Statistical Analysis Plan

Sponsor:	MedImmune, LLC/Ltd, a wholly owned subsidiary of AstraZeneca PLC
Protocol No:	D8860C00005
Version No. / Date:	8.0 / 17-Mar-2021
Title:	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
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1.0 Introduction

This statistical analysis plan (SAP) describes the statistical methods to be used during the reporting and analyses of data collected under Astra Zeneca Protocol D8860C00005.

This SAP should be read in conjunction with the study protocol and case report form (CRF). This version of the plan has been developed using the protocol and the CRF versions included in the title page. Any further changes to the protocol or CRF may necessitate updates to the SAP. Shells for tables, figures, and listings (TFLs) are contained in a separate document.

Versions of the SAP up to initial sponsor approval will be known as a draft SAP. Changes following approval of the first version of the SAP will be tracked in the SAP Change Log. Subsequent versions of the SAP will be considered amended SAPs. A final version of the amended SAP will be issued for sponsor approval prior to database lock.

1.1 Changes from Protocol

- Some populations have been further defined or clarified in the SAP for the purposes of analysis.
- [redacted]
- Section 8.4.1.3 of the protocol states that all RECIST v1.1 assessments will be used in the calculations used for the primary endpoints, regardless of whether the patient discontinues study treatment or receives another anticancer therapy. The SAP clarifies to state that only assessments prior to receiving subsequent systemic anticancer therapy will be included in the assessment of response rate.
- The protocol states that AE's for screen failures will not be recorded in the CRF. However, the sponsor will be instructing sites to record AE's for screen failures. These non-treatment emergent AE's will be displayed in a listing.
- The protocol states concomitant medications will only be listed, but they will also be presented in a table.
- In response to the mixed population of subjects enrolled, analyses have been added split by 1st and 2nd line + therapy and also 1st line split by platinum-refractory and non-refractory.

2.0 Study Objectives

2.1 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 (AEs)/serious adverse events (SAEs) • Collection of hematology, serum chemistry, urinalysis, creatinine phosphokinase (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)/Eastern Cooperative Oncology Group (ECOG) performance status
To evaluate the anti-tumor activity of MEDI0457 in combination with durvalumab in patients with confirmed human papilloma virus (HPV) 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)

2.2 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 (DCR) at 16 weeks by RECIST version 1.1 • Overall survival (OS) • Progression free survival (PFS) as assessed by RECIST version 1.1

[redacted]

3.0 Study Design

3.1 Overview

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) were to be enrolled and assessed for safety before additional patients were enrolled at a recommended dose and schedule for the combination.

[redacted]

[redacted]

3.3 Randomization

There is no randomization in this open-label study.

3.4 Screening 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.

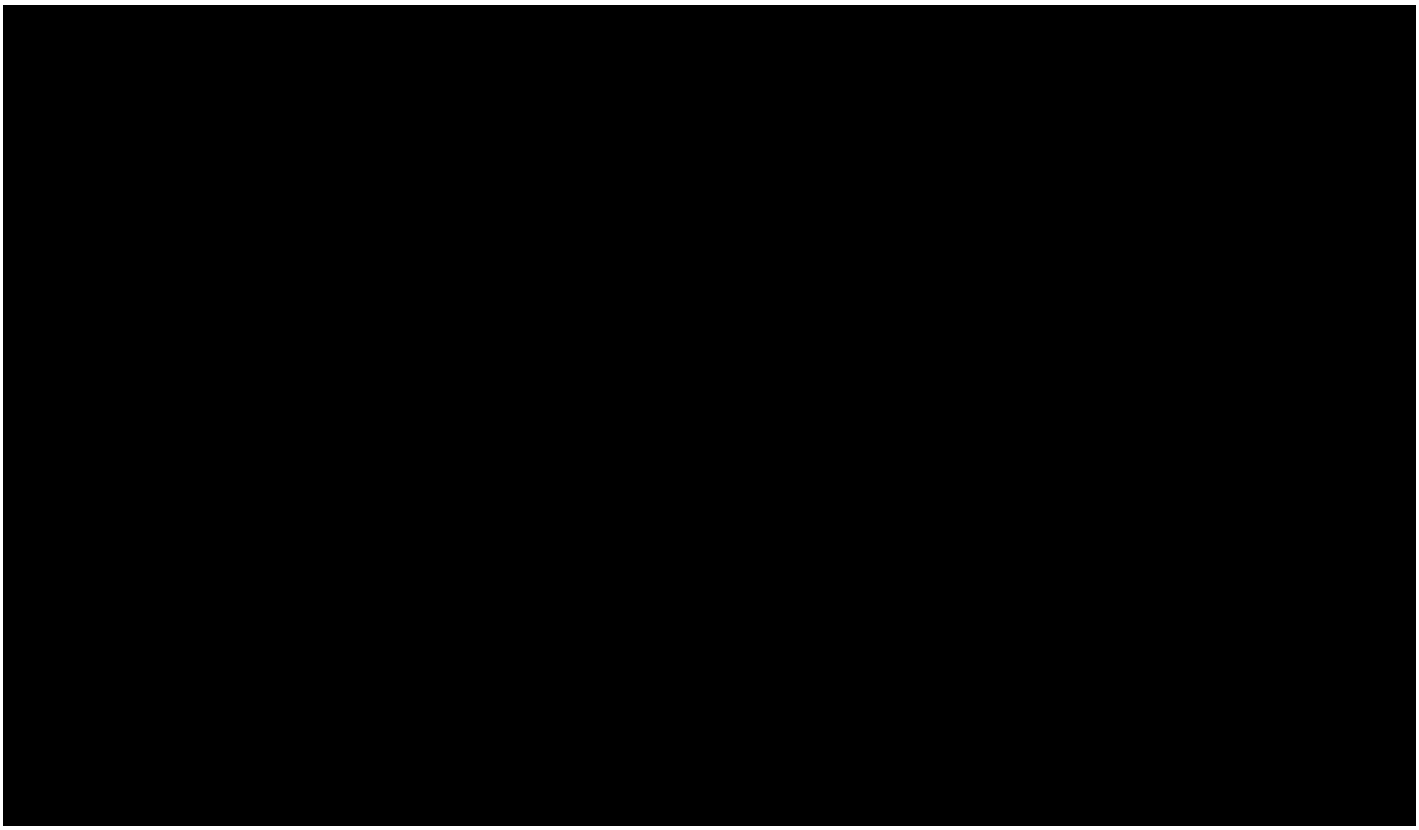
[h] Hepatitis B and C testing is mandatory, while HIV serology is only required if clinically indicated.

[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:
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



3.6 Administration Procedures

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	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
[redacted]									
Study Treatment Procedures									
[redacted]									
Durvalumab administration[h,l]			X		X		X	X	
Download EP data	X	X		X			X		X
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 only required after each infusion of durvalumab is administered if clinically significant infusion reactions are observed during or after the first dose.

[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.

[redacted]

MEDI0457 post-treatment reactions will be assessed 30 to 60 minutes after study treatment and at post-treatment visits.

[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. 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.

Abbreviations:
[redacted]; AZ=AstraZeneca; CR=complete response; CT=computed tomography; ECG=electrocardiogram; ECOG=Eastern Cooperative Oncology Group; [redacted]; EP=electroporation; EOT=end of treatment; [redacted]; 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

3.7 Follow-up Visit Procedures

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

4.0 Study Variables and Covariates

4.1 Primary Variables

4.1.1 Safety

4.1.1.1 Adverse Events

Adverse event means any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Medical condition/diseases present before starting the investigational drug will be considered AEs only if they worsen after starting study treatment. Please refer to the Protocol Section 6.1 for further definition of AEs.

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 investigational product (IP) (yes or no)
- Action taken with regard to each IP
- Administration of treatment for the AE
- Outcome
- Whether AE is of special interest, and if yes, which category per the AE CRF page
- Whether the AE is a DLT
- Whether AE occurred before, during, or after dosing if occurred on same day of dosing

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.

Adverse events and SAEs will be collected from time of signature of informed consent, through 90 days after the last dose of the study treatment. Note: AEs/SAEs that occur post-signature but prior to IP administration are non-treatment-emergent AEs (non-TEAEs)/SAEs. AE's for screen failure patients will not be recorded in the CRF unless they result from the screening biopsy procedure.

4.1.1.2 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 result 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. Please refer to the Protocol Section 6.2 for further definition of SAEs.

The following variables, in addition to those mentioned above for AE, 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

4.1.1.3 Adverse Events of Special Interest

Adverse events of special interest (AESI) are those categorized on the CRF as AESI. These include the categories of diarrhea, colitis, pneumonitis, ALT/AST increases/hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis/rash/pruritus, nephritis, pancreatitis, myocarditis/pericarditis, uveitis, infusion-related reactions/hypersensitivity/analphylactic reactions, and administration site reactions. The same variables are collected for AESI as for other AEs.

4.1.1.4 Clinical Laboratory Tests

Local laboratory values will be graded according to CTCAE v4.03 criteria via PRA programming in Study Data Tabulation Model (SDTM) datasets. Please refer to the SDTM data specifications for lab grading criteria.

Blood samples will be collected for hematology, serum chemistry, luteinizing hormone (LH) and follicle-stimulating hormone (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 serum pregnancy test will be performed for women of childbearing potential at the screening visit and a urine pregnancy test is required to be performed during the treatment period according to the administration procedures chart. The following laboratory variables will be measured for hematology, serum chemistry and urinalysis:

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

Clinical Chemistry (serum)	
Albumin	Glucose
ALP	Lactate dehydrogenase
ALT[a]	Lipase[b]
AST	Magnesium[c]
Amylase[b]	Potassium
Bicarbonate[c]	Sodium
Calcium	Total bilirubin (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

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

4.1.1.5 Pregnancy Testing

For women of reproductive potential, a negative result for serum pregnancy test must be available at the screening visit and a urine beta-human chorionic gonadotropin (β-HCG) pregnancy test is required to be performed during the treatment period at the frequency shown in the administration procedures table. 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).

4.1.1.6 Electrocardiograms

An ECG will be performed at screening within 28 days of Day 0 for all patients to determine patient eligibility. 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.

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.

4.1.1.7 Vital Signs, Height and Weight

Vital signs including temperature (C), respiration rate (respirations/minute), pulse oximetry (percentage), blood pressure (mmHg), pulse rate (beats/min) and weight(kg) will be measured according to the visits schedule in the administration procedures table. Height (cm) will be collected at the screening visit only.

4.1.1.8 Physical Examinations

A complete physical examination will be performed and include an assessment of the following: general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, 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.

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

4.1.1.9 Concomitant Medications and Procedures

Patients will be questioned by the Investigator regarding the occurrence of any concomitant medications during their clinic visits. The medication name, indication, reason, dose, dose unit, dose frequency, route of administration, start and end dates or whether ongoing will be collected on the CRF. Concomitant medications will be coded to the generic term using the current version of the World Health Organization Drug Dictionary.

Concomitant procedures will also be collected. The procedure name, indication, reason, start and end date or whether ongoing will be collected on the CRF. Concomitant procedures will not be coded using a dictionary.

4.1.1.10 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

4.1.2 Efficacy

4.1.2.1 Objective Response by RECIST v1.1

RECIST version 1.1 will be used to assess objective response rate (ORR). The RECIST version 1.1 guidelines for measurable, non-measurable, target and non-target lesions are presented in Appendix F of the protocol. The primary analysis of objective response by RECIST v1.1 will be performed among patients in the Response Evaluable population. Analyses will be performed grouping patients based on line of therapy and platinum sensitivity status.

The methods of assessment of tumor burden used at baseline are computed tomography (CT) and/or or magnetic resonance imaging (MRI) scans, preferably with intravenous (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. [redacted]

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) for 1 year. After the first year on treatment, if complete response (CR)/partial response (PR)/stable disease (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 systemic 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 should continue disease assessments until confirmed PD or start of subsequent systemic anticancer therapy.

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.

[redacted]

General guidance for confirmation of CR and PR per RECIST v1.1 [Eisenhauer, Therasse et al. 2009]:

Best Overall Response When Confirmation of CR and PR Required		
Overall Response First Time Point	**Overall Response Subsequent Time Point**	**Best Overall Response**
CR	CR	CR
CR	PR	SD, PD or PR*
CR	SD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
CR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
PR	CR	PR
PR	PR	PR
PR	SD	SD
PR	PD	SD provided minimum criteria for SD duration met, otherwise, PD
PR	NE	SD provided minimum criteria for SD duration met, otherwise, NE
NE	NE	NE

CR = complete response, PR = partial response, SD = stable disease, PD = progressive disease, and NE = inevaluable

*If a CR is truly met at first time point, then any disease seen at a subsequent time point, even disease meeting PR criteria relative to baseline, makes the disease PD at that time point (since, disease must have reappeared after CR). Best response would depend on whether minimum duration for SD was met. However, sometimes 'CR' may be claimed when subsequent scans suggest small lesions were likely still present and in fact the patient had PR, not CR at the first time point. Under these circumstances, the original CR should be changed to PR and the best response is PR.

PRA will tabulate the best overall response per RECIST v1.1 and confirmation as follows:

Best Overall Response per RECIST v1.1	Criteria (per CRF "Derived RECIST disease response")
Complete response (CR)	CR, followed by another CR at next disease assessment >=4 weeks later, with no other overall response besides CR or NE between these dates
Partial Response (PR)	PR, followed by another PR or CR at next disease assessment >=4 weeks later
Unconfirmed CR	CR, followed by PR at next disease assessment >=4 weeks later, with no other overall response besides PR or NE between these dates
Stable Disease (SD)	SD at least 51 days post first dose, in the absence of confirmed CR or PR from above
Unconfirmed CR	CR, followed by PD, SD, or NE at next disease assessment >=4 weeks later if criteria for SD met
Unconfirmed PR	PR, followed by PD, SD, or NE at next disease assessment >=4 weeks later if criteria for SD met
Progressive disease (PD)	Any PD, in the absence of a prior confirmed CR or PR and no SD
Unconfirmed CR	CR, followed by PD at next disease assessment >=4 weeks later if SD criteria not met
Unconfirmed PR	PR, followed by PD at next disease assessment >=4 weeks later if SD criteria not met
Not Evaluable (NE)	NE, if criteria from other categories above not met
Unconfirmed CR	CR, followed by NE at next disease assessment >=4 weeks later if SD criteria not met
Unconfirmed PR	PR, followed by NE at next disease assessment >=4 weeks later if SD criteria not met

Note: 4 weeks is defined as 28 days. Minimum criteria for SD is the 8 week response assessment (8 weeks post first dose +/- 5 days).

4.2 Secondary Variables

4.2.1 Pharmacokinetics and Antidrug Antibodies

A central laboratory will be used for the collection of blood for pharmacokinetic analysis. 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. 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.

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.

Serum concentration of durvalumab and antidrug antibody response to durvalumab will be summarized by PRA and results will be included in the PRA Clinical Study Report.

4.2.2 Efficacy

4.2.2.1 Objective Response by RECIST v1.1

The secondary analysis of objective response by RECIST v1.1 will be performed among patients in the As-treated population. Refer to SAP section 4.1.2.1 for details of the RECIST v1.1 variables.

4.2.2.2 Objective Response by immune-related RECIST

Please refer to Appendix G of the study protocol for details regarding the guidelines for assessing response by immune-related RECIST (irRECIST). Index lesions and measurable new lesions are taken into account. 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.

[redacted]

PRA will tabulate the best overall response per irRECIST and confirmation as follows:

Best Overall Response per irRECIST	Criteria (per CRF "Investigator irRECIST disease response")
Complete response (irCR)	irCR, followed by another irCR at next disease assessment >=4 weeks later, with no other overall response besides irCR or irNE between these dates
Partial Response (irPR)	irPR, followed by another irPR or irCR at next disease assessment >=4 weeks later
Unconfirmed irCR	irCR, followed by irPR at next disease assessment >=4 weeks later, with no other overall response besides irPR or irNE between these dates
Stable Disease (irSD)	irSD of at least 51 days post first dose, in the absence of confirmed irCR or irPR from above
Unconfirmed irCR	irCR, followed by irPD, irSD, or irNE at next disease assessment >=4 weeks later if irSD criteria met
Unconfirmed irPR	irPR, followed by irPD, irSD, or irNE at next disease assessment >=4 weeks later if irSD criteria met
Confirmed Progressive disease (irPD)	irPD, followed by irPD at next disease assessment >=4 weeks later
Unconfirmed irCR	irCR, followed by irPD at next disease assessment >=4 weeks later if irSD criteria not met (irPD must also be confirmed to count in this category)
Unconfirmed irPR	irPR, followed by irPD at next disease assessment >=4 weeks later if irSD criteria not met (irPD must also be confirmed to count in this category)
Unconfirmed Progressive disease (irPD)	Any other irPD not meeting criteria for confirmed irPD
Unconfirmed irCR	irCR, followed by irPD at next disease assessment >=4 weeks later if irSD criteria not met
Unconfirmed irPR	irPR, followed by irPD at next disease assessment >=4 weeks later if irSD criteria not met
Not Evaluable (irNE)	irNE, if criteria from other categories above not met
Unconfirmed irCR	irCR, followed by irNE at next disease assessment >=4 weeks later if irSD criteria not met
Unconfirmed irPR	irPR, followed by irNE at next disease assessment >=4 weeks later if irSD criteria not met

Note: 4 weeks is defined as 28 days. Minimum criteria for irSD is the 8 week response assessment (8 weeks post first dose +/- 5 days).

4.2.2.3 Disease Control

Disease control at 8, 16, and 24 weeks will be classified as values of CR, PR, and SD (SD maintained for ≥ 8, 16, and 24 weeks, respectively) as recorded on the disease response CRF page according to RECIST v1.1.

4.2.2.4 Overall Survival

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. Date of death will be collected on the Statement of Death CRF page. Date last known alive is defined as the latest among the following dates recorded on the case report forms (CRFs):

- AE start and stop dates
- Admission and discharge dates of hospitalization
- Study treatment date
- Last dose date
- Laboratory test dates
- Date of vital signs, ECOG, concomitant medications, or sample collection dates
- Dates of evaluations for target, non-target, or new lesions
- Start and stop dates of alternative anticancer treatment
- Date last known alive on survival status CRF
- End of study disposition event date

4.2.2.5 Progression Free Survival

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 SAP section 3.6. All study evaluations for disease response must be based on RECIST version 1.1.

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 (+1 day). 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 rules 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.

PRA will not programmatically derive values of PD via RECIST v1.1. Rather, PD will be collected in a CRF-derived field on the Disease Response page per sponsor standards. PD is defined as a value of

"Progressive Disease (PD)" in the field "Derived RECIST disease response". The analysis of PFS does not require confirmation of progression.

The date of PD will be the first date at which any objective diagnostic test provides data indicating PD. Specifically, the date of PD will be the earliest of the following 3 dates:

- Date of PD as indicated by target lesions: If PD is triggered by a change in sum of diameters of target lesions, and the dates of evaluation of the target lesions vary for the same assessment, assign the first evaluation date among target lesions.
- Date of PD as indicated by non-target lesions: If the dates of evaluation of the non-target lesions vary for the same assessment, assign the first evaluation date for which any non-target lesion exhibits a status of Unequivocal Progression.
- Date of PD as indicated by new lesions: If multiple new lesions are identified and the dates of evaluation for the new lesions vary for the same assessment, assign the first evaluation date for which any new lesion is detected.

The following table includes the censoring and event rules that will be used for progression free survival:

Situation	Date of Progression or Censoring	Outcome*
Documented progression or death	Date of PD or death, whichever comes first	Event (unless the censoring rule specified below)
No PD or death at time of analysis or lost to follow-up	Date of last evaluable progression-free disease assessment	Censored
Death or PD immediately after ≥ 2 consecutive missed or non-evaluable disease assessments	Date of the first dose of treatment or last evaluable progression-free disease assessment prior to missed or non-evaluable assessments, whichever occurred last	Censored
No disease assessment at baseline and no evidence of PD at first post-baseline disease assessment or No disease assessment post-baseline without death prior to second scheduled post-baseline disease assessment	Date of the first dose of treatment	Censored
New systemic anticancer treatment started without documented PD	Date of last evaluable progression-free disease assessment prior to start of new anticancer treatment	Censored

Outcomes of deaths and progressions will be considered events for progression free survival. If a subject has two or more consecutive missed or non-evaluable assessments followed by an assessment showing no radiologic disease progression, then the assumption will be that the subject did not progress during the missed or non-evaluable assessments. Two or more consecutive assessments is defined as > 122 days

within the first year or >182 days after the first year (two disease assessments including the ± 5 or 7-day window as per protocol to allow for a late assessment) after the last evaluable post-baseline disease assessment.

4.2.2.6 Time to Response

Time to response (TTR) is defined as the time from the first dose of IP until the first documentation of a subsequently confirmed objective response. Only subjects who have achieved confirmed objective response (CR or PR) will be evaluated for TTR.

4.2.2.7 Duration of Response

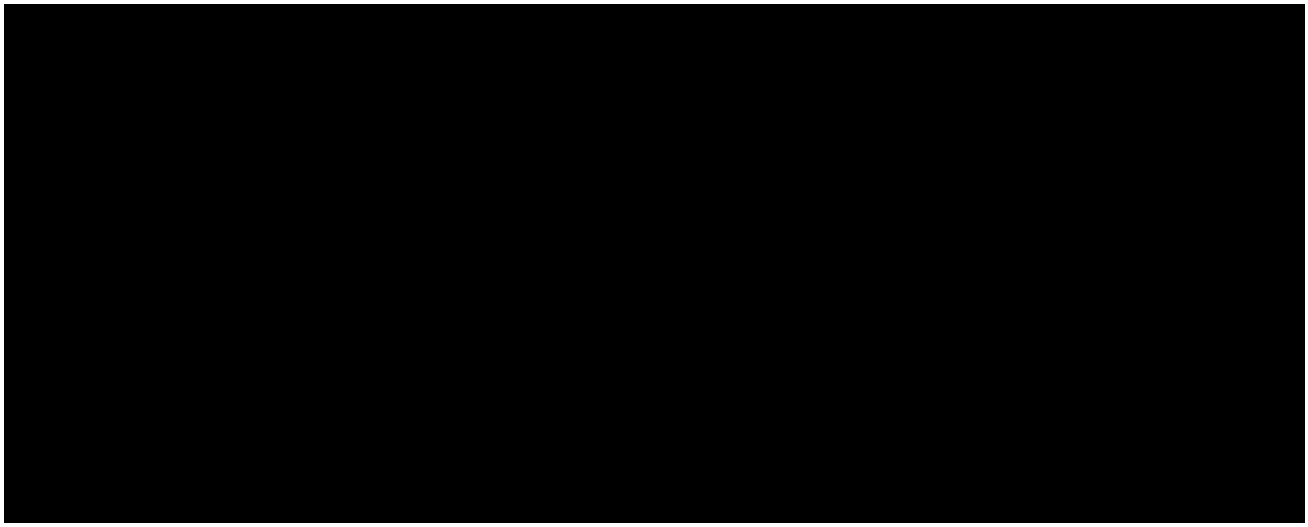
Duration of response (DOR) is defined as the time from the first documentation of objective response (CR or PR) until the first documentation of disease progression according to RECIST v1.1 or death due to any cause, whichever occurs first. Only subjects who have achieved confirmed objective response (CR or PR) will be evaluated for DOR.

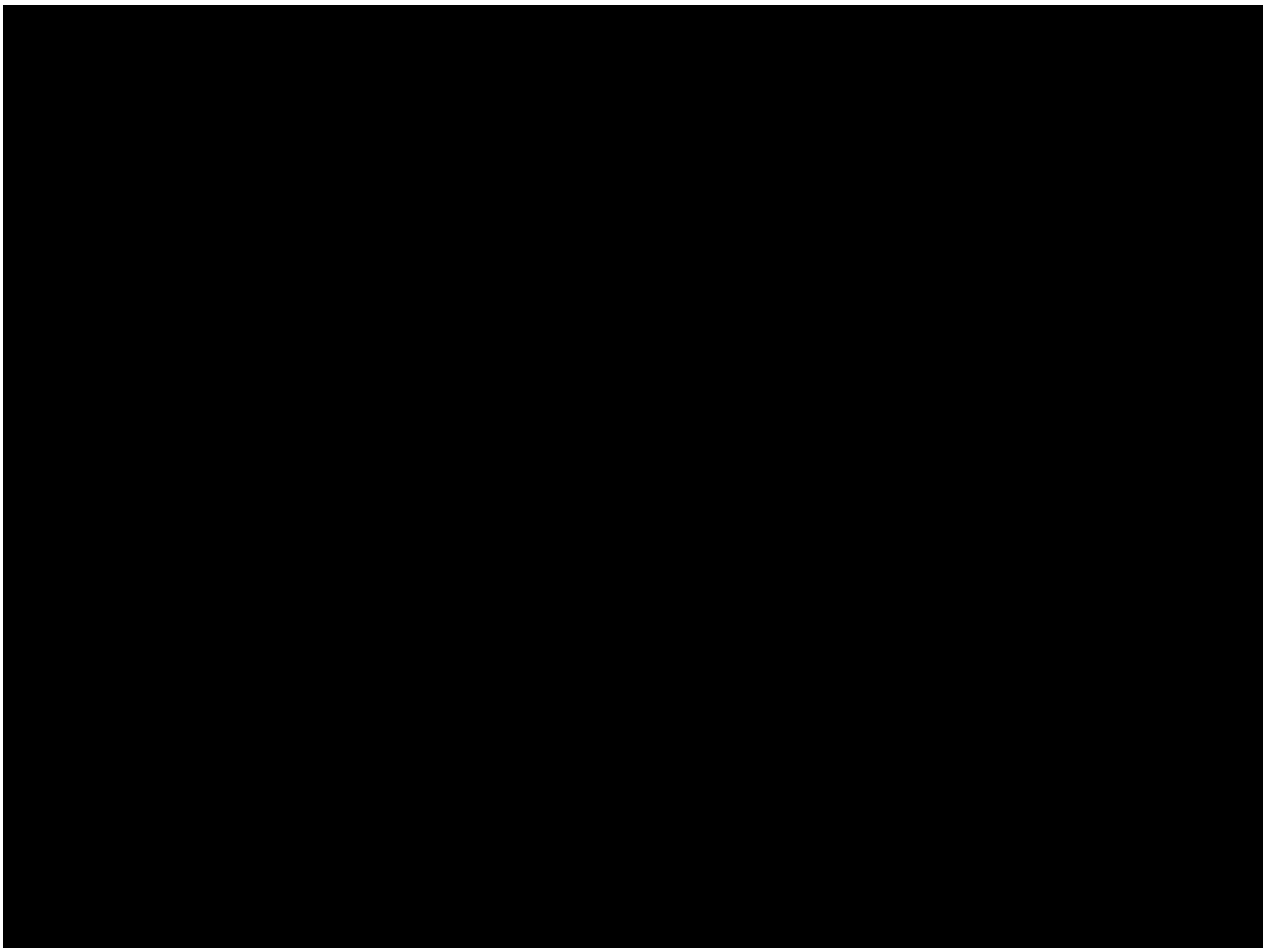
The date of PD/death or censoring should coincide with the date of progression or death from any cause used for the PFS endpoint.

4.3 Other Variables

Other variables will be collected for patient medical history, smoking history, alcohol use, tumor history and current status, prior anticancer treatments (cancer related surgery, radiation, systemic therapy or other), brain metastasis status at study entry and method of evaluation, pneumonitis questionnaire, pulmonary function tests, blood gases, serum interstitial lung disease (ILD) markers, bleeding event questionnaire, whether tumor biopsy collected, and subsequent anticancer treatments (cancer related surgery, radiation, systemic therapy or other). Medical history will be coded using MedDRA.

If an AE is selected as Pneumonitis on the AE CRF, then the Pneumonitis Questionnaire CRF will be triggered to be completed. Blood Gases, Pulmonary Function Tests, and Serum ILD Markers CRF pages are triggered by responses on the Pneumonitis Questionnaire. These pages will be completed as required and completed to the extent the information is available.





5.0 Definitions

Variable	Definition
Age	Date of birth is not collected. Age in years is recorded on the Demographics CRF page.
Any ADA positive	A subject is defined as Any ADA Positive if there are antidrug antibodies at any visit
Any IP	At least one dose of either study drug
Baseline	Baseline is defined as the last assessment prior to the first dose of either study drug.
Change from baseline (for safety data)	Change from baseline will be defined as the maximum post-baseline value minus the baseline value where applicable (on a subject level). Change from baseline will only be calculated for subjects who have both baseline and at least one post-baseline value for any parameter. Note: Change from baseline for tumor assessments is defined below.

Change from baseline (for tumor assessments)	Change from baseline (%) will be calculated for each disease assessment using RECIST v1.1 target lesion measurements. % change from baseline= (target lesion sum at postbaseline – target lesion sum at baseline)/(target lesion sum at baseline)]*100 If at any time point one or more target lesions have an intervention or are not evaluable, then the tumor size change cannot be calculated at that time point. If target lesions split into more lesions, split lesion measurements will also be incorporated into the target lesion sum for that time point. If a target lesion is too small to measure, 5 mm will be used for that target lesion. Maximum tumor size reduction: This will be defined as the maximum tumor size reduction (% change from baseline) up until the time of first RECIST v1.1 PD or start of systemic anticancer therapy. Note: If a patient experiences both tumor size increase and tumor size reduction, the greatest reduction will be taken for this variable.
Body Mass Index (BMI)	BMI will be calculated as Weight/(Height squared), with weight in kg and height in m.
Concomitant mediation	Any medication ongoing at the time of first dose of any IP or with a start date after first dose of any IP
Discontinuation of study	A subject will be considered discontinued from the study when an End of Study page is completed indicating the primary reason for discontinuation.
Disease Response	Refer to Sections 4.1.2.1
Disease Control Rate at 8, 16, and 24 weeks	The percentage of subjects with a best Derived RECIST Disease Response of CR, PR, or SD (SD maintained for ≥ 8, 16, or 24 weeks, respectively) as recorded on the Disease Response CRF
Dose intensity (mg/week)	Dose intensity for each drug is defined as the cumulative dose received* (in mg) divided by duration of exposure (in weeks). *cumulative dose will be derived as the summation of the “prescribed dose (mg)” from the CRF page for each drug Example: If 3 MEDI0457 doses are received at 7mg each, and the duration of exposure to MEDI0457 is 90 days, then Dose intensity (MEDI0457)= (7+7+7)/ (90/7)= 1.63 mg/week (to be displayed to the number of decimal places shown in the table shells)
Actual duration of follow-up (days)	Actual duration of follow-up will be calculated as the date of last contact or death minus date of first dose of any IP + 1 day.

Potential duration of follow-up (days)	Potential duration of follow-up will be calculated as the date of last contact for subjects who were not deceased or the data cut-off date for deceased subjects minus date of first dose of any IP + 1 day.
Duration of exposure (weeks)	Durvalumab: Duration of exposure is defined as the potential end date of durvalumab treatment period plus 1 day minus first dose date. The potential end date of durvalumab treatment period is defined as 27 days after the last dose. For subjects who die prior to 27 days after the last dose, the potential end date is defined as date of death. If database cutoff occurs prior to 27 days after the last dose and the subject remains alive, the potential end date is defined as date of database cutoff. MEDI0457: Duration of exposure is defined as the potential end date of MEDI0457 treatment period plus 1 day minus first dose date. The potential end date of MEDI0457 treatment period is defined as 13, 27, 34 and 55 days after the last dose if the last dose is on week1, 3, 7, and >=12, respectively. For subjects who die prior to the corresponding number of days after the last dose, the potential end date is defined as date of death. If database cutoff occurs prior to the corresponding number of days after the last dose and the subject remains alive, the potential end date is defined as date of database cutoff. Duration of exposure to study treatment is defined as the later potential end date of either drug minus the earlier first dose date of either drug plus 1 day. Duration will be converted to weeks by dividing by 7
Duration of response (months)	DOR (months) = (Date of RECIST v1.1 PD/death or censoring – Date of first disease response per RECIST v1.1 + 1) / (30.4) among confirmed responders (CR,PR) only
Duration of stable disease (months)	Duration of SD= (Date of RECIST v1.1 PD/death or censoring – Date of first dose of any IP + 1)/30.4. Duration of SD will use the same censoring rules as progression-free survival.
End of Treatment (EOT)	EOT is defined separately for MEDI0457 injection and durvalumab infusion using the End of Treatment CRF pages
Enrolled subject	An enrolled subject is a subject that is not a screen failure, who signs informed consent, and receives any IP
First line therapy	Subjects with only one line of therapy in a recurrent/metastatic setting. This includes the study treatment.
Height (cm)	Height that is recorded in inches (in) will be converted to centimeters (cm) for the TFLs cm=in*2.54

HPV-16/HPV-18 positive confirmed disease	A subject who is HPV16+ or HPV18+ by any confirmatory test at baseline or Week 10. Results reported in the CRF at baseline cannot be used for confirmatory status. Note: A subject could have confirmatory tests that were not available at baseline, but if subject has confirmatory positive results at Week 10 then subject will be assumed to have been positive at baseline.
Line of therapy	Line of therapy is calculated from the "Prior anticancer treatment" page of CRF by taking number of lines and adding 1 (to account for study treatment). Subjects without a line of therapy (recorded as NA on the CRF page) count as 1L
Lymph node only disease at baseline	Defined as at least one lesion in local lymph nodes or distant lymph nodes among baseline target and non-target lesions and no other baseline target or non-target lesions in other sites
Measurable disease at baseline	For the purposes of deriving the evaluable population, measurable disease at baseline (Yes or No) will be defined among baseline target lesions as at least 1 target lesion that is ≥10mm (if solid tumor lesion*) or ≥15mm (if Local or Distant Lymph Nodes) *a solid tumor lesion will be any lesion that is located in a site that is not the local lymph nodes or distant lymph nodes per the CRF
Platinum Non- refractory	All subjects not meeting the definition for platinum refractory
Overall survival (months)	Refer to Section 4.2.2.4 (Date of death or date of censor – earliest date of either study drug + 1 day)/30.4
[redacted]	[redacted]
[redacted]	[redacted]
Pharmacokinetics Variables	**Geo CV** — The geometric coefficient of variation is calculated as: $\text{Geo CV} = \sqrt{\exp^{(\ln(\text{GeoSD}))^2} - 1} \times 100\%$ **Geo Mean** — The geometric mean is calculated as: $\text{Geo Mean} = \sqrt[N]{y_1 \times y_2 \times y_3 \ldots y_N} = \exp[\frac{\ln(y_1)+\ldots\ln(y_n)}{n}]$ **Geo SD** — The geometric standard deviation is calculated as: $\text{Geo SD} = \exp^{(SD(\ln(y_1),\ln(y_2),\ln(y_3)\ldots\ln(y_N)))}$ Geo=Geometric http://onbiostatistics.blogspot.com/2008/07/geometric-statistics-geometric-cv-vs.html CV% (not geometric)= (STD/Mean)*100%

Platinum-refractory	A finding of "Platinum Refractory" is specified on the Medical History CRF page. Only defined for those subjects in 1st line setting.
Prior Cisplatin therapy (any)	Defined as Yes if any prior therapy contained Cisplatin; otherwise No.
Prior Carboplatin therapy (any)	Defined as Yes if any prior therapy contained Carboplatin; otherwise No.
Prior platinum therapy (any)	Defined as Yes if any prior therapy contained Cisplatin or Carboplatin; otherwise No.
Prior Platinum therapy intent	For summary table: if the setting is recurrent or metastatic, then it is palliative. Otherwise, curative.
Progression-free survival (months)	Refer to Section 4.2.2.5 (Date of progression, death, or censor – date of first dose of IP+ 1 day)/30.4
Relationship to study treatment	AEs related to study treatment will be defined as those recorded on the CRF page as Related to either investigational product, study-related procedures, or device. MEDI0457 related includes any AE with relationship to MEDI0457; Durvalumab related includes any AE with relationship to Durvalumab; Treatment related total includes any AE with relationship to MEDI0457, Durvalumab, study procedures, or device. AEs with missing relation will be considered treatment related.
Relative dose density	Relative dose density is defined for Durvalumab only as the dose intensity (defined above) divided by the planned dose intensity. The planned dose intensity for Durvalumab is 1500mg/every 4 weeks, unless the patient's weight is <30kg at dosing. If the weight at dosing is <30kg, then the planned dose intensity will be 20mg/kg/every 4 weeks. Planned dose intensity will not be adjusted for dose delays, missed doses, or dose adjustments unless a Revised Dosing Schedule is implemented for all patients.
Temperature	Temperature that is recorded as Fahrenheit (F) will be converted to Celsius (C) for the TFLs. C=(F – 32)/1.8
Time to response (months)	Time to response (months) = (Date of first disease response per RECIST v1.1 – Date of the first dose of IP + 1) / (30.4) among confirmed responders (CR,PR) only
Treatment-emergent adverse event	An AE will be considered to be a TEAE if it begins or worsens on or after the first administration of either study drug up to 90 days following the last dose of the last study treatment.

Visceral metastases at baseline	Defined as at least one lesion in any of the following sites among baseline target and non-target lesions: adrenal, CNS, liver, lung, pleura, peritoneum, prostate, renal, pancreas, small bowel, stomach, ovary, uterus, cervix, colon, biliary tract, testicle, uveal. Subjects may have lesions in other sites as well but at least one lesion among these sites to be classified with visceral metastases at baseline
Weight (kg)	Weight that is recorded in pounds (lb) will be converted to) kilograms (kg) for the TFLs kg= lb * 0.45359237

6.0 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). That is, patients in the Safety Analysis Run-in period will be included in any populations for which they meet the criteria.

6.1 As-treated Population

Patients who receive any investigational product (defined as at least one dose of either study drug) will be included in the As-treated Population.

6.2 DLT-Evaluable Population

The DLT-Evaluable Population will include all patients enrolled in the safety run-in period who receive investigational product per protocol and complete the safety follow-up through the DLT-evaluation period (i.e. safety analysis run-in period) or experience any DLT during the DLT-evaluation period, as defined per protocol or revised by the Safety Data Monitoring Committee. At time of writing this SAP, the DLT population consists of the first three enrolled subjects.

6.3 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 at least one follow-up scan (includes discontinuations due to disease progression or death without follow-up scan) with the opportunity to be followed for ≥ 16 weeks. [redacted]

6.4 Pharmacokinetics Population

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.

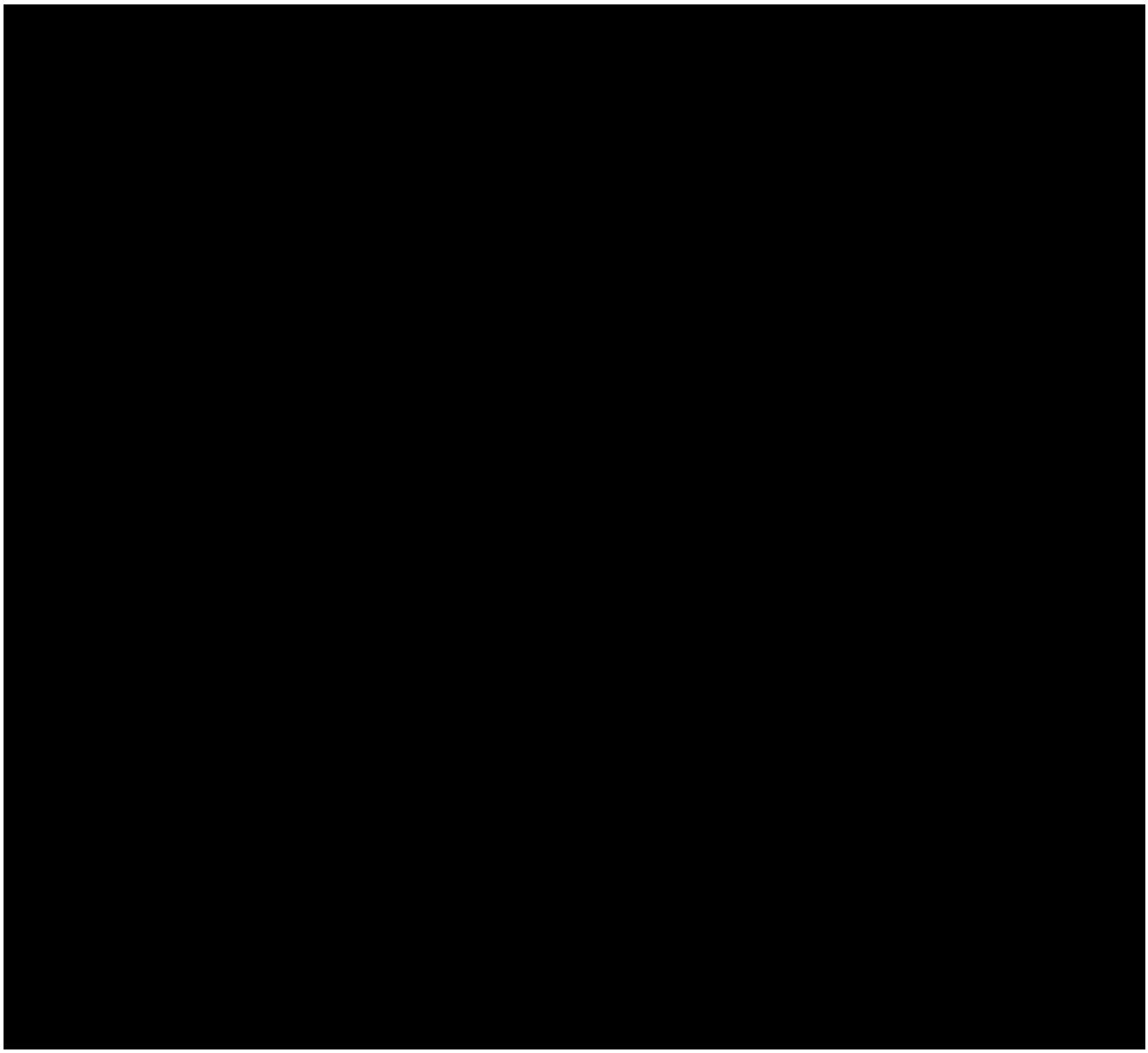
6.5 Antidrug Antibodies Evaluable Population

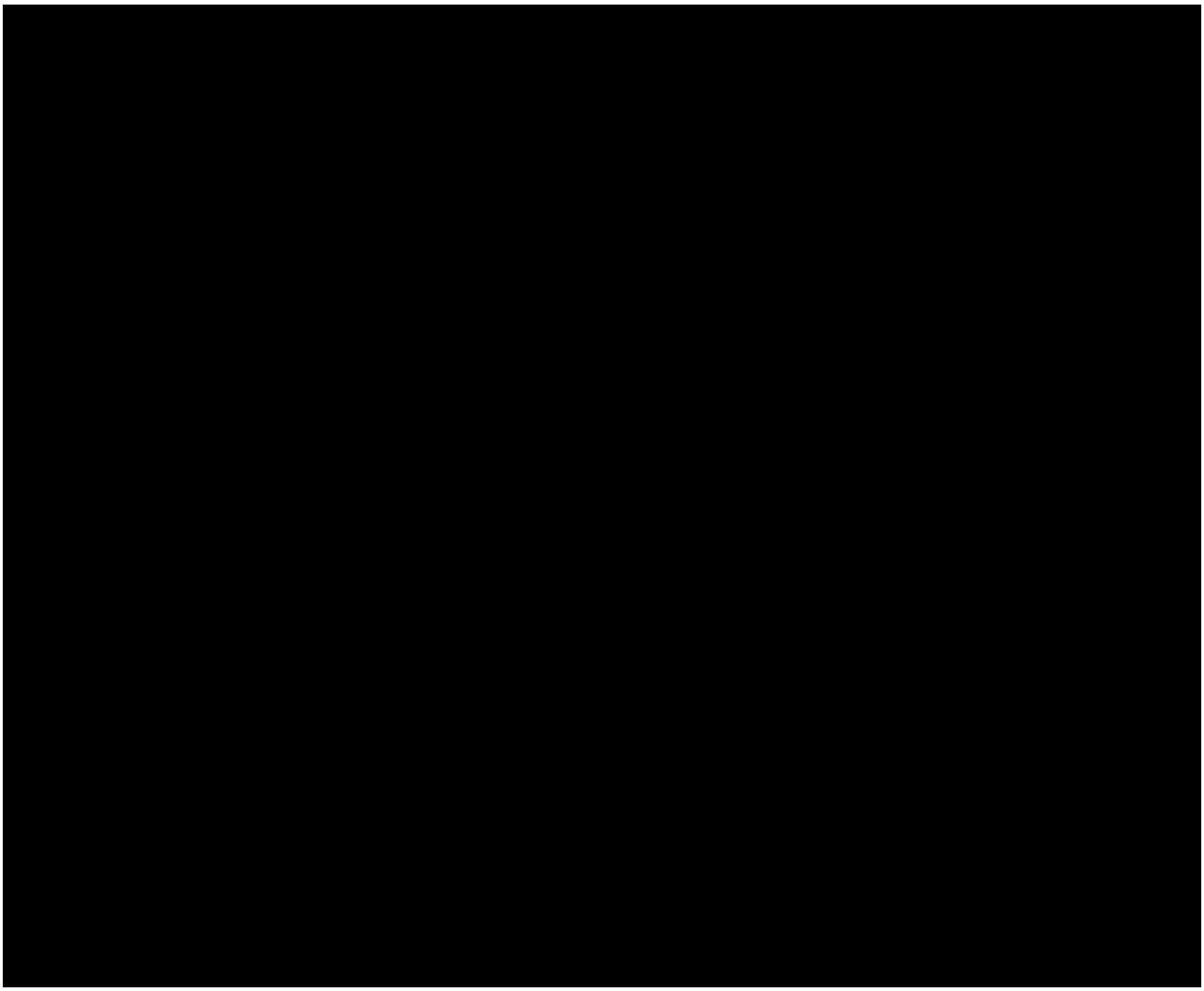
The ADA evaluable population will include subjects who have non-missing baseline ADAs and at least one non-missing post-baseline ADA result.

7.0 Interim Analyses

7.1 Safety Data Monitoring Committee

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. Please refer to the Safety Data Monitoring Committee (SDMC) Charter for full details regarding the SDMC meeting frequency, composition, and requirements.





8.0 Data Review

8.1 Data Handling and Transfer

Please refer to the Data Management Plan for details concerning data handling and transfer.

8.2 Data Screening

Beyond the data screening built into the PRA Data Management Plan, the PRA programming of analysis datasets, tables, figures, and listings (TFLs) provides additional data screening. Presumed data issues will be sent to Data Management.

Prior to database lock, data will first be frozen. The TFLs will be delivered based on data prior to the freeze ("pre-freeze"), after the freeze ("post-freeze"), and after database lock (final TFLs). Review of a pre-freeze TFL run on clean subjects and a post-freeze TFL run on the frozen database allow for further data screening prior to lock. The post-freeze TFL will be discussed with the sponsor in a data review meeting to identify

any final data issues and seek corrections prior to database lock. The PRA statistician and the sponsor must approve database lock.

9.0 Statistical Methods

All analyses will use SAS version 9.4 or higher. Unless otherwise noted, categorical variables will be summarized using counts and percentages. Percentages will be rounded to one decimal place, except 100% will be displayed without any decimal places and percentages will not be displayed for zero counts. Continuous variables will be summarized using the number of observations (n), mean, standard deviation (SD), median, minimum and maximum. The median, minimum and maximum values will be displayed to the same level of precision as the raw data, the mean to a further decimal place and the SD to two additional decimal places.

Confidence intervals will be two-sided and use the exact binomial method at a 95% confidence level.
Time to event endpoints (PFS, OS) will be estimated using the Kaplan-Meier method and Kaplan-Meier figures will be provided.

Selected TFLs as indicated in the TFL shells document may display results for subjects with and without confirmed HPV-18/HPV-18 positive disease as well as by the total number of subjects. Most shells will display by line of therapy and platinum-refractory/non-refractory for first line patients.

The following table details the primary and secondary efficacy endpoints and populations. At this time, these endpoints will be derived using the local assessments captured in the CRF.

Type of efficacy endpoint	Endpoint	Method	Population(s)
Co-primary[1]	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, Kaplan-Meier	Response-evaluable and As-treated
	OS	Kaplan-Meier	Response-evaluable and As-treated

Abbreviations
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
1. The other co-primary objective is the evaluation of safety.

9.1 Subject Disposition

Tabulations of the number and percentage of subjects included in each analysis set, together with a breakdown of the reason for exclusion will be provided. Duration of actual and potential follow-up will be summarized. Subject entry by site will be tabulated.

9.2 Protocol Deviations

Per PRA processes, protocol deviation data will be entered into our Clinical Trials Management System (CTMS). The study team and the sponsor will conduct on-going reviews of the protocol deviation data from CTMS. Important protocol deviations will be summarized in a table and all deviations will be listed. Protocol deviations relating to the COVID-19 pandemic will also be summarized separately.

9.3 Treatments

9.3.1 Extent of Study Drug Exposure

MEDI0457 intramuscular (IM) injection dosing and durvalumab IV infusion dosing will each be summarized. The number and percentage of subjects receiving at least one dose will be provided for each drug.

For MEDI0457 injections, the total number of injections received, reason if injection was omitted, percentage of doses where electroporation was delivered successfully, whether entire dose administered (and reason if not) will be summarized in a table and listing. Other details will be included the listing.

For durvalumab infusion, the total number of infusions and cumulative dose will be summarized. The date of dosing, and start and end times of infusion will be included in the listing.

Dose modifications for each drug such as reason if dose was omitted, whether entire dose was administered, reason if entire dose was not administered, whether dose interrupted and reason, number of interruptions, whether dose was reduced and why, whether dose was delayed and why, and whether dose increased and why will be summarized in a table and listing.

The duration of exposure(in weeks and cycles), relative dose density and dose intensity for each drug will be calculated and summarized using descriptive statistics.

The lot numbers for each investigational product will be provided in a listing.

9.3.2 Concomitant Medications and Procedures

Concomitant medications will be coded to the generic term using the current version of the World Health Organization Drug Dictionary and will be tabulated and listed by subject in the As-treated Population.

Concomitant procedures will not be coded and will be listed by subject in the As-treated Population.

9.3.3 Subsequent Anticancer Treatment

Subsequent anticancer treatment including cancer related surgery, radiation, systemic therapy and other therapies will be summarized for subjects in the As-treated Population. Data that cannot be tabulated (e.g., start and end dates, times, etc.) will be displayed in listings by subject.

9.4 Demographic and Baseline Characteristics

Demographic and baseline disease characteristics will be summarized in the As-treated Population. Data to be tabulated will include demographic features such as sex, age, ethnicity, race, weight and BMI, as well as disease-specific characteristics, such as but not limited to disease stage at initial diagnosis, tumor/lymph node/metastasis (TNM) staging at initial diagnosis, histologic grade at initial diagnosis, baseline ECOG status, and anatomical location of primary tumor. Medical history, smoking history, alcohol use, and prior anticancer treatments will also be tabulated. HPV, [redacted] status will be tabulated at baseline and in a shift table from baseline to Week 10.

9.5 Efficacy Analyses

9.5.1 Primary Efficacy Analysis

Objective response rate is defined as the number (%) of patients with confirmed CR or PR via RECIST 1.1 and will be based on the patients in the Response-evaluable Population for the co-primary endpoint. The number and percentage of subjects with each response category will be displayed. The ORR estimate will be accompanied by a two-sided exact binomial 95% confidence interval. The confirmed CR rate as well as ORR including unconfirmed and confirmed CR and PR will also be provided and accompanied by a two-sided exact binomial 95% confidence interval. This analysis may also be explored in the subset of patients in the Response-Evaluable population excluding patients with selected important protocol deviations. Protocol deviations leading to exclusion from analysis may include (but are not limited to):

- Inclusion criteria: Diagnosis not confirmed as per protocol
- Informed consent: Failure to obtain Informed Consent
- Study drug: Study drug prepared incorrectly
- Study Drug: Administration error
- Assessment of efficacy: Protocol defined evaluations not performed before administration of 1st dose of study drug
- Assessment of efficacy: Failure to use the same assessment method for disease assessment imaging
- Assessment of efficacy: Missed determination of cancer progression
- Assessment of efficacy: Assessment of tumor response not performed/documented as per protocol
- Assessment of efficacy: Failure to obtain baseline radiology scan to document pre-therapy tumor size
- Use of Prohibited co-medication

Decisions on subjects to be excluded will be made prior to database lock and recorded in the Data Review Meeting minutes.

All RECIST v1.1 assessments, whether scheduled or unscheduled, will be included in the calculations but only those prior to the start of subsequent systemic anti-cancer therapy will be included in the calculations, regardless of treatment termination.

At each visit, patients will be assigned a RECIST version 1.1 visit response of CR, PR, SD, NE or PD depending on the status of their disease compared with baseline and previous assessments by the Investigator-reported and derived results. Baseline will be assessed within the 28 days prior to enrollment.

Lesions assessed by the investigator (target, non-target, and new lesions) and both investigator-reported and derived RECIST v1.1 disease assessments will be presented in listings.

9.5.2 Secondary Efficacy Analyses

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. The number and percentage of subjects with each response category will be displayed. The ORR estimates will be accompanied by a two-sided exact binomial 95% confidence interval. These tables will also be presented for subjects based on their line of therapy and platinum refractory status. Disease assessments per irRECIST will be provided in a listing.

PFS and OS will be summarized descriptively using the Kaplan-Meier method. Please refer to SAP Section 4.0 Variables and Section 5.0 Definitions for more details regarding event and censoring definitions. The total number of censored patients and total number of patients with events will be provided. In addition, the median survival estimates (along with 95% confidence interval), 25th and 75th Kaplan-Meier percentiles,

and Kaplan-Meier survival rates at 3, 6, 9, 12, and 24 months (along with 95% confidence intervals) will be provided. These analyses will be performed for patients in the response-evaluable and as-treated population.

Disease control rate is defined as N (%) patients with CR, PR, or SD at 8, 16, and 24 weeks (SD maintained for ≥ 8, 16, or 24 weeks, respectively) using RECIST version 1.1. For SD determination for DCR, the patient must have lack of progression for the first X number of weeks on study, where X corresponds to 8, 16, and 24 weeks as applicable. Disease control rate will be assessed in the Response-evaluable and As-treated populations. The estimate will be accompanied by a two-sided exact binomial 95% confidence interval.

Time to response and duration of response according to RECISTv1.1 will be estimated using the Kaplan-Meier method and summarized descriptively (median, percentiles, and 95% confidence interval). Kaplan-Meier plots will be provided for the Response-Evaluable population, with separate curves for patients in 1L platinum-refractory, 1L platinum non-refractory and 2L+ groups, and [redacted].

Time to response, duration of response, OS and PFS will be presented in listings.

Spaghetti plot of tumor size change from baseline and waterfall plots of maximum tumor size reduction from baseline as assessed by the investigator according to RECISTv1.1 will be provided for the As-treated and Response Evaluable populations.

[redacted]

9.6 Safety Analyses

9.6.1 Adverse Events

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

AE occurring before treatment with IP (eg, non-treatment emergent) will be included in the data listings but will not be included in the summary tables of AEs. Any AE occurring after first dose of IP and within 90 days of last dose of IP will be included in the AE summaries.

A separate data listing of AEs occurring more than 90 days after last dose of IP will be included in the listing for non-treatment emergent AE. These events will not be included in AE summaries.

An AE will be considered to be a TEAE if it begins or worsens on or after the first administration of either study drug up to 90 days following the last dose of the last study treatment. AEs/SAEs that occur post informed consent signature but prior to IP administration are non-treatment-emergent AEs/SAEs.

A summary of TEAEs, including the number of events reported, the number and percentage of patients reporting at least one AE, the number and percentage of patients discontinuing due to an AE, the number and percentage of patients with at least one SAE, and the number and percentage of deaths will be presented. In reality all AEs which change in severity or relationship to study drug are assigned a new start date and captured as a new record.

A breakdown of the number and percentage of patients reporting each AE, categorized by system organ class and preferred term coded according to the MedDRA dictionary v22.0, will be presented. Note that

counting will be by patients not event and patients are only counted once within each system organ class or preferred term.

A further tabulation of these data, categorized by relationship to study drug, will be presented. Patients with multiple events within a particular system organ class or preferred term will be counted under the category of their related event within that system organ class or preferred term. Relationship will be categorized as MEDI0457-related, Durvalumab-related, study procedure related, device related, or treatment related (any relation or missing relation).

A summary of events reported, categorized by severity (CTCAE version 4.03 Grades 1-5) will also be provided. Patients with multiple events within a particular system organ class or preferred term will be counted under the category of their most severe event within that system organ class or preferred term.

Summaries of AEs leading to discontinuation from either study drug or modifications (delay, interruption, reduction, or omission) of either study drug will be provided, grouped by system organ class and preferred term.

Adverse events of special interest are categorized on the CRF and described in SAP Section 4.1.1.3. The number and percentage of patients reporting at least one AESI will be tabulated, as well as the number and percentage of patients in each category. Adverse events of special interest may be further tabulated by severity, treatment relation, and seriousness. Administration site reactions will be graded using CTCAE and the Administration Site Reaction Grading Scale (Mild: Grade 1, Moderate: Grade 2, Severe: Grade 3, Potentially life threatening: Grade 4) (See Appendix I of the protocol).

A listing of DLTs will be provided.

A listing of AEs for patients that are any ADA positive will be provided.

A table of non-serious treatment-emergent AE occurring in greater than 5% of subjects will be provided by system organ class and preferred term. If there are no classes or terms with greater than 5% frequency, this percentage may be reduced to >2%.

9.6.2 Deaths and Serious Adverse Events

All deaths will be reported in a subject listing, which will include the date of death, primary cause of death, and date of first and last doses of study treatment. A table of mortality will be presented to indicate time of death while on study (<=90 days post-last dose, >90 days post-last dose) and cause of death in relation to investigational product. Another table will be presented for treatment-emergent AE resulting in death by system organ class and preferred term.

The number and percentage of patients experiencing SAEs will be presented by SAE criteria and total. Serious AE and treatment-related serious AE will be tabulated by system organ class and preferred term.

9.6.3 Laboratory Data and other Observations Related to Safety

Descriptive statistics will be provided for the clinical laboratory results (chemistry, hematology, urinalysis and thyroid function testing) and vital signs and changes from baseline by visit for visits with more than 5 subjects. Standard shift tables will be prepared for hematology and serum chemistry parameters presenting worst post-baseline CTCAE toxicity grade vs baseline. A shift table by reference range (low, normal, high) will be presented for other laboratory parameters that have references ranges but are not coded by CTCAE version 4.03.

A table and listing will be provided for laboratory results for subjects with potential Hy's law.

ECG change from baseline for minimum, maximum, and last record on treatment will be tabulated. The number and percentage of subjects meeting criteria for notable QTC intervals will be presented. For each planned visit for which a triplicate ECG is obtained, the average of the 3 values should be calculated for each parameter at each timepoint. The average values will be used for the ECG tables. Listings will include individual and averaged values.

A shift summary of ECOG performance status will be provided presenting worst post-baseline status vs baseline.

Laboratory and safety data will be listed by subject per the TFL shells. Where applicable and described in the TFL shells, change from baseline will be included in the listings. Pregnancy testing and physical exam data will be listed only.

Bleeding and pneumonitis questionnaire data will be presented in listings. Blood gases, serum ILD markers, and pulmonary function tests will not be tabulated or listed (some of these data will be provided as part of the listings for questionnaires). Tumor biopsy sample collection from the CRF will also not be tabulated or listed.

9.7 Pharmacokinetics and Antidrug Antibodies

Pharmacokinetics and immunogenicity data (secondary objectives) will be summarized and tabulated by PRA and will be reported in the PRA Clinical Study Report.

9.7.1 Pharmacokinetic Analysis

Pharmacokinetic (PK) concentration data summary statistics will be tabulated by visit (including n, geometric mean and geometric CV%, minimum and maximum (list non-exhaustive)). Individual serum concentration-time profiles of durvalumab will be reported as listing. Due to the sparse PK sampling used in this study, formal non-compartmental analysis to derive PK parameters (e.g. terminal half-life) will not be conducted. A population PK model may be developed by Astrazeneca or vendor with similar data from other studies to further characterize the PK properties of durvalumab when administered in combination with MEDI0457 but will be reported outside of the CSR if conducted.

9.7.2 Immunogenicity Analysis

Immunogenicity results will be analyzed descriptively by summarizing the number and percentage of patients who develop detectable anti-durvalumab antibodies. The immunogenicity titers will be reported in the listing for samples confirmed positive for the presence of ADAs. The effect of immunogenicity on PK and safety may be performed, if the data allow, by Astrazeneca.

9.8 Exploratory Analyses

[redacted].

9.9 Methods for Handling Dropouts and Missing Data

There will be no imputation of missing data for analysis. It is expected that year will always be provided in the CRF; however, unknown day and unknown month is allowed for historic (pre-study) dates (medical history, prior anticancer treatment, pre-study concomitant medications). Missing day will be displayed as UN and missing month as UNK.

9.10 Multiplicity

There is no formal statistical testing in this study. [redacted]

9.11 Pooling of Sites

Data will be pooled across centers for all analyses.

10.0 Validation

PRA's goal is to ensure that each TFL delivery is submitted to the highest level of quality. Our quality control procedures will be documented separately in the study specific quality control plan.

References

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Oken MM, Creech R, Tormey DC, Horton J, Davis TE, McFadden ET al. Toxicity and Response Criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5:649-55.

Appendix 1 Glossary of Abbreviations

Glossary of Abbreviations:	
ADA	Antidrug antibodies
AE	Adverse event
AESI	Adverse event of special interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
β-HCG	Beta-Human Chorionic Gonadotropin
BMI	Body Mass Index
C	Celsius
CPK	Creatine Phosphokinase
CRF	Case Report Form
CR	Complete response
CSR	Clinical Study Report
CT	Computed Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CTMS	Clinical Trials Management System
DCR	Disease control rate
DCR-16w	Disease Control Rate at 16 weeks
DLT	Dose limiting toxicity
SDMC	Safety Data Monitoring Committee
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISPOT	Enzyme-linked immunospot
EOT	End of treatment
EP	Electroporation
F	Fahrenheit
FSH	Follicle-Stimulating Hormone
HIV	Human Immunodeficiency Virus
HPV	Human papilloma virus

HPV-16	Human Papilloma Virus Type 16
HPV-18	Human Papilloma Virus Type 18
HR	Heart rate
IHC	Immunohistochemistry
ILD	Interstitial Lung Disease
IM	Intramuscular
INR	International Normalized Ratio
IP	Investigational Product
irRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
IV	Intravenous
IVRS	Interactive Voice Response System
KM	Kaplan Meier
LH	Luteinizing Hormone
MTD	Maximum tolerated dose
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
ORR	Objective response rate
OS	Overall survival
PD	Progressive disease
[redacted]	[redacted]
[redacted]	[redacted]
PK	Pharmacokinetic
PFS	Progression free survival
PP	Per Protocol
PR	Partial response
PRA	PRA Health Sciences
PR interval	Interval on the electrocardiogram, from the start of the P wave to the start of the R wave
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

RECISTv1.1	Response Evaluation Criteria in Solid Tumors version 1.1
RR interval	Interval on the electrocardiogram, time elapsing between two consecutive R waves
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event
SCCHN	Squamous cell carcinoma of the head and neck
SD	Stable disease
SDMC	Safety Data Monitoring Committee
SDTM	Study Data and Tabulation Model
T_3	Triiodothyronine
T_4	Thyroxine
TBL	Total Bilirubin
TEAE	Treatment-Emergent Adverse Event
TFL	Tables, Figures, and Listings
[redacted]	[redacted]
TNM	TNM Classification of Malignant Tumors
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WHO	World Health Organization