Brochure and Durvalumab Investigator's Brochure), unless otherwise specified in this protocol.

Any overdose of a study patient with IP, with or without associated AEs / SAEs, is required to be reported within 24 hours of knowledge of the event to the Sponsor designee. If the overdose results in an AE, the AE must also be recorded as an AE (see Section 6.7). Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and

reported as an SAE (see Section 6.8). There is currently no specific treatment in the event of an overdose of MEDI0457 or durvalumab.

The Investigator will use clinical judgment to treat any overdose.

Hepatic Function Abnormality

Hepatic function abnormality (as defined in Section 6.12.4) in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the Sponsor or designee unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to IP has been confirmed.

If the definitive underlying diagnosis for the abnormality has been established and is unrelated to IP, the decision to continue administration of the study patient will be based on the clinical judgment of the investigator.

If no definitive underlying diagnosis for the abnormality is established, administration of IP to the study patient must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay. Each reported event of hepatic function abnormality will be followed by the Investigator and evaluated by the Sponsor.

Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT $\geq$ 3 x ULN together with TBL $\geq$ 2 x ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of Hy's Law (HL).

Pregnancy

If a patient becomes pregnant during the course of the study, the IP should be discontinued immediately.

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities or birth defects and spontaneous miscarriages should be reported and handled as SAEs. 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 patient was discontinued from the study.

If any pregnancy occurs in the course of the study, then the Investigator or other site personnel should inform the Sponsor or designee within 1 day, i.e., immediately, but no later than 24 hours of when he or she becomes aware of it.

The designated Sponsor representative will work with the Investigator to ensure that all relevant information is provided to Sponsor or its designee within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies. The same timelines apply when outcome information is available.

6.12.2.3 Events requiring reporting within 72 hours

The following events must be reported to Sponsor within 72 hours of the occurrence of the event to discuss whether further administration should continue for the participant.

- Grade 3 or greater injection site reaction.
- Grade 3 or greater fever, not associated with above listed events (a to f) in Section 6.12.2.1, assessed by Principal Investigator as related to study treatment.
- Grade 3 or greater systemic symptoms, not associated with above listed events (a to e) in Section 6.12.2.1, assessed by Principal Investigator as related to study treatment.

6.12.3 Stopping rules

The Sponsor reserves the right to temporarily pause or terminate the study at any time. The reasons for temporarily pausing or terminating the study may include but are not limited to the following:

- If at any time during the study one-third or more patients experience any DLT assessed as related to study treatment, further enrollment and study treatments may be halted until a thorough investigation has been conducted by the Sponsor.
- If a death occurs within 8 weeks of a dose of MEDI0457 or durvalumab and it is assessed as related to study treatment, further enrollment and study treatments may be halted depending upon further discussions between the Sponsor and / or investigator.
- In the event of any unexpected Grade 4 toxicities, assessed as related to study treatment, further enrollment and study treatments may be halted until a thorough investigation has been conducted by the Sponsor and / or investigator.
- The study may be halted for any report of Grade 3 anaphylaxis from study treatment with MEDI0457 or durvalumab in two or more patients.
- Non-compliance that might significantly jeopardize the validity or integrity of the study.
- Sponsor decision to terminate development.
- Sponsor decision to terminate the study based on a planned futility analysis.

6.12.4 Adverse events of special interest

An AESI is of scientific and medical interest specific to understanding of the IP 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 IP.

Adverse events of special interest for MEDI0457 and durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and / or interventions such as steroids, immunosuppressants and / or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An irAE is defined as an AE that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE. If the Investigator has any questions in regards to an AE being an irAE, the Investigator should promptly contact the Study Physician. Identified risks (listed / expected reactions) for durvalumab include: diarrhea, ALT increase, AST increase, pneumonitis, and colitis / enterocolitis.

Adverse events of special interest observed with MEDI0457 and durvalumab include:

- Diarrhea / colitis
- Pneumonitis
- ALT / AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e., events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e., events of hypophysitis, hypopituitarism, adrenal insufficiency, type 1 diabetes, hypothyroidism and hyperthyroidism)
- Dermatitis / rash / pruritus
- Nephritis
- Pancreatitis (or laboratory tests suggestive of pancreatitis - increased serum lipase, increased serum amylase)
- Myocarditis / pericarditis
- Uveitis

- Infusion-related reactions / hypersensitivity / anaphylactic reactions
- Administration site reactions (any administration site reaction other than pain, and if the event is pain it must be Grade 3 or greater pain)

Further information on these risks (e.g., presenting symptoms) can be found in the current version of the MEDI0457 Investigator's Brochure or the Durvalumab Investigator's Brochure. For more specific guidelines for their evaluation and treatment refer to Appendix H.

Adverse events of special interest are required to be reported **within 24 hours of knowledge of the event** on the electronic CRF, even if the event is considered to be non-serious.

Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥ 3 x ULN together with TBL ≥ 2 x ULN may need to be reported as SAEs. Please refer to Appendix D for further instruction on cases of increases in liver biochemistry and evaluation of HL.

Colitis:

Diarrhea, colitis, and enterocolitis are irAEs that have been reported with durvalumab. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Diarrhea / colitis in patients receiving durvalumab should be managed as per the guidelines for the management of diarrhea and enterocolitis (refer to Appendix H).

Pneumonitis:

Adverse events of pneumonitis are also of interest for the Sponsor. Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. For guidelines for management of patients with pneumonitis refer to Appendix H.

Hypersensitivity Reactions:

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

wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness. For guidelines for management of patients with hypersensitivity reactions (including anaphylactic reactions) refer to Appendix H.

Infusion-Related 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. For all infusion reactions, the electronic CRF should be completed as instructed in Section 6.7, and all SAEs should be reported to MedImmune Patient Safety as described in Section 6.8. For guidelines for management of patients with infusion-related reactions refer to Appendix H.

Administration Site Reactions:

Adverse events of administration site reactions are of special interest to the Sponsor. These are defined, for the purpose of this protocol, as all AEs occurring as a result of the administration of the study treatment (vaccine and / or EP). Guidelines for the grading and management of administration site reactions are outlined in Appendix I.

6.12.5 Unanticipated (serious) adverse device effect

Unanticipated adverse device effect means any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of patients.

Per the definition above, an unanticipated adverse device effect is a type of SAE that requires expedited reporting on the part of the Sponsor. As a reminder, all SAEs regardless of relationship to device, drug or procedure are to be reported to Sponsor by the study Investigator within 24 hours. Sponsor will assess each device related SAE to determine if anticipated based on prior identification within the investigational plan.

6.13 Study governance and oversight

The safety of all MedImmune clinical studies is closely monitored on an ongoing basis by MedImmune representatives in consultation with Patient Safety. Issues identified will be addressed; for instance this could involve amendments to the study protocol and letters to investigators.

7. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

7.1 Identity of investigational product(s)

7.1.1 MEDI0457

CCI

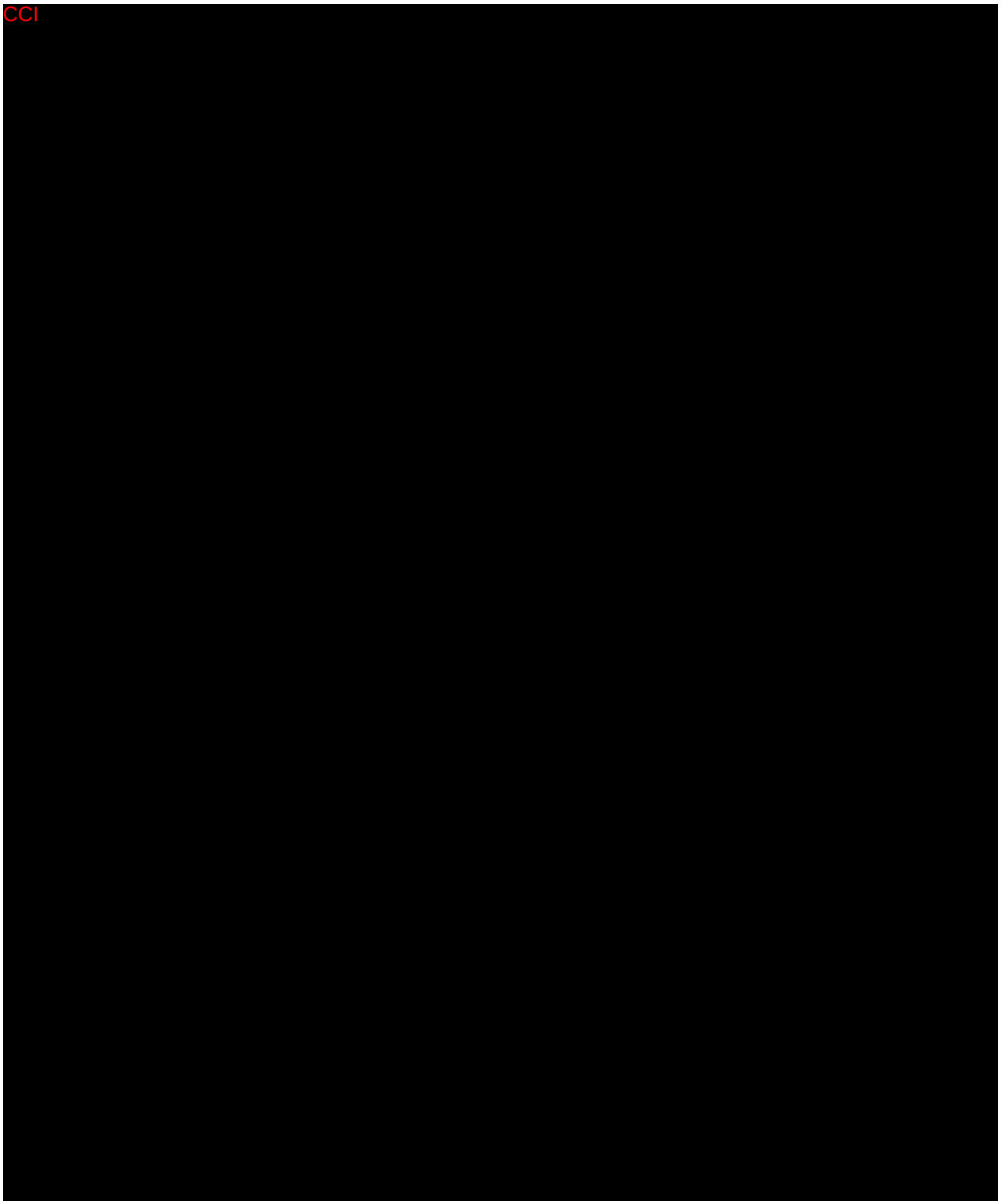
7.1.2 Durvalumab

Durvalumab (also known as MEDI4736) is a human IgG1 kappa monoclonal antibody directed against human PD-L1. Durvalumab selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and CD80. The fragment crystallizable 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).

Durvalumab will be supplied by MedImmune or its designee as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine /

histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL. Durvalumab must be used within the individually assigned expiry date on the label.

CCI



7.2 Dose and treatment regimens

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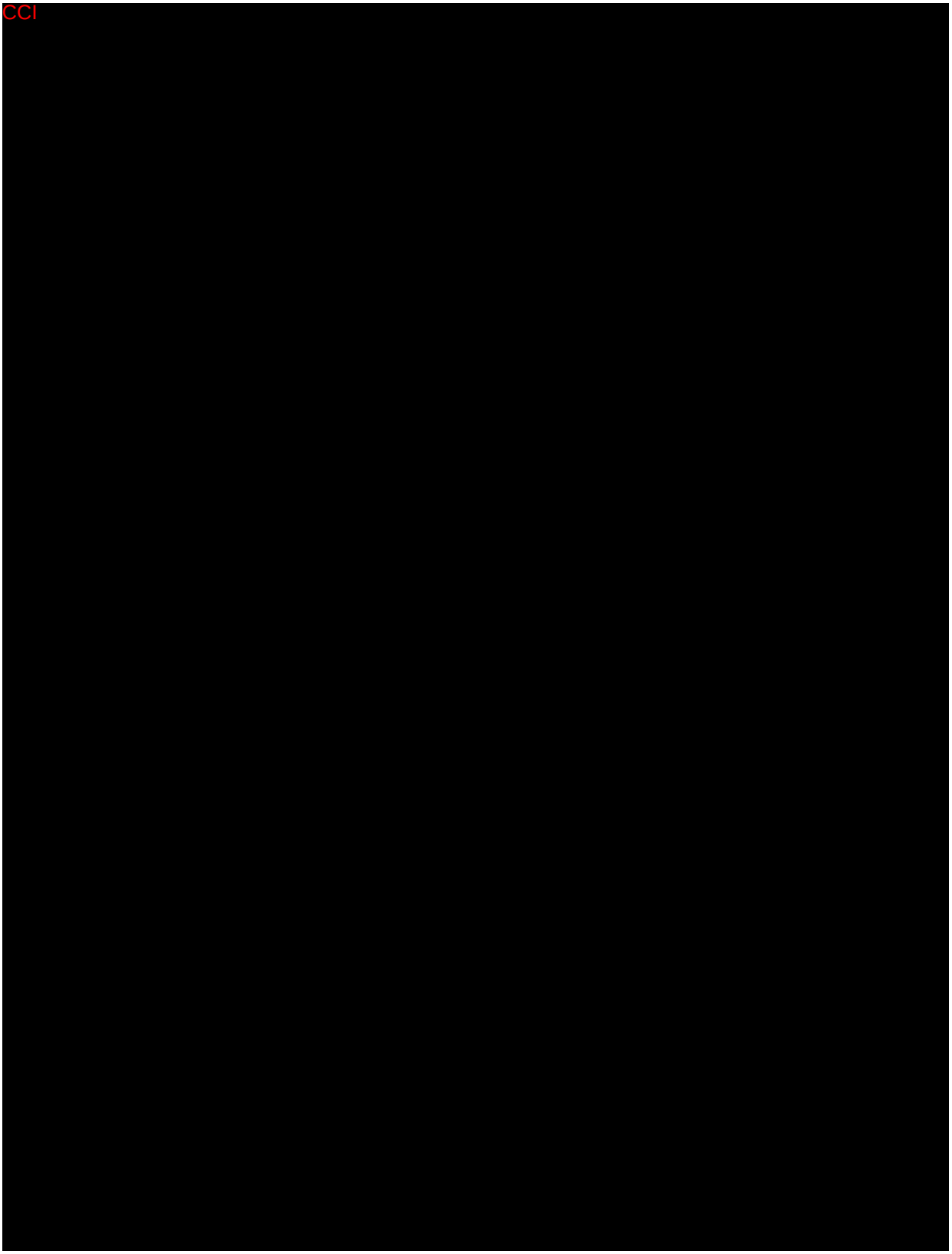

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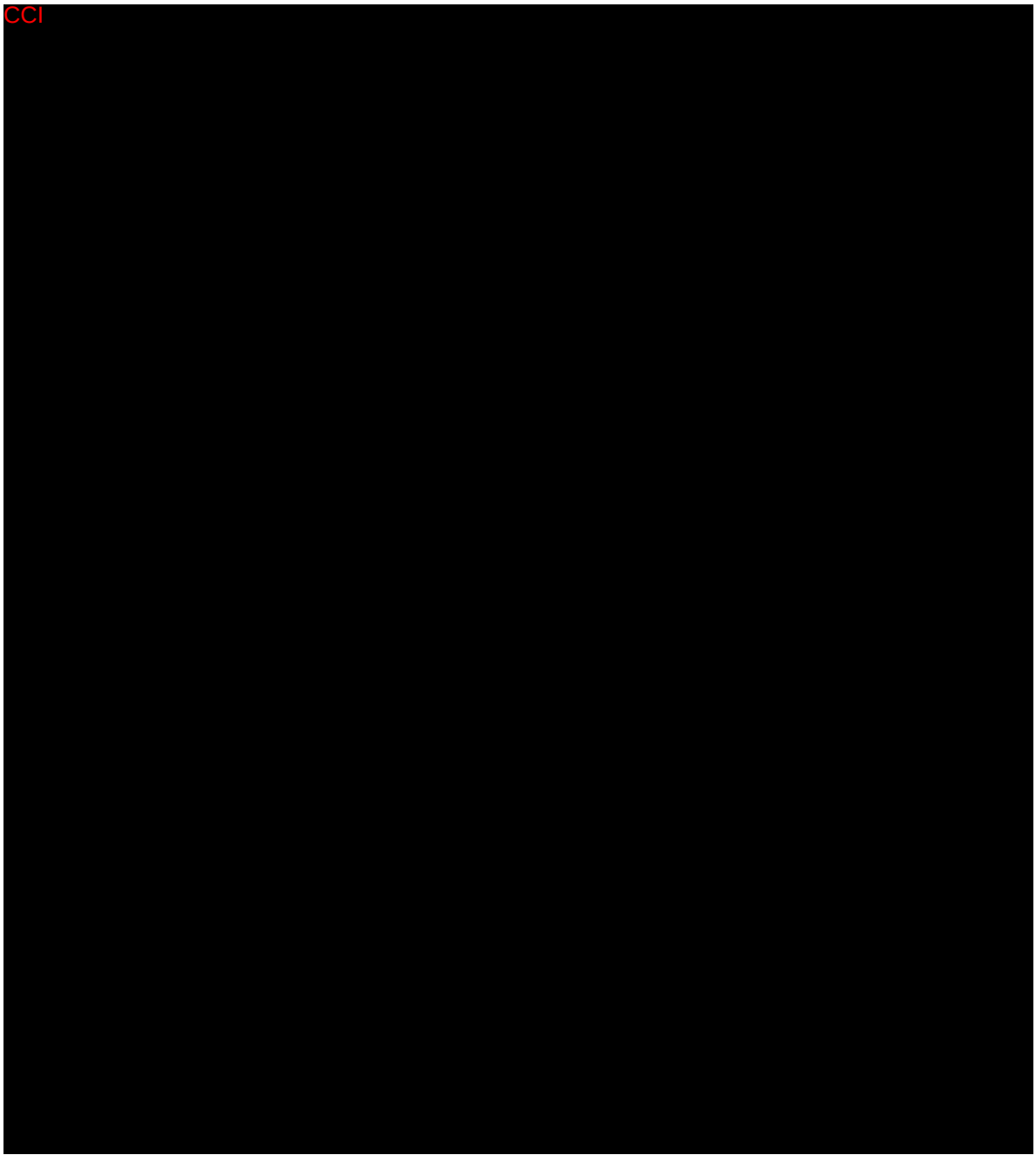
7.3 Labeling

This study is open-labeled. Therefore the patient, the investigator's site personnel and the Sponsor or its designee are not blinded to study treatment. Each vial of IP will be labeled with a single panel label.

Labels will be prepared in accordance with Good Manufacturing Practice and local regulatory guidelines. The labels will fulfill Good Manufacturing Practice Annex 13 requirements for labeling. Label text will be translated into local language.

Example labels for the CELLECTRA®5P Device (Pulse Generator, Applicator and Array) are shown below.



7.4 Storage

All study drugs should be kept in a secure place under appropriate storage conditions. The IP label on the vial and kit specifies the appropriate storage.

The study Sponsor will be responsible for assuring that the quality of the IP is adequate for the duration of the study.

7.4.1 Storage - MEDI0457

Vials must be stored at -25°C to -15°C (-13°F to 5°F) inside a -20°C freezer at all times upon receipt at the clinical site. A freezer temperature log must be monitored daily and maintained at the site.

7.4.2 Storage - Durvalumab

Vials will be shipped under refrigerated condition. A temperature monitor will track the temperature throughout the shipment and will indicate any excursion during the shipment. Vials must be stored at 2°C to 8°C (36°F to 46°F) upon receipt in a secure area with restricted access. A refrigerator temperature log must be monitored daily and maintained at the site. Vials should not be frozen.

7.5 Preparation and dispensing

It is the responsibility of the Investigator to ensure that IP is dispensed to study participants. It must be dispensed only from official study sites by authorized personnel according to local regulations and must be recorded appropriately on the IP accountability record.

7.5.1 Preparation and dispensing - MEDI0457

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7.5.2 Preparation and dispensing - Durvalumab

The dose of durvalumab for administration must be prepared by the investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

- 24 hours at 2°C to 8°C (36°F to 46°F)
- 4 hours at room temperature

Durvalumab will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

For the 1500 mg dose add 30 mL (750 mg dose add 15 mL) of durvalumab to the IV bag such that final concentration is within 1 mg/mL to 20 mg/mL. Mix the bag by gentle inversion to ensure homogeneity of the dose in the bag. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

Durvalumab will be administered at room temperature by controlled infusion into a peripheral or central vein. Following preparation of durvalumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 60 minutes (±5 minutes), using a 0.2 or 0.22-μm in-line filter. Less than 55 minutes is considered a deviation.

The IV line will be flushed with a volume of IV bag diluent 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.

Standard infusion time is 1 hour. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

In the event that either preparation time or infusion time exceeds the time limits, a new dose must be prepared from new vials. Durvalumab does not contain preservatives, and any unused portion must be discarded.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed.

7.6 Investigational product inspection

Each vial selected for dose preparation should be inspected.

During the inspection, if the solution is not clear or any turbidity, discoloration, or particulates are observed, notify your site monitor and store the vial(s) in QUARANTINE at refrigerated temperature of the IP under the appropriate storage conditions for drug accountability and potential future inspection.

If there are any defects noted with the IP, the Investigator and site monitor should be notified immediately.

7.7 Compliance

The administration of all study drugs (including IP) should be recorded in the appropriate sections of the CRF.

Treatment compliance will be assured by site reconciliation of the medication dispensed and returned.

7.8 Accountability

7.8.1 Accountability - investigational products

The study drug provided for this study will be used only as directed in the study protocol. Study drug accountability will be captured in the Interactive Voice and Web Response System.

It is the responsibility of the Investigator to ensure that a current record of IP disposition is maintained at each study site where IP is inventoried and disposed. Records or logs must comply with applicable regulations and guidelines, and should include:

- Amount received and placed in storage area
- Amount currently in storage area
- Label ID number or batch number and use date or expiry date
- Dates and initials of person responsible for each IP inventory entry / movement
- Amount dispensed to each patient, including unique patient identifiers
- Amount transferred to another area / site for dispensing or storage
- Amount returned to Sponsor or its designee
- Amount destroyed at study site, if applicable

7.8.2 Accountability - investigational device

Each clinical site is responsible for maintaining investigational device accountability. This includes recording the CELLECTRA®5P serial number, IM applicator serial number, and IM array lot number used for injection / EP of each patient. Site personnel will be required to download EP data and provide to MedImmune after each treatment.

7.9 Return and destruction of investigational products and investigational device

Upon completion or termination of the study, all unused and / or partially used IP must be returned to MedImmune, if not authorized by MedImmune or local regulations to be destroyed at the site.

If the IP is to be destroyed on site, it is the investigator's responsibility to ensure that arrangements have been made for the disposal, written authorization has been granted by MedImmune, procedures for proper disposal have been established according to applicable regulation and guidelines and institutional procedures, and appropriate records of the disposal have been documented. The unused IP can only be destroyed after being inspected and reconciled by the responsible Study Monitor.

The Study Monitor will account for all study drugs received at the site, unused study drugs and for appropriate destruction. Certificates of delivery, destruction and return should be signed.

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7.11 Post study access to study treatment

There are no plans to provide MEDI0457 or durvalumab (MEDI0457) after the completion of the study.

8. STATISTICAL ANALYSES

8.1 Statistical considerations

Statistical analyses will be performed by PRA.

A comprehensive Statistical Analysis Plan (SAP) will be developed.

8.2 Sample size estimate

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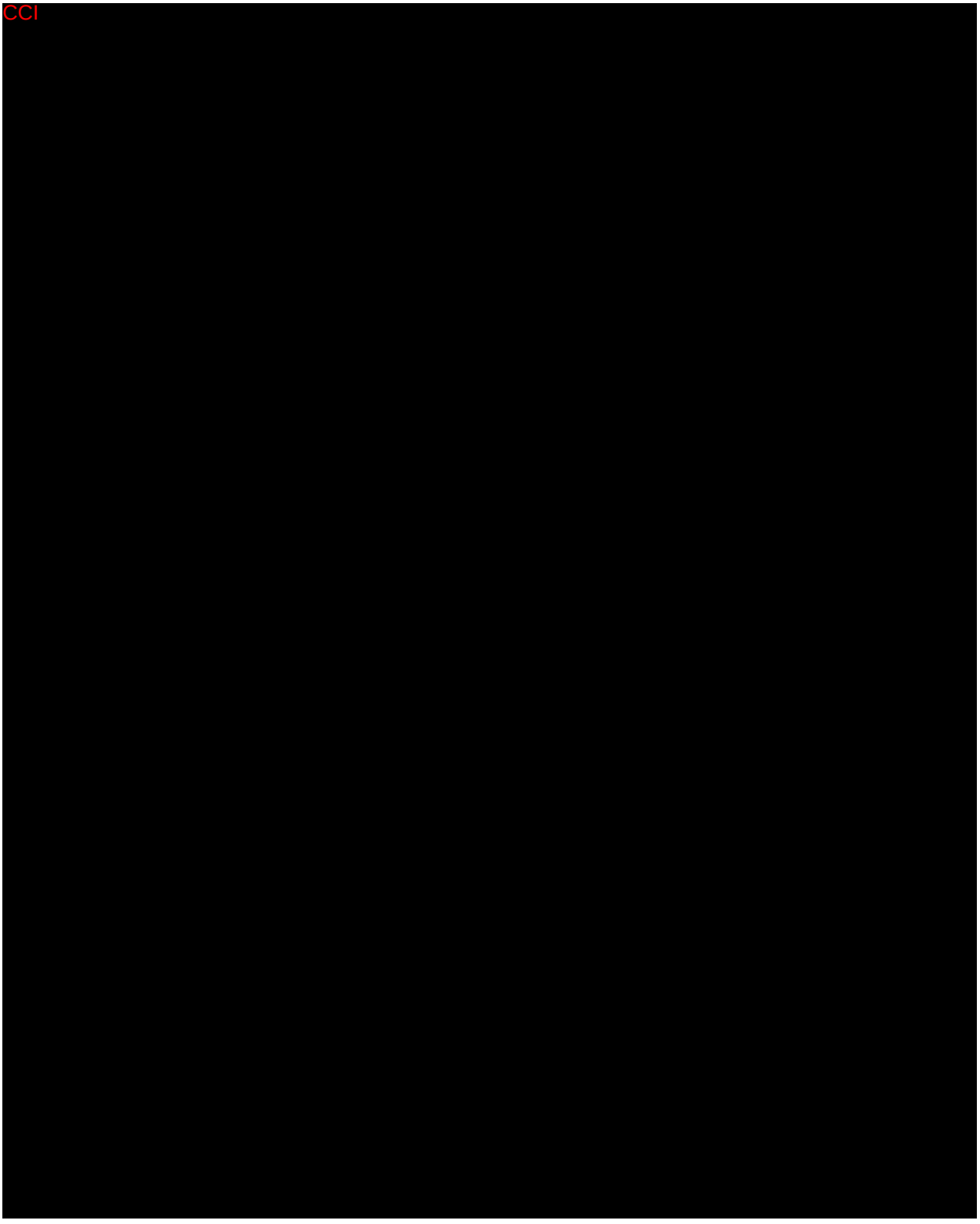
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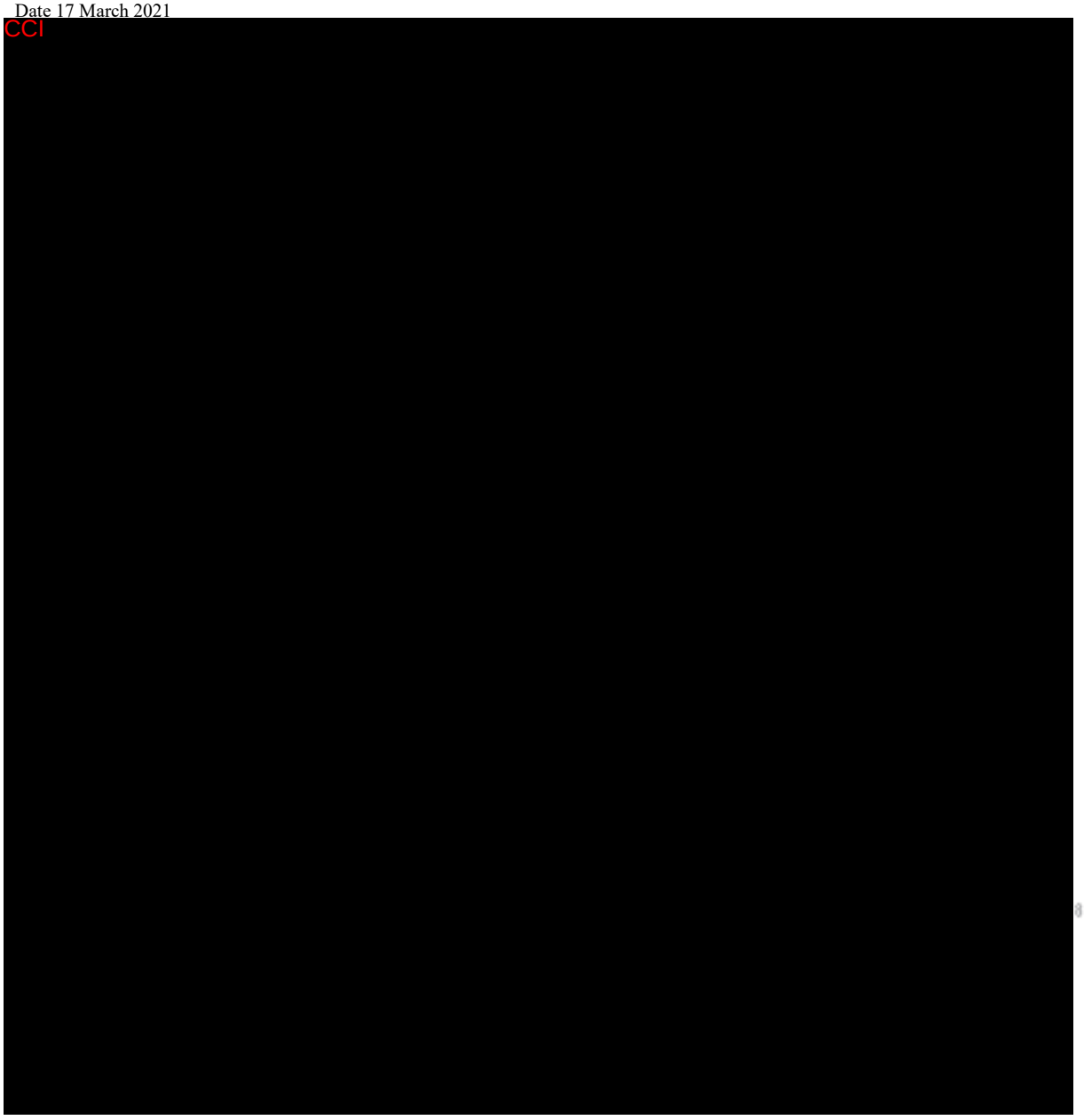

8.3 Definitions of analysis sets

The analysis of data will be based on different subsets according to the purpose of the analysis, i.e., efficacy, safety and pharmacokinetic, respectively. Patients in the Safety Analysis Run-in period will be included in the analysis sets as applicable (i.e., meet the analysis set definitions).

8.3.1 Efficacy analysis set

Response-evaluable Population: The co-primary endpoint of ORR by RECIST version 1.1 will be based on the Response-evaluable Population. This population will include all patients with confirmed HPV-16 or HPV-18 associated disease who have received one dose of both study drugs, have a baseline scan with measurable disease at baseline and either (i) at least one

on treatment scan or (ii) patients who discontinue due to disease progression or (iii) death without an on-treatment scan.

Secondary efficacy analyses will be based on both the Response-evaluable and the As-treated populations. The As-treated Population will include all patients who receive any IP (defined as at least one dose of either study drug).

Table 9 provides a summary of the efficacy endpoints with their corresponding methods of assessment and populations.

Table 9 A Summary of Efficacy Endpoints with Corresponding Methods of Assessment and Populations

Type of efficacy endpoint	Endpoint	Method	Population(s)
Co-primary	ORR	RECIST version 1.1	Response-evaluable
Secondary	ORR	RECIST version 1.1	As-treated
	ORR	irRECIST	Response-evaluable and As-treated
	DCR-16w	RECIST version 1.1	Response-evaluable and As-treated
	PFS	RECIST version 1.1	Response-evaluable and As-treated
	OS	Kaplan-Meier	Response-evaluable and As-treated

Abbreviations
DCR-16w=disease control rate at 16 weeks, irRECIST=Immune-Related Response Evaluation Criteria in Solid Tumors, ORR=objective response rate, OS=overall survival, PFS=progression free survival, RECIST= Response Evaluation Criteria in Solid Tumors

8.3.2 Safety analysis set

The safety evaluation will be based on the As-treated Population and the Safety Analysis Set will include all patients who receive any IP (defined as at least one dose of either study drug).

8.3.3 Pharmacokinetics analysis set

The Pharmacokinetic Analysis Set will include all patients who receive at least one dose of durvalumab and have at least one evaluable post-dose serum concentration measurement of durvalumab.

8.4 Outcome measures for analyses

8.4.1 Primary endpoints

The co-primary endpoints are the assessment of safety (including AEs, SAEs, laboratory evaluations, vital signs, ECG, performance status assessments, physical examinations and concomitant medications) and ORR by RECIST version 1.1.

8.4.1.1 Adverse events

Adverse event data will be summarized by the percentage of patients with AEs. Adverse events (both in terms of MedDRA preferred terms and CTCAE grade) will be listed individually by patient.

Any AE occurring before treatment with IP will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring within 90 days of discontinuation of IP may be included in the AE summaries, but the majority of those summaries will omit those AEs observed after a patient has received further therapy for cancer. Further details will be provided in the SAP. Any events in this period that occur after a patient has received further therapy for cancer (following discontinuation of IP) will be flagged in the data listings.

A separate data listing of AEs occurring more than 90 days after discontinuation of IP will be produced. These events will not be included in AE summaries.

8.4.1.2 Safety assessments

For the change from baseline summaries for vital signs, laboratory data, ECGs, performance status, and physical examination, the baseline value will be the latest result obtained prior to the start of study treatment. Concomitant medication data will be listed only.

8.4.1.3 Investigator RECIST version 1.1-based assessments

All RECIST assessments, whether scheduled or unscheduled, will be included in the calculations. This is also regardless of whether a patient discontinues study treatment or receives another anticancer therapy.

At each visit, patients will be assigned a RECIST version 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments by the Investigator. Note: at the discretion of the Sponsor, an independent central review of all scans used in the assessment of tumors by RECIST version 1.1 and/or irRECIST may be conducted (refer to Section 5.3 for further details). Baseline will be assessed within the 28 days prior to enrollment. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (unless there is evidence of progression in which case the response will be assigned as PD).

Please refer to Appendix F for the definitions of CR, PR, SD, and PD.

Objective Response Rate (ORR)

Objective response rate is defined as the number (%) of patients with at least one visit response of CR or PR via RECIST 1.1 and will be based on the Response-evaluable Population for the co-primary endpoint.

8.4.2 Secondary efficacy endpoints

Objective Response Rate (ORR)

Objective response rate will be assessed as a secondary endpoint in the As-treated Population using RECIST version 1.1. Objective response rate will be also assessed in the Response-evaluable and As-treated populations using irRECIST (Appendix G).

Progression Free Survival (PFS)

Progression free survival measures progression by growth of the primary tumor, nodal spread metastases, death from the cancer, or death from other causes. Progression free survival will be assessed by the periodic tumor assessment using imaging per the institutional guidelines at the schedules according to Table 3.

All study evaluations for disease response must be based on RECIST version 1.1 (Appendix F).

Progression free survival will be defined as the time from the date of start of IP treatment until the documentation of disease progression according to RECIST version 1.1 or death due to any cause, whichever occurs first. Patients who have not progressed or died at the time of the analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST version 1.1 assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST version 1.1 assessment prior to two missed visits.

The PFS time will always be derived based on scan / assessment / death dates and not visit dates.

RECIST version 1.1 assessment / scans contributing towards a particular visit may be performed on different dates. The following rule will be applied:

For investigator assessments, the date of progression will be determined based on the earliest of the RECIST version 1.1 assessment / scan dates of the component that indicates progression.

When censoring a patient for PFS, the patient will be censored at the latest of the dates contributing to a particular overall visit assessment.

Note: For target lesions, only the latest scan date is recorded out of all scans performed at that assessment for the target lesions, and similarly for non-target lesions, only the latest scan date is recorded out of all scans performed at that assessment for the non-target lesions.

PFS will be assessed in the Response-evaluable and As-treated populations.

Disease Control Rate (DCR)

Disease control rate is defined as N (%) patients with CR, PR, or SD by 16 weeks on study using RECIST version 1.1. For SD determination for DCR, the patient must have lack of progression for the first 16 weeks on study. Disease control rate will be assessed in the Response-evaluable and As-treated populations.

Overall Survival (OS)

Overall survival is defined as the time from the date of start of IP treatment until death (+1 day) due to any cause. Any patient not known to have died at the time of analysis will be censored based on the last recorded date on which the patient was known to be alive. Overall survival will be assessed in the Response-evaluable and As-treated populations.

8.4.2.1 Pharmacokinetics and antibodies for durvalumab

The actual sampling times will be used in the pharmacokinetic calculations. Durvalumab concentration data and summary statistics will be tabulated. Individual and mean serum durvalumab concentration-time profiles will be generated.

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADA for durvalumab. The immunogenicity titer will be reported for samples confirmed positive for the presence of ADA.

8.5 Methods for statistical analyses

Demographic and baseline characteristics will be summarized with means, medians, standard deviations, ranges or percentages.

8.5.1 Analysis of the primary variable(s)

8.5.1.1 Safety

Safety will be summarized by the percentage of patients with AEs, with grading according to NCI CTCAE version 4.03 and attribution. Summary statistics will also be provided for serious AEs, hematology, urinalysis, CPK, thyroid function testing, pregnancy test, ECG, vital sign, performance status, physical examinations and concomitant medications.

8.5.2 Analysis of the secondary variable(s)

8.5.2.1 Pharmacokinetic analysis

Pharmacokinetic concentration data and summary statistics will be tabulated. Individual and mean blood concentration-time profiles will be generated. Due to the sparse pharmacokinetic sampling used in this study, formal non-compartmental analysis to derive pharmacokinetic parameters (e.g., terminal half-life) will not be conducted. A population pharmacokinetic model may be developed with similar data from other studies to further characterize the pharmacokinetic properties of durvalumab when administered in combination with MEDI0457.

8.5.2.2 Anti-drug antibody analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable ADA for durvalumab. The immunogenicity titers will be reported for samples confirmed positive for the presence of ADA. The effect of immunogenicity on pharmacokinetic and its potential association with efficacy, safety and / or tolerability will be performed, if the data allow.

8.5.2.3 Anti-tumor analysis – objective response rate, disease control rate at 16 weeks, progression free survival and overall survival

Summary statistics will be provided for ORR and DCR. Progression free survival and OS will be estimated using the Kaplan-Meier method. Median survival times and corresponding 95% confidence intervals will be provided.

8.5.3 Exploratory analysis

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8.5.4 Subgroup analysis

Any subgroup analysis will be pre-planned and specified in the SAP.

9. STUDY AND DATA MANAGEMENT

9.1 Training of study site personnel

Before the first patient is entered into the study, it is necessary for a representative of PRA to visit the investigational study site to:

- Determine the adequacy of the facilities
- Determine availability of appropriate patients for the study
- Discuss with the investigator(s) (and other personnel involved with the study) their responsibilities with regard to protocol adherence, and the responsibilities of MedImmune or its representatives. This will be documented in the Clinical Study Agreement between PRA and the Investigator.

Site personnel will be required to complete Electronic Data Capture training before the first patient is entered into the study.

Before the first patient is entered into the study, a PRA 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 the WBDC 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).

9.2 Monitoring of the study

PRA will perform the monitoring of the study.

During the study, a PRA 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 CRFs, 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 CRFs with the patient's medical records at the hospital or practice, and other records relevant to the study) including verification of informed consent of participating patients. This will require direct access to all original records for each patient (e.g., clinic charts)

- Ensure withdrawal of informed consent to the use of the patient's biological samples is reported and biological samples are identified and disposed of / destroyed accordingly, and the action is documented, and reported to the patient.

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

9.2.1 Source data

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

9.2.2 Study agreements

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

Agreements between MedImmune and the Principal Investigator should be in place before any study-related procedures can take place, or patients are enrolled.

9.2.3 Archiving of study documents

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

9.2.4 Deviation from the clinical study protocol

The investigator(s) must not deviate from or make any changes to the protocol without documented agreement between the Principal Investigator and MedImmune or the Institutional Review Board (IRB) approval based on its deliberations. However, this shall not apply to cases where the deviation or change is necessary to avoid an immediate hazard to the patients or for other compelling medical reasons, or where the changes involve only logistical or administrative aspects of the clinical study (e.g., changes to the organization / structure of the MedImmune, the name / department name of the study site, the address or phone number of the study site or MedImmune, the job title of the investigator, and monitors).

The investigator(s) should document any deviation from the protocol regardless of their reasons. Only when the protocol was not followed in order to avoid an immediate hazard to the patients or for other medically compelling reason, the Investigator should prepare and submit the records explaining the reasons thereof to MedImmune and the head of study site, and retain a copy of the records.

The investigator(s) may deviate from or make a change to the protocol without documented agreement between the Principal Investigator and MedImmune or the IRB approval, only in the event of a medical emergency, e.g., it is only way to avoid an immediate hazard to the patients. In such case, the Principal Investigator must notify details of the deviation or change, the reason, and a proposed revision in the protocol if required, to MedImmune and the head of the study site and IRB via the head of the study site as soon as possible, in order to obtain their approval. A certificate of approval by the head of the study site as well as MedImmune should be obtained via the head of the study site.

9.3 Study timetable and end of study

The end of the study is defined as 'the last visit of the last patient undergoing the study'.

The study started in Quarter 4 2016 and is expected to end by Quarter 4 2019.

The study may be terminated at individual centers if the study procedures are not being performed according to Good Clinical Practice (GCP), or if recruitment is slow. MedImmune may also terminate the entire study prematurely if concerns for safety arise within this study or in any other study with MEDI0457 and durvalumab.

9.4 Data management

Data management will be performed by PRA Data Management Center staff according to the Data Management Plan.

Data will be entered in the WBDC system at the study site. Trained study staff will be responsible for entering data on the observations, tests and assessments specified in the protocol into the WBDC system and according to the CRF instructions. The CRF instructions will also guide the study site in performing data entry. Data entered in the WBDC system will be immediately saved to a central database and changes tracked to provide an audit trail. The data will then be Source Data Verified, reviewed / queried and updated as needed. The data will be validated as defined in the Data Management Plan.

Data queries will be raised for inconsistent, impossible or missing data. All entries to the study database will be available in an audit trail. Quality control procedures will be applied to each stage of data handling to ensure that all data are reliable and have been processed correctly.

Adverse events and medical / surgical history will be classified according to the terminology of the latest version of the MedDRA and the WHO Drug Reference Dictionary. Medications will be classified according to the WHO Reference Drug Dictionary. All coding will be performed by the Medical Coding Team at PRA. Note: the most current version of WHO Drug Reference Dictionary will be used. Laboratory data will be coded using NCI CTCAE version 4.03.

Relevant pain scale forms will be filled in by the patients or study staff according to age-appropriate guidelines within this protocol.

The data will be frozen and then locked to prevent further editing. When all data have been coded, validated, signed, and locked, a clean file will be declared. A copy of the completed CRFs will be archived at the study site when the study has been locked.

Serious adverse event reconciliation

Serious adverse event reconciliation reports are produced and reconciled with the Patient Safety database and / or the investigational site.

Data management of genotype data

Refer to Appendix C.

Data associated with human biological samples

Data associated with biological samples will be transferred from laboratory(ies) internal or external to MedImmune.

10. ETHICAL AND REGULATORY REQUIREMENTS

10.1 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 International Council for Harmonisation (ICH) / GCP, applicable regulatory requirements and the MedImmune policy on Bioethics and Human Biological Samples.

10.2 Patient data protection

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

10.3 Ethics and regulatory review

An Ethics Committee (EC) 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 patients. The Investigator will ensure the distribution of these documents to the applicable EC, and to the study site staff.

The opinion of the EC should be given in writing. The Investigator should submit the written approval to MedImmune before enrollment of any patient into the study.

The EC should approve all advertising used to recruit patients for the study.

PRA 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 EC annually.

Before enrollment of any patient 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.

PRA will handle the distribution of any of these documents to the national Regulatory Authorities.

PRA will provide Regulatory Authorities, ECs and Principal Investigators with safety updates / reports according to local requirements.

Each Principal Investigator is responsible for providing the ECs / IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP. PRA will provide this information to the Principal Investigator so that he / she can meet these reporting requirements.

10.4 Informed consent

The Principal Investigator(s) at each center will:

- Ensure each patient is given full and adequate oral and written information about the nature, purpose, possible risk and benefit of the study.
- Ensure each patient is notified that they are free to discontinue from the study at any time.
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided.
- Ensure each patient 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 patient.
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC.

10.5 Changes to the protocol and informed consent form

Study procedures will not be changed without the mutual agreement of the Principal 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 (Revised Clinical Study Protocol).

The amendment is to be approved by the relevant EC 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 EC see Section 10.3.

If a protocol amendment requires a change to a center's ICF, MedImmune and the center's EC 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 EC.

10.6 Audits and inspections

Authorized representatives of MedImmune, a regulatory authority, or an EC 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 center.

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Durvalumab Investigator's Brochure

Durvalumab (MEDI4736) Investigator's Brochure

European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4)

European Medicines Agency's "Guideline on the evaluation of anti-cancer medicinal products in man" (EMA/CHMP/205/95/Rev.4)

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MEDI0457 Investigator's Brochure

MEDI0457 (INO-3112) Investigator's Brochure

NCI CTCAE version 4.03

The CTCAE version 4.03 can be accessed via the following link: https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf

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Appendix A Additional Safety Information

Further Guidance on the Definition of a Serious Adverse Event (SAE)

Life-threatening

'Life-threatening' means that the patient was at immediate risk of death from the adverse event (AE) as it occurred or it is suspected that use or continued use of the product would result in the patient's death. 'Life-threatening' does not mean that had an AE occurred in a more severe form it might have caused death (e.g., hepatitis that resolved without hepatic failure).

Hospitalization

Outpatient treatment in an emergency room is not in itself a serious AE, although the reasons for it may be (e.g., bronchospasm, laryngeal edema). Hospital admissions and / or surgical operations planned before or during a study are not considered AEs if the illness or disease existed before the patient was enrolled in the study, provided that it did not deteriorate in an unexpected way during the study.

Important medical event or medical intervention

Medical and scientific judgment should be exercised in deciding whether a case is serious in situations where important medical events may not be immediately life-threatening or result in death, hospitalization, disability or incapacity but may jeopardize the patient or may require medical intervention to prevent one or more outcomes listed in the definition of serious. These should usually be considered as serious.

Simply stopping the suspect drug does not mean that it is an important medical event; medical judgment must be used.

- Angioedema not severe enough to require intubation but requiring IV hydrocortisone treatment
- Hepatotoxicity caused by acetaminophen overdose requiring treatment with N-acetylcysteine
- Intensive treatment in an emergency room or at home for allergic bronchospasm
- Blood dyscrasias (e.g., neutropenia or anemia requiring blood transfusion, etc) or convulsions that do not result in hospitalization
- Development of drug dependency or drug abuse

A Guide to Interpreting the Causality Question

When making an assessment of causality consider the following factors when deciding if there is a 'reasonable possibility' that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, other host or environmental factors.

- Re-challenge experience. Did the AE reoccur if the suspected drug was reintroduced after having been stopped? MedImmune would not normally recommend or support a re-challenge.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship.

In difficult cases, other factors could be considered such as:

- Is this a recognized feature of overdose of the drug?

- Is there a known mechanism?

Causality of 'related' is made if following a review of the relevant data, there is evidence for a 'reasonable possibility' of a causal relationship for the individual case. The expression 'reasonable possibility' of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship.

The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as 'not related'.

Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

Appendix B International Airline Transportation Association (IATA) 6.2 Guidance Document

Labeling and shipment of biohazard samples

International Airline Transportation Association (IATA) classifies biohazardous agents into three categories. For transport purposes the classification of infectious substances according to Risk Groups was removed from the Dangerous Goods Regulations in the 46th edition (2005). Infectious substances are now classified either as Category A, Category B or Exempt. There is no direct relationship between Risk Groups and categories A and B.

Category A Infectious Substances are infectious substances in a form that, when exposure to it occurs, is capable of causing permanent disability, life-threatening or fatal disease in otherwise healthy humans or animals. Category A pathogens are e.g., Ebola, Lassa fever virus:

- Are to be packed and shipped in accordance with IATA Instruction 602.

Category B Infectious Substances are infectious Substances that do not meet the criteria for inclusion in Category A. Category B pathogens are e.g., Hepatitis A, B, C, D, and E viruses, Human immunodeficiency virus types 1 and 2. They are assigned the following UN number and proper shipping name:

- UN 3373 – Biological Substance, Category B
- Are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

- Clinical trial samples will fall into Category B or exempt under IATA regulations.
- Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.
- Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.
- IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.
- Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging / containment materials at all times. The IATA 650 biological sample

containment standards are encouraged wherever possible when road or rail transport is used.

Appendix C Pharmacogenetics Research

Background and Rationale

MedImmune intends to perform genetic research in the MEDI0457 and durvalumab clinical development programme to explore how genetic variations may affect the clinical parameters associated with MEDI0457 and durvalumab. Collection of DNA samples from populations with well described clinical characteristics may lead to improvements in the design and interpretation of clinical trials and, possibly, to genetically guided treatment strategies.

Future research may suggest other genes or gene categories as candidates for influencing not only response to MEDI0457 and durvalumab but also susceptibility to recurrent / metastatic head and neck cancer associated with HPV-16 and / or HPV-18 for which MEDI0457 and durvalumab may be evaluated. Thus, this genetic research may involve study of additional un-named genes or gene categories, but only as related to disease susceptibility and drug action.

Genetic Research Objectives

The objective of this research is to collect and store DNA for future exploratory research into genes / genetic variation that may influence response (i.e., distribution, safety, tolerability and efficacy) to recurrent / metastatic head and neck cancer associated with HPV-16 and / or HPV-18.

Genetic Research Plan and Procedures

Selection of genetic research population

Study selection record

All patients will be asked to participate in this genetic research. Participation is voluntary and if a patient declines to participate there will be no penalty or loss of benefit. The patient will not be excluded from any aspect of the main study.

Inclusion criteria

For inclusion in this genetic research, patients must fulfill all of the inclusion criteria described in the main body of the Clinical Study Protocol **and**:

- Provide informed consent for the genetic sampling and analyses.

Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main study or any of the following:

- Previous allogeneic bone marrow transplant
- Non-leukocyte depleted whole blood transfusion in 120 days of genetic sample collection

Discontinuation of patients from this genetic research

Specific reasons for discontinuing a patient from this genetic research are:

Withdrawal of consent for genetic research: Patients may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in Section 3.9 of the main Clinical Study Protocol.

Collection of samples for genetic research

The blood sample for genetic research will be obtained from the patients at Week 1, Week 8, Week 10 and Week 16 (Table 3). Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding patients who may withdraw due to an adverse event (AE), such patients would be important to include in any genetic analysis. If for any reason the sample is not drawn at a scheduled visit at Week 1, Week 8, Week 10 and Week 16, it may be taken at any visit until the last study visit. Samples will be collected, labeled, stored and shipped as detailed in the Laboratory Manual.

Coding and storage of DNA samples

The processes adopted for the coding and storage of samples for genetic analysis are important to maintain patient confidentiality. Samples will be stored for a maximum of 25 years, from the date of last patient last visit, after which they will be destroyed. DNA is a finite resource that is used up during analyses. Samples will be stored and used until no further analyses are possible or the maximum storage time has been reached.

For all samples irrespective of the type of coding used the DNA will be extracted from the blood sample. The DNA sample will be assigned a unique number replacing the information on the sample tube. Thereafter, the DNA sample will be identifiable by the unique DNA number only. The DNA number is used to identify the sample and corresponding data at the MedImmune genetics laboratories, or at the designated contract laboratory. No personal details identifying the individual will be available to any person (MedImmune employee or contract laboratory staff working with the DNA.)

The samples and data for genetic analysis in this study will be single coded. The link between the patient enrollment code and the DNA number will be maintained and stored in a secure environment, with restricted access within the Clinical Genotyping Group Laboratory

Information Management System (LIMS) at MedImmune. The link will be used to identify the relevant DNA samples for analysis, facilitate correlation of genotypic results with clinical data, allow regulatory audit and to trace samples for destruction in the case of withdrawal of consent.

Ethical and Regulatory Requirements

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in Section 10 of the main Clinical Study Protocol.

Informed consent

All patients must sign the informed consent prior to any study-related procedures being performed.

Patient data protection

MedImmune will not provide individual genotype results to patients, 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 patient. In exceptional circumstances, however, certain individuals might see both the genetic data and the personal identifiers of a patient. For example, in the case of a medical emergency, a MedImmune Physician or an Investigator might know a patient's identity and also have access to his or her genetic data. Also Regulatory Authorities may require access to the relevant files, though the patient's medical information and the genetic files would remain physically separate.

Data management

Any genotype data generated in this study will be stored in the MedImmune genotyping LIMS database, or other appropriate secure system within MedImmune and / or third party contracted to work with MedImmune to analyze the samples.

The results from this genetic research may be reported in the Clinical Study Report for the main study, or in a separate report as appropriate.

Genotype data will be transferred to the clinical database, and merged with the clinical data from the main study, prior to the statistical analysis and reporting of the study.

Statistical methods and determination of sample size

The number of patients that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A SAP will be prepared where appropriate.

Appendix D Actions Required in Cases of Increases in Liver Biochemistry and Evaluation of Hy's Law

Introduction

During the course of the study the Investigator will remain vigilant for increases in liver biochemistry. The Investigator is responsible for determining whether a patient meets potential Hy's Law (PHL) criteria at any point during the study.

The Investigator participates, together with MedImmune clinical project representatives, in review and assessment of cases meeting PHL criteria to agree whether Hy's Law (HL) criteria are met. Hy's Law criteria are met if there is no alternative explanation for the elevations in liver biochemistry other than Drug Induced Liver Injury (DILI) caused by the Investigational Product (IP).

The Investigator is responsible for recording data pertaining to PHL / HL cases and for reporting adverse events (AEs) and serious adverse events (SAEs) according to the outcome of the review and assessment in line with standard safety reporting processes.

Definitions

Potential Hy's Law

A PHL case is defined as a study patient with an increase in serum aspartate aminotransferase (AST) or alanine aminotransferase (ALT) ≥ 3 x upper limit of normal (ULN) **together with** total bilirubin (TBL) ≥ 2 x ULN, irrespective of an increase in alkaline phosphatase (ALP), at any point during the study following the start of study medication.

Hy's Law

A HL case is defined as a study patient with an increase in serum AST or ALT ≥ 3 x ULN **together with** TBL ≥ 2 x ULN, where no other reason, other than the IP, can be found to explain the combination of increases, e.g., elevated ALP indicating cholestasis, viral hepatitis, another drug.

For PHL and HL, the elevation in transaminases must precede or be coincident with (i.e., on the same day) the elevation in TBL, but there is no specified timeframe within which the elevations in transaminases and TBL must occur.

Identification of Potential Hy's Law Cases

In order to identify cases of PHL, it is important to perform a comprehensive review of laboratory data for any patient who meets any of the following identification criteria in isolation or in combination:

- ALT ≥ 3 x ULN
- AST ≥ 3 x ULN
- TBL ≥ 2 x ULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the Investigator (also sent to MedImmune representative).

The Investigator will also remain vigilant for any local laboratory reports where the identification criteria are met, where this is the case the Investigator will:

- Notify the MedImmune representative.
- Request a repeat of the test (new blood draw) by the central laboratory.
- Complete the appropriate unscheduled laboratory CRF module(s) with the original local laboratory test result.

When the identification criteria are met from central or local laboratory results the Investigator will without delay:

- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits (including both central and local laboratory results).

The Investigator will without delay review each new laboratory report and if the identification criteria are met will:

- Notify the MedImmune representative.
- Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits. Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.
- Promptly enter the laboratory data into the laboratory CRF.

Follow-up

Potential Hy's Law Criteria not Met

If the patient does not meet PHL criteria the Investigator will:

- Perform follow-up on subsequent laboratory results according to the guidance provided in the Clinical Study Protocol.

Potential Hy's Law Criteria Met

If the patient does meet PHL criteria the Investigator will:

- Determine whether PHL criteria were met at any study visit prior to starting study treatment (See Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment).

- Notify the MedImmune representative who will then inform the central Study Team.

The Study Physician contacts the investigator, to provide guidance, discuss and agree an approach for the study patients' follow-up and the continuous review of data. Subsequent to this contact the Investigator will:

- Monitor the patient until liver biochemistry parameters and appropriate clinical symptoms and signs return to normal or baseline levels, or as long as medically indicated.

- Investigate the etiology of the event and perform diagnostic investigations as discussed with the Study Physician.

- Complete the three Liver CRF Modules as information becomes available.

- If at any time (in consultation with the Study Physician) the PHL case meets serious criteria, report it as an SAE using standard reporting procedures.

Review and Assessment of Potential Hy's Law Cases

The instructions in this Section should be followed for all cases where PHL criteria are met.

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the Investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP. The MedImmune Medical Science Director and Global Safety Physician will also be involved in this review together with other patient matter experts as appropriate.

According to the outcome of the review and assessment, the Investigator will follow the instructions below.

If there is an agreed alternative explanation for the ALT or AST and TBL elevations, a determination of whether the alternative explanation is an AE will be made and subsequently whether the AE meets the criteria for an SAE:

- If the alternative explanation is **not** an AE, record the alternative explanation on the appropriate CRF.
- If the alternative explanation is an AE / SAE, record the AE / SAE in the CRF accordingly and follow the AZ standard processes.

If it is agreed that there is **no** explanation that would explain the ALT or AST and TBL elevations other than the IP:

- Report an SAE (report term 'Hy's Law') according to MedImmune standard processes.
  - The 'Medically Important' serious criterion should be used if no other serious criteria apply.
  - As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

If, there is an unavoidable delay, of over 3 weeks, in obtaining the information necessary to assess whether or not the case meets the criteria for HL, then it is assumed that there is no alternative explanation until such time as an informed decision can be made:

- Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above.
- Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment

This section is applicable to patients with liver metastases who meet PHL criteria on study treatment having previously met PHL criteria at a study visit prior to starting study treatment.

At the first on study treatment occurrence of PHL criteria being met the Investigator will:

- Determine if there has been a significant change in the patients' condition[#] compared with the last visit where PHL criteria were met[#]

  – If there is no significant change no action is required

  – If there is a significant change notify the MedImmune representative, who will inform the central Study Team, then follow the subsequent process described in Potential Hy's Law Criteria Met of this Appendix

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of whether there has been a significant change will be at the discretion of the investigator, this may be in consultation with the Study Physician if there is any uncertainty.

Actions Required for Repeat Episodes of Potential Hy's Law

This section is applicable when a patient meets PHL criteria on study treatment and has already met PHL criteria at a previous on study treatment visit.

The requirement to conduct follow-up, review and assessment of a repeat occurrence(s) of PHL is based on the nature of the alternative cause identified for the previous occurrence.

The Investigator should determine the cause for the previous occurrence of PHL criteria being met and answer the following question:

- Was the alternative cause for the previous occurrence of PHL criteria being met found to be the disease under study e.g., chronic or progressing malignant disease, severe infection or liver disease, or did the patient meet PHL criteria prior to starting study treatment and at their first on study treatment visit as described in Actions Required When Potential Hy's Law Criteria are Met Before and After Starting Study Treatment?

If No: follow the process described in Potential Hy's Law Criteria Met of this Appendix

If Yes:

Determine if there has been a significant change in the patient's condition[#] compared with when PHL criteria were previously met

- If there is no significant change no action is required.

- If there is a significant change follow the process referred to in Appendix H.

[#] A 'significant' change in the patient's condition refers to a clinically relevant change in any of the individual liver biochemistry parameters (ALT, AST or TBL) in isolation or in combination, or a clinically relevant change in associated symptoms. The determination of

whether there has been a significant change will be at the discretion of the investigator; this may be in consultation with the Study Physician if there is any uncertainty.

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

Appendix E CELLECTRA®5P Error Reporting Form

Please complete the form and fax to PPD **or scan the form to** PPD

Protocol#_________ **Site#**______ **Patient ID**_________ **Week#**_______ **Visit Date**_______

DEVICE INFORMATION

CELLECTRA®5P Serial No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the front cover

CELLECTRA®5P Applicator Serial No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the handle

CELLECTRA® Array Lot No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the package

Time of Electroporation (EP): _________ **Location of Treatment/EP:** ☐ Deltoid **R**ight/**L**eft __________

☐ Other Location, specify:_______________ **IM-5P, was the EP Guide used?** ☐ YES ☐ NO

If EP Guide was used, please provide reason and include patient's BMI.

Was injection successful? ☐ YES ☐ NO

If NO, please provide reason and include needle gauge and syringe volume used.

Did the display on the device read Electroporation successful? ☐ YES ☐ NO

If NO, please check all complications that led to failure and describe complication below

☐ Impedance Test Error message displayed, fill out Impedance Test Error section below

☐ Electroporation Error message displayed, fill out Electroporation Error section below

☐ EP aborted by trigger or keypad error message displayed

☐ Battery level too low for EP message displayed

☐ Difficulty inserting array into muscle or skin

☐ Other, please specify below

Describe device complication below (continue on back if necessary):

Total # of arrays used: _____________

<u>Impedance Test Error</u>

Was the array inserted in patient's arm? ☐ YES ☐ NO Total # of attempts: __________

Were all attempts performed on the same day? ☐ YES ☐ NO (provide other date(s):___________)

Was a different location used for each attempt? ☐ YES ☐ NO

Was a new array used for each attempt? ☐ YES ☐ NO

Please provide any additional information below (continue on back if necessary):

<u>Electroporation Error</u>

Were there 3 (IM) or 4 (ID) involuntary muscle contractions? ☐ YES ☐ NO (how many__________

Was the array fully inserted in the patient's arm? ☐ YES ☐ NO

Was the array inserted perpendicular to the patient's skin? ☐ YES ☐ NO

Did the needles of the array appear damaged in any way? ☐ YES ☐ NO

If you were provided a sharps shuttle, please eject the array into a shuttle and ship to Inovio.

Please provide any additional information below (continue on back if necessary):

Appendix F Guidelines for Evaluation of Objective Tumor Response using RECIST version 1.1 Criteria (Response Evaluation Criteria in Solid Tumors)

DEFINITION OF MEASURABLE, NON-MEASURABLE, TARGET AND NON-TARGET LESIONS

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least one measurable lesion (by RECIST version 1.1) lesion which has not been previously irradiated. A tumor lesion in a previously irradiated field can be assessed as measurable disease provided the lesion has been deemed to demonstrate progression.

Measurable disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter [LD] to be recorded) as ≥ 20 mm with conventional techniques (computed tomography [CT], magnetic resonance imaging [MRI], x-ray) or as ≥ 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Non-measurable lesions

All other lesions (or sites of disease), including small lesions (LD < 20 mm with conventional techniques or < 10 mm using spiral CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural / pericardial effusion, inflammatory breast disease, lymphangitis cutis / pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI) and cystic lesions are all non-measurable.

Target lesions

All measurable lesions up to a maximum of five lesions per organ and 10 lesions in total representative of all involved organs should be identified as ***target lesions*** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the LD) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the LD for *all target lesions* will be calculated and reported as the baseline sum LD. The baseline sum LD will be used as reference by which to characterize the objective tumor.

Non-target lesions

All other lesions (or sites of disease) should be identified as ***non-target lesions*** and should also be recorded at baseline. Non-target lesions include measurable lesions that exceed the maximum number per organ or total of all involved organs as well as non-measurable lesions. Measurements of these lesions are not required but the presence or absence of each should be noted throughout follow-up.

Guidelines for Evaluation of Measurable Disease

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

Note: Tumor lesions that are situated in a previously irradiate area might or might not be considered measurable. Lesions progressing after previous irradiation are measurable; lesions not progressing after previous irradiation are not measurable.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the anti-tumor effect of treatment.

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

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

Conventional CT and MRI These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually required specific protocols.

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

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

Endoscopy, Laparoscopy The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological

response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and prostrate-specific antigen response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

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

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

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

- Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.

- No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

- FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution / sensitivity.

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

Response Criteria

Evaluation of target lesions

CR:	Disappearance of all target lesions
PR:	At least a 30% decrease in the sum of the LD of target lesions, taking as reference the baseline sum LD
PD:	At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions
SD:	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started

Evaluation of non-target lesions

CR:	Disappearance of all non-target lesions and normalization of tumor marker level
Incomplete Response / SD:	Persistence of one or more non-target lesion(s) or / and maintenance of tumor marker level above the normal limits
PD:	Appearance of one or more new lesions and / or unequivocal progression of existing non-target lesions

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

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

Evaluation of best overall response

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

Target lesions	Non-Target lesions	New Lesions	Overall response
CR	CR	No	CR
CR	Incomplete response / SD	No	PR
PR	Non-PD	No	PR
SD	Non-PD	No	SD
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances, it may be difficult to distinguish residual disease from normal tissue. When the evaluation of CR depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate / biopsy) to confirm the CR status.

Confirmation

The main goal of confirmation of objective response is to avoid overestimating the response rate observed. In cases where confirmation of response is not feasible, it should be made clear when reporting the outcome of such studies that the responses are not confirmed.

To be assigned a status of PR or CR, changes in tumor measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. Longer intervals as determined by the study protocol may also be appropriate.

In the case of SD, follow-up measurements must have met the SD criteria at least once after study entry at a minimum interval (in general, not less than 6-8 weeks) that is defined in the study protocol

Duration of overall response

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

Duration of stable disease

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

The clinical relevance of the duration of SD varies for different tumor types and grades. Therefore, it is highly recommended that the protocol specify the minimal time interval required between two measurements for determination of SD. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study.

Response review

For trials where the response rate is the primary endpoint it is strongly recommended that all responses be reviewed by an expert(s) independent of the study at the study's completion. Simultaneous review of the patients' files and radiological images is the best approach.

Reporting of results

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) CR, 2) PR, 3) SD, 4) PD, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data).

All of the patients who met the eligibility criteria should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered as failing to respond to treatment (disease progression). Thus, an incorrect treatment schedule or drug administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients.

Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (e.g., early death due to other reasons,

early discontinuation of treatment, major protocol violations, etc). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported.

The 95% confidence intervals should be provided.

Appendix G Guidelines for Evaluation of Progression Free Survival using Immune-related RECIST Criteria

Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH and Hodi FS. Developing a Common Language for Tumor Response to Immunotherapy: Immune-Related Response Criteria Using Unidimensional Measurements. Clin Cancer Res; 19(14) July 15, 2013

For the immune-response response criteria (irRC), only index and measurable new lesions are taken into account (in contrast to conventional World Health Organization [WHO] criteria, which do not require the measurement of new lesions, nor do they include new lesion measurements in the characterization of evolving tumor burden).

The longest diameter of each target lesion will be recorded. Measurable lesions will be defined as ≥ 10 mm in the longest diameter as in RECIST as opposed to ≥5 x 5 mm^2 in WHO / irRC.

For unidimensional measurements, the cut-off values by RECIST (≥ 20% increase from the nadir for progression, ≥ 30% decrease from baseline for partial response, and disappearance of lesions for complete remission) will be used.

Table 1. Summary of measurement and response assessment approaches for bidimensional and unidimensional assessment based on irRC

	Bidimensional assessment (the original irRC (7))	Unidimensional assessment
Measurable lesions	≥5 × 5 mm^2 by bidimensional measurements	≥10 mm in the longest diameter
Measurement of each lesion	The longest diameter × the longest perpendicular diameter (cm^2)	The longest diameter (cm)
The sum of the measurements	The sum of the bidimensional measurements of all target lesions and new lesions if any	The sum of the longest diameters of all target lesions and new lesions if any
Response assessment	PD: ≥25% increase from the nadir PR: ≥50% decrease from baseline CR: Disappearance of all lesions	PD: ≥20% increase from the nadir PR: ≥30% decrease from baseline CR: Disappearance of all lesions
New lesions	The presence of new lesion(s) does not define progression. The measurements of the new lesion(s) are included in the sum of the measurements.	
Confirmation	Confirmation by 2 consecutive observations not less than 4 weeks apart was required for CR, PR, and PD	

Appendix H Durvalumab Dose Modification for Toxicity Management

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy are provided in the Dosing Modification and Toxicity Management Guidelines. The most current version of these guidelines is an annex to this protocol and is also maintained within the Site Master File.

Patients should be thoroughly evaluated, and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the immune-mediated AE. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an immune-mediated AE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued (see Section 6.12.1 of this protocol and the Dosing Modification and Toxicity Management Guidelines).

Following the first dose of durvalumab subsequent administration of durvalumab can be modified based on toxicities observed as described in the Dosing Modification and Toxicity Management Guidelines. These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to durvalumab monotherapy regimen by the reporting Investigator.

Dose reductions are not permitted. In case of doubt, the Investigator should consult with the Study Physician.

Appendix I Administration Site Reaction Grading and Management

Grading:

- Grading should be done using two systems: Common Terminology Criteria for Adverse Events version 4.03 (which should be used for all dose delay / withdrawal decisions) and the system outlined below.
- Table: Administration Site Reaction Grading Scale (adapted from "FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials").

Local Reaction to Injectable Product	**Mild (Grade 1)**	**Moderate (Grade 2)**	**Severe (Grade 3)**	**Potentially Life Threatening (Grade 4)**
Pain	Does not interfere with activity	Repeated use of non-narcotic pain reliever > 24 hours or interferes with activity	Any use of narcotic pain reliever or prevents daily activity	Emergency room visit or hospitalization
Tenderness	Mild discomfort to touch	Discomfort with movement	Significant discomfort at rest	Emergency room visit or hospitalization
Erythema / Redness *	2.5 – 5 cm	5.1 – 10 cm	> 10 cm	Necrosis or exfoliative dermatitis
Induration / Swelling**	2.5 – 5 cm and does not interfere with activity	5.1 – 10 cm or interferes with activity	> 10 cm or prevents daily activity	Necrosis

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.
** Induration / Swelling should be evaluated and graded using the functional scale as well as the actual measurement

Management:

Grade from Table	Dose Modification	Management
Any Grade	For any grade: Per guidance below	For any grade: • Manage per institutional standard at the discretion of investigator. • Monitor patients for signs and symptoms of administration site reactions. • Educate patients on infection control.
Grade 1	For Grade 1: No changes in dose or schedule are recommended	For Grade 1: • Consider symptomatic treatment with over-the-counter analgesics and supportive care (i.e., cold compress)
Grade 2	For Grade 2: If persistent injection site reaction lasting more than 10 days despite optimal management, MEDI0457 next dose of vaccine should be omitted. Durvalumab to continue dependent on discussion of Investigator with medial monitor. For second occurrence of Grade 2: In the setting of second occurrence of persistent ≥ Grade 2 injection site reaction for more than 7 days despite optimal medical management, permanently discontinue MEDI0457 and durvalumab.	• Symptomatic treatment with over-the-counter analgesics (opioids should be avoided unless necessary) and supportive care (i.e. cold compress) • If pain persists for 3 days, contact Investigator
Grade 3 or Grade 4	For Grade 3: Injection should be held until the toxicity resolves to Grade 1 or baseline. • If resolution occurs within 5 days, consider continued dosing of MEDI0457 and durvalumab at the current schedule as long as the adverse event of concern was not considered life-threatening. • If the Grade 3 injection site toxicity only improves to Grade 2 within 5 days then omit next dose of MEDI0147 and continue durvalumab dependent on discussion of Investigator with Medical Monitor. • If no change of Grade 3 reaction within 5 days, then permanently discontinue MEDI0457 and durvalumab. For Grade 4: Permanently discontinue MEDI0457 and durvalumab.	For Grade 3 or Grade 4: • Consult Investigator for evaluation (rule out infection or other causes) and treatment (opioids may be considered) • Obtain dermatology / surgical consult • Consider hospitalization