



Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

**A PHASE II EXPLORATORY STUDY OF DURVALUMAB
(MEDI4736) IN HIV-1 PATIENTS WITH ADVANCED SOLID
TUMORS**

DURVAST: Durvalumab in solid tumors

Study Sponsor: Spanish Lung Cancer Group (SLCG/GECP)

EudraCT Number: 2016-004524-38

Sponsor code: GECP 16/04

Astra Zeneca Study number: ESR 15-10869

Version 4.0

Protocol Signature Page

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Approved by:

Signature



Dr. Rafael Rosell
Principal Investigator

Signature



Dr. González Cao
Study coordinator

Signature



Dr. Mariano Provencio
SLCG President

Principal Investigator Protocol Signature Page

Study Title: “A phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors”

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Protocol version: v 4.0, 16th April 2018

As principal investigator of this site, I hereby confirm that:

I have read the protocol and agree that it contains all necessary details for conducting this trial. I will conduct the trial as outlined in the following protocol and in compliance with GCP, and will apply due diligence to avoid protocol deviations.

I will provide copies of the protocol and all drug information relating to pre-clinical and prior clinical experience furnished to me by the SLCG, to all physicians responsible to me who participate in this trial. I will discuss this material with them to assure that they are fully informed regarding the drug and the conduct of the trial.

I agree to keep accurate records on all patient information including patient's informed consent statement, drug shipment and return forms, and all other information collected during the trial for a minimum period of 25 years according to the new Royal Decree 1090/2015 approved in Spain.

Name of Principal Investigator: _____

Institution's name and place: _____

Signature

Date

Clinical Study Protocol

Drug Substance Durvalumab (Medi4736)

Sponsor code: GECP 16/04_ Astra Zeneca Study number: **ESR 15-10869**

Version Number 4.0

Date 16^h April 2018

Investigational Drug Substance(s)	Durvalumab (Medi4736)
Version	4.0
Date	16 th April 2018

A phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors

Sponsor:

Spanish Lung Cancer Group (SLCG)

Av. Meridiana, 358 6^a Planta

08027 Barcelona

Phone:+34 93 430 20 06 / Fax: +34 93 419 17 68

E-mail: gecp@gecp.org

Principal Investigator:

Dr. Rafael Rosell

Instituto Oncológico Dr. Rosell

Oncology Department

Sabino Arana 5

08028 Barcelona

Phone: +34935460135 / Fax: +34935460196

E-mail: rrosell@iconcologia.net

Study Coordinator:

Dr. María Gonzalez-Cao

Instituto Oncológico Dr. Rosell

Oncology Department

Sabino Arana 5

08028 Barcelona

Phone: +34935460135

E-mail: mgonzalezcao@oncorosell.com

PROTOCOL SYNOPSIS

Clinical Protocol GECP16/04 (ESR 15-10869)

Study Title: Phase II exploratory study of durvalumab (MEDI4736) in HIV-1 patients with advanced solid tumors
Protocol Number: GECP 16/04 (ESR-15-10869)
Clinical Phase: II
Study Duration: Recruitment period will be 12 months First subject in: Q1, 2016 Last subject out: Q1, 2018 Survival follow-up will continue until 5 years after the last subject receives the last dose of durvalumab
Investigational Product(s) and Reference Therapy: Durvalumab will be supplied in glass vials containing 500 mg of liquid solution at a concentration of 50 mg/mL for intravenous (IV) administration.
Research Hypothesis PD-1/ PD-L1 coinhibitory pathway plays a significant role in the regulation of the immune response in both chronic infectious diseases and cancer. Preclinical and animal data support the safety and promising activity of anti-PD-1 antibody in HIV-1 infection. Demonstrated anticancer activity and safety profile of durvalumab (MEDI4736) in cancer clinical trials. Unlikely drug interactions of durvalumab (MEDI4736) and antiretroviral treatments. We propose a phase II clinical study designed to assess the feasibility of durvalumab (MEDI4736) in HIV-1-infected individuals with solid tumors. Additionally we hope to obtain data that let us understand

the possible benefit of this treatment in cancer patients and HIV infection, exploring if activity of durvalumab (MEDI4736) could be higher in cancer that has been produced at least in part due to the chronic immunosuppression. Simultaneously, it will allow us to investigate the effect of disrupting this immunoregulatory pathway might have in reversing cancer pathways and HIV-specific T-cell function during persistent chronic HIV infection in humans.

In this regard, our hypothesis is:

HIV patients with cancer have a similar outcome in terms of tolerability when treated with durvalumab (MEDI4736) monotherapy at the recommended dose than non HIV infected patients.

Objectives:

Primary Objectives:

To explore the feasibility of durvalumab (MEDI4736) monotherapy at the recommended dose of 1500mg every 4 weeks in solid tumors in HIV-1-infected patients.

Secondary Objective(s):

- To assess ORR (RECIST 1.1 and irRECIST) and duration of response.
- To evaluate the PFS rate at 6 months.
- To evaluate the OS rate at 12 months.

Exploratory Objective(s):

- To measure activity of durvalumab (MEDI4736) in terms of antiviral activity, exploring:
 - Changes in the viral reservoir.
 - Changes in residual viral replication.
 - Changes in the composition and function of circulating T lymphocytes.
- To explore molecular predictive factors of antitumoral activity in pretreatment tumor samples.

Study Design:

This is a multicenter, national, nonrandomized, open label trial, phase II trial in subjects with advanced solid tumors and HIV-1 infection. Twenty patients will receive durvalumab.

Patients have to be diagnosed of advanced (metastatic or locally advanced disease without cure options with surgery or radiotherapy) cancer of any of these types: lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastro-esophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity.

Adverse events (AEs) will be assessed throughout and evaluated using National Cancer Institute (NCI)

Common Technology Criteria version of Adverse Events version 4.03 (CTCAE v 4.03).

Tumor measurements by PET-CT, CT scan or MRI will be performed every 8 weeks to determine response to treatment. Response will be evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and immune related response criteria (irRECIST).

Treatment will continue until disease progression, significant clinical deterioration, unacceptable toxicity, any criterion for withdrawal from the trial or trial drug is fulfilled. Treatment may continue past the initial determination of disease progression per RECIST1.1 if the subject's performance status has remained stable, and if the opinion of the Investigator, the subject will benefit from continued treatment and if other criteria are fulfilled as outline in the protocol.

Number of Centers: between 5 and 10

Number of Subjects: 20

Study Population:

The study will be performed in 20 HIV patients with a histological confirmed diagnosed of advanced solid tumors (lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastro-esophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity) for which no additional oncologic standard treatment is available, or for which the subject declines standard treatment.

Recruitment period will be 12 months.

Patients will continue their antiretroviral treatment during study time, following standard HIV-1 treatment recommendations.

Inclusion Criteria:

1. Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
2. Age \geq 18 years at time of study entry.
3. Eastern Cooperative Oncology Group (ECOG) 0-2
4. Life expectancy of \geq 16 weeks
5. Adequate normal organ and marrow function as defined below:

- Haemoglobin ≥ 9.0 g/dL
- Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9/L$ (≥ 1500 per mm^3)
- Platelet count $\geq 100 \times 10^9/L$ ($\geq 100,000$ per mm^3)
- Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5 x ULN
- Serum creatinine $\text{CL} > 40$ mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight(kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

6. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥ 60 years old and no menses for ≥ 1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.
7. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

8. Subjects with histologically or cytologically advanced/metastatic-documented lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastroesophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity, refractory to standard treatment, intolerant of standard treatment, or for which no standard therapy exists or who refuse the standard treatment.
9. Subjects may be included irrespectively of number of previous lines of treatment for advanced disease.
10. Prior palliative radiotherapy must have been completed at least 2 weeks prior to start the study treatment (subjects may receive localized palliative radiotherapy while receiving study drug).
11. Documented HIV-1 infection
12. Undetectable viral load in the last analysis.
13. Subjects with brain metastases are eligible if they are asymptomatic, are treated or are neurological stable for at least 2 weeks without the use of steroids or on stable or decreasing dose of < 10 mg daily prednisone or equivalent.
14. Subjects must be following an antiretroviral therapy at the moment of the inclusion.

Exclusion Criteria:

1. Involvement in the planning and/or conduct of the study. Previous enrollment in the present study.
2. Participation in another clinical study with an investigational product during the last 4 weeks.
3. Other untreated coexisting HIV related malignancies.
4. Any previous treatment with a PD1, PD-L1 or PD-L2 inhibitor, including durvalumab.
5. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine

therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) 28 days prior to the first dose of study drug.

6. Mean QT interval corrected for heart rate (QTc) ≥ 470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.
7. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
8. Any unresolved toxicity (CTCAE grade 2) from previous anti-cancer therapy. *Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy).*
9. Any prior Grade ≥ 3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE $>$ Grade 1.
10. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
11. Any syndrome that requires systemic corticosteroid/immunosuppressive medications EXCEPT for syndromes which would not be expected to recur in the absence of an external trigger (vitiligo, autoimmune thyroiditis, or type 1 diabetes mellitus are permitted to enroll)
12. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).
13. History of primary immunodeficiency.
14. History of allogeneic organ transplant.
15. History of hypersensitivity to durvalumab or any excipient.
16. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic

hepatitis B or C, or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

17. Known history of active tuberculosis.
18. Any serious or uncontrolled medical disorder or active infection non HIV, that would impair the ability of the subject to receive the treatment of protocol therapy under treating physician criteria.
19. Subjects with previous malignances (except non melanoma skin cancer, and cancer in situ of: bladder, gastric, colon, cervical/dysplasia, melanoma, breast) are excluded unless a complete remission was achieved at least 5 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.
20. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.
21. Female subjects who are pregnant, breast-feeding, male, or female patients of reproductive potential who are not employing an effective method of birth control.
22. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
23. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
24. Subjects with uncontrolled seizures.
25. Patients with tumoral disease in the head and neck region, such as peritracheal or periesophageal lymph node involvement, with infiltration of structures of the digestive, aerea or vascular pathways that represent a risk of increased bleeding.
26. Patients with neuroendocrine tumors of pulmonary origin or pulmonary metastases with evidence of active bleeding.
27. Patients with digestive bleeding.

Investigational Product(s), Dose and Mode of Administration:

Durvalumab, 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) if > 30 kg.

If patient is ≤ 30 kg, weight-based dosing, equivalent to 20 mg/kg Q4W, should be used (Appendix 2).

Study Assessments and Criteria for Evaluation:

Safety Assessments:

- Safety assessments will be based on adverse event reports, results of clinical laboratory tests, immune safety tests, physical examinations, vital sign measurements, ECOG performance status during the study and up to six months following the last study drug administration. It will be reported based on Common Terminology Criteria for Adverse Events (CTCAE) v4.0.

Efficacy Assessments:

- Tumor response evaluation will be classified according to RECIST 1.1 criteria and irRECIST criteria.
- Progression free survival at 6 months and overall survival at 12 months.

Translational study

All patients will undergo baseline tumor tissue acquisition (paraffin-embedded cores) prior to enrollment. If it is not possible to perform a new biopsy, patient can be included if they have an archival tissue biopsy.

Peripheral blood samples will be collected: pretreatment, after 2 weeks, 4 weeks, 12 weeks, 24 weeks. Patients that continue on treatment after 24 weeks will have peripheral blood samples every 12 weeks until disease progression or at least until week 72 in the absence of progression.

Statistical Methods and Data Analysis:

The primary endpoint of the study is the feasibility of durvalumab monotherapy at the recommended dose of 1500 mg every 4 weeks in solid tumors in HIV-1-infected patients.

Feasibility will be defined based on the rate of patients that will complete at least 4 treatment cycles. One cycle is four weeks with infusions every four weeks. It is assumed that at least 50% of patients must be complete 4 cycles for considering feasible the treatment with durvalumab.

Kaplan Meier method will be used to estimate the survival function. Secondary measurements will be PFS rate at 6 months and OS rate at 12 months.

Sample Size Determination:

Sample size calculation for an estimated proportion of 50% with a level of confidence of 95% and a

Clinical Study Protocol

Drug Substance Durvalumab (Medi4736)

Sponsor code: GECP 16/04_ Astra Zeneca Study number: **ESR 15-10869**

Version Number 4.0

Date 16^h April 2018

accuracy of 22%: 20 patients must be included in this study.

Table 1. SCHEDULE OF STUDY ASSESSMENTS

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	Screening	Baseline	Every 4 weeks	Every 8 Weeks	Every 12 Weeks	First Follow up	Follow up month 2 and 3 since last dose	Follow up months 4, 6, 8 and 10 since last dose	Follow up month 12 since last dose, then every 6 month
Day	-28 to -1	1				30 days since last dose			
Week	-4 to -1	0	4, 8, 12, 16, 20, etc	8, 16, 24, 32, 40 and 48	12, 24, 36, 48				
			(-3/+1 days)			(±3 days)	(±7 days)	(±7 days)	(±14 days)
Written informed consent/assignment of subject identification number	X								
Preliminary eligibility fulfillment (investigator's opinion)	X								
Demography and history of tobacco	X								
Previous treatments for solid tumors	X								
Archival FFPE tumor tissue sample	X								

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Week	-4 to -1	0	4, 8, 12, 16, 20, etc	8, 16, 24, 32, 40 and 48	12, 24, 36, 48				
			(-3/+1 days)			(±3 days)	(±7 days)	(±7 days)	(±14 days)
Archived or new biopsy, (Section 8.3 further detail)	X								
Formal verification of eligibility criteria	X								
Medical and surgical history	X								
HIV infection history	X								
Hepatitis B and C; HIV serology	X								
Urine hCG or serum βhCG ^b	X			X		X		X (only in month 4 and if the patient ends treatment for a different reason than progression disease)	

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Week	-4 to -1	0	4, 8, 12, 16, 20, etc	8, 16, 24, 32, 40 and 48	12, 24, 36, 48				
			(-3/+1 days)			(±3 days)	(±7 days)	(±7 days)	(±14 days)
Durvalumab administration (monotherapy)		X	X						
Physical examination ^c	X	X	X			X			
Vital signs (pre- during and post-infusion vital signs assessments)	X	X ^d	X ^d			X			
Weight	X	X	X			X			
Electrocardiogram ^e	X	X (as clinically indicated)		X (week 16 only)					
Adverse event/serious adverse event assessment ^k	X	X	X	X	X	X	X		
Concomitant medications ^k	X	X	X	X	X	X	X		

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Day	-28 to -1	1				30 days since last dose			
Week	-4 to -1	0	4, 8, 12, 16, 20, etc	8, 16, 24, 32, 40 and 48	12, 24, 36, 48				
			(-3/+1 days)			(±3 days)	(±7 days)	(±7 days)	(±14 days)
ECOG performance status	X	X	X	X	X	X	X	X (only in months 6 and 9 since last dose and if the patient completed the treatment without progression)	X (only if the patient completed the treatment without progression)
Serum Chemistry (complete clin chem. panel including Liver enzymes)	X	X ^f	X			X	X		
Thyroid function tests (TSH and fT3 and fT4) ^g	X	X	X			X			
Hematology, CD4+ T cell counts, CD8+ T cell counts and Plasma viral load	X	X ^f	X			X	X		X

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Day	-28 to -1	1				30 days since last dose			
Week	-4 to -1	0	4, 8, 12, 16, 20, etc	8, 16, 24, 32, 40 and 48	12, 24, 36, 48				
			(-3/+1 days)			(±3 days)	(±7 days)	(±7 days)	(±14 days)
Urinalysis ^h	X	X	X						
Coagulation parameters ⁱ	X								
Blood samples translational study and plasma viral load ^l	X		X (only week 2 and 4)		X				
Flow cytometry collection of whole blood CD4, CD8 subsets ^l	X		X (only week 2 and 4)		X				
Tumor assessment (PET-CT, CT or MRI) ^j	X			X (-5 days)	X (±7 days) (after 48 weeks)				
Palliative radiotherapy						As clinically indicated			
Subsequent anti-cancer therapy						X	X	X	X
Survival status ^m							X	X	X (every 2 month)

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- b Pre-menopausal female subjects of childbearing potential only. This test has to be done every 2 cycles and in the first follow up.
- c Full physical examination at baseline; targeted physical examination at other timepoints.
- d Subjects will have their blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):
- At the beginning of the infusion (at 0 minutes)
 - At 30 minutes during the infusion (± 5 minutes)
 - At the end of the infusion (at 60 minutes ± 5 minutes)
 - In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (± 5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated. If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should be collected every 30 minutes (± 5 minutes) and as described above or more frequently if clinically indicated.
- e ECG during screening, at Day 1 and week 16. Thereafter as clinically indicated. Screening and abnormal ECG at any time in triplicate others single. On Day 1 and week 16, ECGs should be taken within an hour prior to the start of the infusion and at least one time point 0 to 3 hours after the infusion.
- f If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Gamma glutamyltransferase tested at Screening, Day 1 and as clinically indicated.
- g Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.
- h Urinalysis performed at Screening, Day 1, every 4 weeks and as clinically indicated.
- i Coagulation tests: prothrombin time, APTT and INR – only performed at Screening and as clinically indicated.
- j CT (preferred) or MRI scans, preferably with IV contrast, are collected during screening (for baseline) and as close to and prior to initiation of study treatment. Timing of on-treatment (follow-up) CT/MRI scans is every 8 weeks (-5 days) for the first 48 weeks and then every 12 weeks (± 1 week) until PD or off-study. Response according to RECIST 1.1 criteria (CR, PR) requires a confirmatory scan preferably at the next regularly scheduled imaging visit and no earlier than 4 weeks after the prior assessment of CR, PR, or SD. If MRI is used, CT of chest is mandatory). A brain MRI scan is required only following the investigator criteria. For subjects who achieve disease control following 12 months of treatment, tumour assessments should be performed every 12 weeks (± 1 week) relative to the date of first infusion thereafter until confirmed PD by RECIST 1.1 by investigational site review. For subjects who discontinue durvalumab due to toxicity (or symptomatic deterioration), tumour assessments should be performed relative to the date of first infusion as follows: every 8 weeks (± 1 week) for the first 48 weeks, then every 12 weeks (± 1 week) until confirmed PD by RECIST 1.1 by investigational site review. Upon confirmed PD, scans should be conducted according to local standard clinical practice and submitted for central review until a new treatment is started (these scans are optional).

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- k AEs and concomitant medications will be documented at each trial visit and between visits by weekly telephone contact.
- l Blood samples for determination of soluble factors will be collected from all subjects prior to infusion on Day 1 (baseline samples for soluble factors may also be collected at Screening, instead of on Day 1 prior to dosing) and **within 2 hours** before infusion.
- m Phone contact with subjects who refuse to return for evaluations and agree to be contacted

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ABBREVIATIONS AND DEFINITION OF TERMS

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

Abbreviation or special term	Explanation
ADA	anti-drug antibody
ADCC	antibody-dependent cell-mediated cytotoxicity
AE	adverse event
AESI	adverse event of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
APC	antigen-presenting cells
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
CDC	Complement dependent cytotoxicity
CI	confidence interval
CL	clearance
C _{max}	peak concentration
C _{max,ss}	peak concentration at steady state
C _{min}	trough concentration
C _{min,ss}	trough concentration at steady state
CNS	central nervous system
CR	complete response
CT	computed tomography
CTLA-4	cytotoxic T-lymphocyte-associated antigen-4
DC	disease control

Abbreviation or special term	Explanation
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response
ECG	electrocardiogram
ECOG	Eastern Cooperative Oncology Group
EDTA	disodium edetate dihydrate
Fc	fragment crystallizable
FFPE	formalin fixed paraffin embedded
FSH	follicle-stimulating hormone
FTIH	first-time-in-human
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GLP	Good Laboratory Practice
HCl	hydrochloride
HIV	human immunodeficiency virus
ICF	informed consent form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IFN	interferon
IGF	insulin-like growth factor
IgG1	immunoglobulin G1
IgG2	immunoglobulin G2
IGSF	immunoglobulin superfamily
IHC	immunohistochemistry

Abbreviation or special term	Explanation
IL	interleukin
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous(ly)
MAb	monoclonal antibody
MDSC	Myeloid derived suppressor cells
MedDRA	Medical Dictionary for Regulatory Activities
miRNA	micro ribonucleic acid
MRI	magnetic resonance imaging
mRNA	messenger ribonucleic acid
MTD	maximum tolerated dose
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events
NK	natural killer
NOAEL	no-observed-adverse-effect level
NSCLC	non-small cell lung cancer
OR	objective response
ORR	objective response rate
OS	overall survival
PD	progressive disease
PD-1	programmed cell death 1
PD-L1	programmed cell death ligand 1
PD-L2	programmed cell death ligand 2
PFS	progression-free survival
PK	pharmacokinetic(s)

Abbreviation or special term	Explanation
PR	partial response
PRO	patient-reported outcome
PVC	polyvinyl chloride
Q2W	every 2 weeks
Q3M	every 3 months
Q3W	every 3 weeks
Q4W	every 4 weeks
Q12W	every 12 weeks
QoL	quality of life
QTc	the time between the start of the Q wave and the end of the T wave corrected for heart rate
QTcF	QT interval on ECG corrected using the Frederica's formula
RCC	renal cell carcinoma
RECIST	Response Evaluation Criteria in Solid Tumors
RNA	ribonucleic acid
SAE	serious adverse event
SD	stable disease
SID	subject identification
sPD-L1	soluble programmed cell death ligand 1
SOCS3	suppressor of cytokine signaling 3
SUSAR	suspected unexpected serious adverse reaction
$t_{1/2}$	half-life
TEAE	treatment-emergent adverse event
TIL	tumor infiltrating lymphocyte
Tmax	time to peak concentration

Clinical Study Protocol

Drug Substance Durvalumab (Medi4736)

Sponsor code: GECP 16/04_ Astra Zeneca Study number: **ESR 15-10869**

Version Number 4.0

Date 16th April 2018

Abbreviation or special term	Explanation
Tmax,ss	time to peak concentration at steady state
TNF- α	tumor necrosis factor alpha
TSH	thyroid stimulating hormone
ULN	upper limit of normal
USA	United States of America
WFI	water for injection
WHO	World Health Organization

1. INTRODUCTION

1.1 Disease Background

After more than three decades fighting the Human Immunodeficiency Virus type 1 (HIV-1) – the etiologic agent of the acquired immunodeficiency syndrome (AIDS) – this lentivirus has spread worldwide, causing a pandemic that seriously challenges public health. In 2012, 35 million people were living with HIV-1, 1.6 million people had died from AIDS and 2.3 million people got newly infected (AIDS epidemic update 2013; <http://www.unaids.org>). Major advances in Antiretroviral Therapy (ART) have resulted in a dramatic decline in HIV-related deaths. However, no current treatment regimen leads to viral eradication or restoration of HIV-specific immune responses capable of durable viral control after cessation of ART. Thus, there is a need for novel interventions that could complement ART in order to eliminate virus or reach a state of "functional cure"(1, 2). It has been shown in murine models and humans that the negative co-signaling molecule programmed-death 1 (PD-1) plays an active and reversible role in mediating T-cell exhaustion in chronic infections (3). Therefore, there is a potential of immunotherapeutic interventions targeting PD-1 in order to augment immune responses or facilitate viral eradication.

Malignancies account for more than a third of all deaths in human immunodeficiency virus (HIV)-positive patients. Although acquired immunodeficiency syndrome-related mortality is decreasing with the introduction of effective antiretroviral therapy, it has been reported a significant increase in the proportion of non-acquired immunodeficiency syndrome defining malignancies (NADC) from 20% in the pre-HAART era to 71% of all tumors now. People infected with HIV are at least 25 times more likely to be diagnosed with anal cancer than uninfected people, 5 times as likely to be diagnosed with liver cancer and 3 times as likely to be diagnosed with lung cancer(4). Often these patients present with advanced disease and at a younger age than general population(5). As HAART has reduced the number of deaths from AIDS, the HIV-infected population has grown in size and become older. The fastest growing proportion of HIV-infected individuals is the over-40 age group. These individuals are now developing cancers common in older age. In 2003, the proportion of these other cancers exceeded the number of AIDS-defining malignancies(6). Lung cancer has now become the leading cause of mortality among the non-acquired immunodeficiency syndrome defining malignancies. Development of lung cancer in patients with HIV has been linked to various factors including not only smoking habit, but also CD4 count, viral load and the intensity and duration of immune deficiency(4).

Immune responses directed against tumors are one of the body's natural defenses against the growth and proliferation of cancer cells. However, over time and under pressure from immune attack, cancers develop strategies to evade immune-mediated killing allowing them to develop unchecked. One such mechanism involves upregulation of surface proteins that deliver inhibitory signals to cytotoxic T cells. Programmed cell death ligand 1 (PD-L1) is one such protein, and is upregulated in a broad range of cancers with a high frequency, with up to 88% expression in some tumor types. In a number of these cancers, including lung(7), renal(8), pancreatic(9), ovarian cancer(10) and hematologic malignancies(11, 12) tumor cell expression of PD-L1 is associated with reduced survival and an unfavorable prognosis.

Programmed cell death ligand 1 is part of a complex system of receptors and ligands that are involved in controlling T-cell activation. PD-L1 acts at multiple sites in the body to help regulate normal immune responses and is utilized by tumors to help evade detection and elimination by the host immune system tumor response. In the lymph nodes, PD-L1 on antigen-presenting cells binds to PD-1 or CD80 on activated T cells and delivers an inhibitory signal to the T cell(13, 14). This results in reduced T-cell activation and fewer activated T cells in circulation. In the tumor microenvironment, PD-L1 expressed on tumor cells binds to PD-1 and CD80 on activated T cells reaching the tumor. This delivers an inhibitory signal to those T cells, preventing them from killing target cancer cells and protecting the tumor from immune elimination (15).

1.1.1 Immunotherapies

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors (**¡Error! No se encuentra el origen de la referencia.**). PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor (**¡Error! No se encuentra el origen de la referencia.**) and to CD80 (**¡Error! No se encuentra el origen de la referencia.**). PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by the immune system. Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (e.g., IFN γ) and can be found on both tumor cells (TC) and tumor-infiltrating IC. The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, preventing them from killing target TC and protecting the tumor from immune elimination (). PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated (**¡Error! No se encuentra el origen de la referencia.; ¡Error! No se encuentra el origen de la referencia.**).

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on

immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28.

In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell–dependent mechanism (**¡Error! No se encuentra el origen de la referencia.**).

PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti–PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti–PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients (**¡Error! No se encuentra el origen de la referencia.; ¡Error! No se encuentra el origen de la referencia.; ¡Error! No se encuentra el origen de la referencia.; ¡Error! No se encuentra el origen de la referencia.; ¡Error! No se encuentra el origen de la referencia.**) with responses that tend to be more pronounced in patients with tumors that express PD-L1 (**¡Error! No se encuentra el origen de la referencia.; ¡Error! No se encuentra el origen de la referencia.; ¡Error! No se encuentra el origen de la referencia.**). In addition, high mutational burden (e.g., in bladder carcinoma [**¡Error! No se encuentra el origen de la referencia.**]) may contribute to the responses seen with immune therapy.

In contrast, cytotoxic T-lymphocyte-associated antigen-4 (CTLA-4) is constitutively expressed by regulatory T cells and upregulated on activated T cells. CTLA-4 delivers a negative regulatory signal to T cells upon binding of CD80 (B7.1) or CD86 (B7.2) ligands on antigen-presenting cells (**¡Error! No se encuentra el origen de la referencia.**). Blockade of CTLA-4 binding to CD80/86 by anti–CTLA-4 antibodies results in markedly enhanced T-cell activation and antitumor activity in animal models, including killing of established murine solid tumors and induction of protective antitumor immunity. Therefore, it is expected that treatment with an anti–CTLA-4 antibody will lead to increased activation of the human immune system, increasing antitumor activity in patients with solid tumors.

Pre-clinical data have now been added to with a wealth of clinical data showing that blockade of negative regulatory signals to T-cells such as cytotoxic T-lymphocyte antigen 4 (CTLA-4) and programmed death ligand 1 (PD-L1) has promising clinical activity. Ipilimumab was granted United States (US) Food and Drug Administration (FDA) approval for the treatment of metastatic melanoma and is currently under investigation for several other malignancies, whilst nivolumab and pembrolizumab, two anti–PD-1 agents, and atezolizumab, an anti–PD-L1, agent have been granted approvals by agencies such as the US FDA and the European Medicines Agency approval for the treatment of a number of malignancies including metastatic melanoma, squamous and non-squamous cell non-small-cell lung cancer and

urothelial carcinoma. In addition, there are data from agents in the anti-PD-1/PD-L1 class showing clinical activity in a wide range of tumor types.

1.2 Durvalumab Background

Investigators should be familiar with the current durvalumab Investigator Brochure (IB Version 12.0)

Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumors. Durvalumab is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1 κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fc γ) receptors involved in triggering effector function.

1.2.1 Summary of non-clinical experience

The non-clinical experience is fully described in the current version of the durvalumab Investigator's Brochure (IB Version 12.0).

Durvalumab binds with high affinity and specificity to human PD-L1 and blocks its interaction with PD-1 and CD80. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma (IFN- γ). Additionally, durvalumab demonstrated a lack of antibody-dependent cell-mediated cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) in cell-based functional assays. *In vivo* studies show that durvalumab inhibits tumor growth in a xenograft model via a T lymphocyte (T-cell) dependent mechanism. Moreover, an anti-mouse PD-L1 antibody demonstrated improved survival in a syngeneic tumor model when given as monotherapy and resulted in complete tumor regression in > 50% of treated mice when given in combination with chemotherapy. Combination therapy (dual targeting of PD-L1 and cytotoxic T-lymphocyte-associated antigen 4 [CTLA-4]) resulted in tumor regression in a mouse model of colorectal cancer.

Cynomolgus monkeys were selected as the only relevant species for evaluation of the pharmacokinetics (PK)/pharmacodynamics and potential toxicity of durvalumab. Following intravenous (IV) administration, the PK of durvalumab in cynomolgus monkeys was nonlinear. Systemic clearance (CL) decreased and concentration half-life ($t_{1/2}$) increased with increasing doses, suggesting saturable target binding-mediated clearance of durvalumab. No apparent gender differences in PK profiles were observed for durvalumab.

In general, treatment of cynomolgus monkeys with durvalumab was not associated with any durvalumab-related adverse effects that were considered to be of relevance to humans. Adverse findings in the non-Good Laboratory Practice (GLP) PK/pharmacodynamics and dose range-finding study, and a GLP 4-week repeat-dose toxicity study were consistent with antidrug antibody (ADA)-associated morbidity and mortality in individual animals. The death of a single animal in the non-GLP, PK/pharmacodynamics, and dose range-finding study was consistent with an ADA-associated acute anaphylactic reaction. The spectrum of findings, especially the clinical signs and microscopic pathology, in a single animal in the GLP, 4-week, repeat-dose study was also consistent with ADA immune complex deposition, and ADA:durvalumab immune complexes were identified in a subsequent non-GLP, investigative immunohistochemistry study. Similar observations were reported in cynomolgus monkeys administered human mAbs unrelated to durvalumab. Given that immunogenicity of human mAbs in nonclinical species is generally not predictive of responses in humans, the ADA-associated morbidity and mortality were not considered for the determination of the no-observed-adverse-effect level (NOAEL) of durvalumab.

Data from the pivotal 3-month GLP toxicity study with durvalumab in cynomolgus monkeys showed that subchronic dosing of durvalumab was not associated with any adverse effects. Therefore, the NOAEL of durvalumab in all the general toxicity studies was considered to be 100 mg/kg, the highest dose tested in these studies. In addition to the *in vivo* toxicology data, no unexpected membrane binding of durvalumab to human or cynomolgus monkey tissues was observed in GLP tissue cross-reactivity studies using normal human and cynomolgus monkey tissues.

Preclinical data suggests that blocking PD-L1 may improve also immune function in HIV patients (16). Different studies have shown that during chronic HIV-1 infection PD-1 expression on HIV-1-specific T cells correlates with viral load and that blocking PD-1 engagement restores T cell effector functions *in vitro*. Additionally, *in vivo* PD-1 blockade in chronic SIV infection restored CD8⁺ T cell function, reduced viral load levels, and increased survival of SIV-infected macaques (17). However, the consequence of *in vivo* PD-1 blockade

to restored CD8+ T cell function, and ultimately reduce viral persistence and reservoirs in HIV-1-infected patients with effective ART, remains to be determined.

1.2.2 Summary of clinical experience

Clinical experience with durvalumab is fully described in the current version of the durvalumab Investigator's Brochure (Version 12.0).

As of the DCO date (12 July 2016), a total of 2878 patients have been exposed to 1 or more doses of durvalumab in ongoing open-label AstraZeneca-or MedImmune-sponsored Phase I-III monotherapy and combination therapy studies across all indications. Details on the safety profile of durvalumab monotherapy are summarized in Section **;****Error! No se encuentra el origen de la referencia.** and Section **;****Error! No se encuentra el origen de la referencia.** Refer to the current durvalumab Investigator's Brochure for a complete summary of non-clinical and clinical information including safety, efficacy and pharmacokinetics. .

Durvalumab (MEDI4736) is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that inhibits binding of PD-L1 and is being developed by AstraZeneca/MedImmune for use in the treatment of cancer (MedImmune is a wholly owned subsidiary of AstraZeneca; AstraZeneca/MedImmune will be referred to as AstraZeneca throughout this document). As durvalumab is an engineered mAb, it does not induce antibody-dependent cellular cytotoxicity or complement-dependent cytotoxicity. The proposed mechanism of action for durvalumab is interference of the interaction of PD-L1 with PD-1 and CD80.. It is engineered with a triple mutation in the Fc domain to avoid Fc-mediated ADCC. Preliminary results from the phase I study of patients with solid tumors reported clinical activity and durable disease stabilization in different tumor types, with no dose limiting toxicities or grade 3–4 treatment-related adverse events(18). In the phase II trial the drug was tested on 85 pretreated NSCLC patients. From 53 evaluable patients, 12 had an objective response by RECIST criteria (23%). At 2014 ASCO meeting, results from a phase I multi-arm expansion study of the anti PD-L1 MEDI4736 were presented. It was reported that the dose-escalation phase has been completed for doses of 0.1 to 10 mg/kg every 2 weeks with extension to 15 mg/kg every 3 weeks. MEDI4736 was well tolerated at all doses tested, with no treatment-related serious adverse events such as colitis, hyperglycemia, or pneumonitis at any grade(19). Neil Segal and colleagues presented preliminary data on the ongoing study of MEDI4736 at a dosage of 10 mg/kg every 2 weeks for 1 year for 346 patients with solid tumors, including 143 with NSCLC. The median duration of treatment was 8 weeks. As of May 18, 2014, there were very few (6%) grade 3/4 drug-related serious adverse events. Clinical activity was observed as early as 6 weeks, with maintenance for over 67 weeks and off active therapy; overall response rate (ORR) rate in NSCLC was 13%(20). Development is most advanced in non-small cell lung cancer, with a program currently comprising two phase

III trials (NCT02352948, NCT02125461) and several phase I combination studies (NCT02000947, NCT02179671, NCT02143466). A pivotal program for MEDI4736 in head and neck cancer began in late 2014.

PD-1 interacts with the ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), which result in diminished T-cell proliferation, altered cytokine production and initiation of T-cell exhaustion and/or apoptosis leading to tumor initiation and progression(21).

Pharmacokinetics and Product Metabolism

Study CD-ON-durvalumab-1108: As of 09Feb2015, PK data were available for 378 subjects in the dose-escalation and dose-expansion phases of Study CD-ON-durvalumab-1108 following treatment with durvalumab 0.1 to 10 mg/kg every 2 weeks (Q2W) or 15 mg/kg every 3 weeks (Q3W). The maximum observed concentration (C_{max}) increased in an approximately dose-proportional manner over the dose range of 0.1 to 15 mg/kg. The area under the concentration-time curve from 0 to 14 days (AUC_{0-14}) increased in a greater than dose-proportional manner over the dose range of 0.1 to 3 mg/kg and increased dose-proportionally at ≥ 3 mg/kg. These results suggest durvalumab exhibits nonlinear PK likely due to saturable target-mediated CL at doses < 3 mg/kg and approaches linearity at doses ≥ 3 mg/kg. Near complete target saturation (soluble programmed cell death ligand 1 [sPD-L1] and membrane bound) is expected with durvalumab ≥ 3 mg/kg Q2W. Exposures after multiple doses showed accumulation consistent with PK parameters estimated from the first dose. In addition, PK simulations indicate that following durvalumab 10 mg/kg Q2W dosing, $> 90\%$ of subjects are expected to maintain PK exposure ≥ 40 $\mu\text{g/mL}$ throughout the dosing interval.

As of 09Feb2015, a total of 388 subjects provided samples for ADA analysis. Only 8 of 388 subjects (1 subject each in 0.1, 1, 3, and 15 mg/kg cohorts, and 4 subjects in 10 mg/kg cohort) were ADA positive with an impact on PK/pharmacodynamics in 1 subject in the 3 mg/kg cohort.

Safety

The safety profile of durvalumab as monotherapy and combined with other anticancer agents was consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed

with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy. These events are manageable by available/established treatment guidelines as described in the study protocols.

AEs reported with durvalumab monotherapy in key clinical studies are described below.

Adverse Event Profile of durvalumab Monotherapy

Study CD-ON-durvalumab-1108: The safety profile of durvalumab monotherapy in the 694 subjects with advanced solid tumors treated at 10 mg/kg Q2W in Study CD-ON-durvalumab-1108 has been broadly consistent with that of the overall 1,279 subjects who have received durvalumab monotherapy (not including subjects treated with blinded investigational product) across the clinical development program. The majority of treatment-related AEs were manageable with dose delays, symptomatic treatment, and in the case of events suspected to have an immune basis, the use of established treatment guidelines for immune-mediated toxicity. As of 07May2015, among the 694 subjects treated with durvalumab 10 mg/kg Q2W in Study CD-ON-durvalumab-1108, a total of 378 subjects (54.5%) experienced a treatment-related AE, with the most frequent (occurring in $\geq 5\%$ of subjects) being fatigue (17.7%), nausea (8.6%), diarrhea (7.3%), decreased appetite (6.8%), pruritus (6.3%), rash (6.1%), and vomiting (5.0%). A majority of the treatment-related AEs were Grade 1 or Grade 2 in severity with \geq Grade 3 events occurring in 65 subjects (9.4%). Treatment-related \geq Grade 3 events reported in 3 or more subjects ($\geq 0.4\%$) were fatigue (12 subjects, 1.7%); increased aspartate aminotransferase (AST; 7 subjects, 1.0%); increased gamma-glutamyltransferase (GGT; 6 subjects, 0.9%); increased alanine aminotransferase (ALT; 5 subjects, 0.7%); and colitis, vomiting, decreased appetite, and hyponatremia (3 subjects, 0.4% each). Six subjects had treatment-related Grade 4 AEs (upper gastrointestinal hemorrhage, increased AST, dyspnea, neutropenia, colitis, diarrhea, and pneumonitis) and 1 subject had a treatment-related Grade 5 event (pneumonia). Treatment-related serious adverse events (SAEs) that occurred in ≥ 2 subjects were colitis and pneumonitis (3 subjects each). A majority of the treatment-related SAEs were \geq Grade 3 in severity and resolved with or without sequelae. AEs that resulted in permanent discontinuation of durvalumab were considered as treatment related in 18 subjects (2.6%), with colitis being the most frequent treatment-related AE resulting in discontinuation (3 subjects). A majority of the treatment-related AEs resulting in discontinuation of durvalumab were \geq Grade 3 in severity and resolved with or without sequelae.

Study D4191C00003/ATLANTIC: The safety profile of durvalumab monotherapy in Study CD-ON-durvalumab-1108 is generally consistent with that of Study D4191C00003/ATLANTIC in subjects with locally advanced or metastatic non-small-cell lung cancer (NSCLC) treated with durvalumab 10 mg/kg Q2W. As of 05May2015, 264 of 303 subjects (87.1%) reported any AE in Study D4191C00003/ATLANTIC. Overall, events reported in $\geq 10\%$ of subjects were dyspnea (18.8%), fatigue (17.8%), decreased appetite (17.5%), cough (14.2%), pyrexia (12.2%), asthenia (11.9%), and nausea (11.2%). Nearly two-thirds of the subjects experienced AEs that were Grade 1 or 2 in severity and manageable by general treatment guidelines as described in the current durvalumab study protocols. Grade 3 or higher AEs were reported in 107 of 303 subjects (35.3%). A total of 128 subjects (42.2%) reported AEs that were considered by the investigator as related to investigational product. Treatment-related AEs (all grades) reported in $\geq 2\%$ of subjects were decreased appetite (6.6%); fatigue (5.9%); asthenia (5.0%); nausea (4.6%); pruritus (4.3%); diarrhea, hyperthyroidism, hypothyroidism, and pyrexia (3.3% each); rash (2.6%); weight decreased (2.3%); and vomiting (2.0%). Treatment-related Grade 3 AEs reported in ≥ 2 subjects were pneumonitis (3 subjects) and increased GGT (2 subjects). There was no treatment-related Grade 4 or 5 AEs. Ninety-four of 303 subjects (31.0%) reported any SAE. SAEs that occurred in $\geq 1.0\%$ of subjects were dyspnea (6.6%); pleural effusion, general physical health deterioration (2.3% each); pneumonia (2.0%); hemoptysis, pulmonary embolism (1.3% each); and pneumonitis, respiratory failure, disease progression (1.0% each). Nine subjects had an SAE considered by the investigator as related to durvalumab. Each treatment-related SAE occurred in 1 subject each with the exception of pneumonitis, which occurred in 3 subjects. Fifteen of 303 subjects (5.0%) have died due to an AE (pneumonia [3 subjects]; general physical health deterioration, disease progression, hemoptysis, dyspnea [2 subjects each]; pulmonary sepsis, respiratory distress, cardiopulmonary arrest [verbatim term (VT)], hepatic failure, and sepsis [1 subject each]). None of these events was considered related to durvalumab. Twenty-three of 303 subjects (7.6%) permanently discontinued durvalumab treatment due to AEs. Events that led to discontinuation of durvalumab in ≥ 2 subjects were dyspnea, general physical health deterioration, and pneumonia. Treatment-related AEs that led to discontinuation were increased ALT and increased hepatic enzyme, which occurred in 1 subject each.

Efficacy

Study CD-ON-durvalumab-1108: Overall, 456 of 694 subjects treated with durvalumab 10 mg/kg Q2W were evaluable for response (defined as having ≥ 24 weeks

follow-up, measurable disease at baseline, and ≥ 1 follow-up scan, or discontinued due to disease progression or death without any follow-up scan). In PD-L1 unselected patients, the objective response rate (ORR), based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST)v1.1, ranged from 0% in uveal melanoma (n = 23) to 20.0% in bladder cancer (n = 15), and disease control rate at 24 weeks (DCR-24w) ranged from 4.2% in triple-negative breast cancer (TNBC; n = 24) to 39.1% in advanced cutaneous melanoma (n = 23). PD-L1 status was known for 383 of the 456 response evaluable subjects. Across the PD-L1-positive tumors, ORR was highest for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (HCC; n = 3 each, 33.3% each), NSCLC (n = 86, 26.7%), and squamous cell carcinoma of the head and neck (SCCHN; n = 22, 18.2%). In the PD-L1-positive subset, DCR-24w was highest in advanced cutaneous melanoma (n = 3, 66.7%), NSCLC (n = 86, 36.0%), HCC and bladder cancer (n = 3 each, 33.3% each), and SCCHN (n = 22, 18.2%).

Study D4190C00007: Of the 32 subjects with myelodysplastic syndrome (MDS) treated in Study D4190C00007, 21 subjects had at least 1 post-baseline disease assessment. Among these subjects, the best overall responses were marrow complete remission (mCR) in 4 subjects (19.0%); stable disease (SD) in 4 subjects (19.0%); and progressive disease (PD) in 5 subjects (23.8%). The remaining 8 subjects (38.1%) did not meet the criteria for complete remission (CR), mCR, partial remission (PR), SD, or PD at the date of assessment.

Study CD-ON-durvalumab-1161: Of the 65 subjects with metastatic or unresectable melanoma treated with the combination of durvalumab and BRAF inhibitor (BRAFi; dabrafenib)/MEK inhibitor (MEKi; trametinib), 63 subjects were evaluable for response. A total of 35 subjects (55.6%) had a best overall response of confirmed or unconfirmed PR. The disease control rate (DCR; CR + PR [regardless of confirmation] + SD ≥ 12 weeks) was 79.4%.

Fixed Dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase 1 study (*study 1108*; N=292; doses= 0.1 to 10 mg/kg Q2W or 15 mg/kg Q3W; solid tumors). Population PK analysis indicated only minor impact of body weight (WT) on PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 patients were simulated using body WT distribution of 40–120 kg. Simulation

results demonstrate that body WT-based and fixed dosing regimens yield similar median steady state PK concentrations with slightly less overall between-subject variability with fixed dosing regimen.

Similar findings have been reported by others [Ng et al 2006, Wang et al. 2009, Zhang et al, 2012, Narwal et al 2013]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies. In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters [Zhang et al 2012].

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4Wdurvalumab (equivalent to 20 mg/kg Q4W) is included in the current study. Fixed dosing of durvalumab is recommend only for subjects with > 30kg body weight due to endotoxin exposure. Patients with a body weight less than or equal to 30 kg should be dosed using a weight-based dosing schedule (Appendix 2).

1.3 Research hypothesis

Taking into account:

- PD-1/ PD-L1 coinhibitory pathway plays a significant role in the regulation of the immune response in both chronic infectious diseases and cancer.
- Preclinical and animal data support the safety and promising activity of anti-PD-1 antibody in HIV-1 infection
- Demonstrated anticancer activity and safety profile of durvalumab (MEDI4736) in cancer clinical trials.
- Unlikely drug interactions of durvalumab (MEDI4736) and antiretroviral treatments.

We propose a phase II clinical study designed to assess the feasibility of durvalumab (MEDI4736) in HIV-1-infected individuals with solid tumors. Additionally we hope to obtain data that let us understand the possible benefit of this treatment in cancer patients and HIV, exploring if activity of durvalumab (MEDI4736) could be higher in cancer that has been

produce at least in part due to the chronic immunosuppression. Simultaneously, it will allow us to investigate the effect of disrupting this immunoregulatory pathway might have in reversing cancer pathways and HIV-specific T-cell function during persistent chronic HIV infection in humans.

In this regard, our hypothesis is:

HIV infected patients with cancer have a similar outcome in terms of tolerability when treated with MEDI4736 monotherapy at the recommended dose than non-HIV infected patients.

1.4 Rationale for conducting this study

HIV-1-infected patients with cancer have been systematically excluded from clinical trials of anti cancer drugs because of concerns related to drug interactions and the unknown effect of the underlying HIV infection on the safety and activity of the investigational drugs. Anti PD-L1 antibody durvalumab (MEDI4736) could be an active treatment both for cancer and for HIV infection, with non-expected drugs interactions.

1.5 Benefit/risk and ethical assessment

The benefit-risk relationship has been carefully considered in the planning of the trial. Based on the nonclinical and clinical studies available to date, the conduct of the trial is considered justifiable using the dose and dose regimen of the durvalumab as specified in this clinical trial protocol.

The trial shall be discontinued in the event of any new findings that indicate a relevant deterioration of the risk-benefit relationship that would render continuation of the trial unjustifiable.

The primary known risks of exposure to durvalumab include:

- Infusion-related reactions and
- irAEs

In addition, since durvalumab could induce antibody-dependent cell-mediated cytotoxicity (ADCC), there is a potential risk of tumor lysis syndrome.

Clinical trials with antibodies that block PD-1/PD-L1 interaction have been reported to produce objective response rates of 7% to 38% in patients with advanced or metastatic solid tumors, with response duration of 1 year or more for the majority of patients(22-30).

Given the suboptimal treatment options for patients with recurrent locally advanced or metastatic solid tumors in HIV-1 infected patients, and the safety profile of durvalumab, the risk-benefit ratio of treatment with durvalumab in the targeted trial population is considered positive.

This clinical trial protocol will be conducted in compliance with the clinical trial protocol, ICH GCP and the applicable national regulatory requirements.

2. STUDY OBJECTIVES

2.1 Primary objective(s)

To explore the feasibility of durvalumab (MEDI4736) monotherapy at the recommended dose of 1500 mg every 4 weeks in solid tumors in HIV-1-infected patients.

HIV-1-infected patients with cancer have been systematically excluded from clinical trials of anti cancer drugs because of concerns related to drug interactions and the unknown effect of the underlying HIV infection on the safety and activity of the investigational drugs. Anti PD-L1 antibody durvalumab (MEDI4736) could be an active treatment both for cancer and for HIV infection, with non-expected drugs interactions. The aim of this study is to explore the feasibility of durvalumab (MEDI4736) in HIV-1-infected patients who are diagnosed with a solid tumor (lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastroesophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity) for which no additional oncologic standard treatment is available, or for which the subject declines standard treatment.

2.2 Secondary objective(s)

- To assess ORR (RECIST 1.1 and irRECIST) and duration of response
- To evaluate the PFS rate at 6 months
- To evaluate the OS rate at 12 months

Durvalumab (MEDI4736) has demonstrated activity in several cancer types in the general population. In this study, as secondary objective, we will analyze activity of the drug as activity in terms of Response rate according to RECIST1.1 criteria, and according to OS rate at 12 months and PFS at 6 months.

Several data indicate that anti PD-1/PD-L1 treatments in oncology could have activity in terms of OS with long responders, that it is not always correlated to classical endpoint of response rate or median survival.

In this trial given that patients will be included with different solid tumors, and different lines of treatment, activity of the drug is a secondary objective, in order to determine if activity looks similar to activity reported in solid tumors without HIV- infection.

2.3 Exploratory objective(s)

Anti PD-1/PD-L1 antibodies could have a therapeutic effect on HIV infection. We will measure activity of durvalumab (MEDI4736) in terms of antiviral activity, measuring the changes in the viral reservoir, measuring the changes in residual viral replication and exploring changes in the composition and function of circulating T lymphocytes.

For this analysis we will use blood samples (pretreatment and shortly after treatment initiation (2, 4, 12, 24 weeks), and then in the longer time frame every 12 weeks) (+/-3 days). This will include the following:

- Analysis by digital droplet PCR (ddPCR) of HIV-1 DNA associated to CD4+ T cells obtained from peripheral blood.
- Analysis of residual plasma viremia using an ultrasensitive single copy assay (these patients would be on antiretroviral treatment, so standard techniques for determine viral load with not be useful).
- Analysis by ddPCR of HIV-1 RNA expression on CD4+ T cells obtained from peripheral blood.
- Change in 2LTR mean levels in CD4+ T cells.
- Analysis by multicolor flow cytometry of the percentage of naïve, memory and activated CD4+ and CD8+ T-cell subsets in peripheral blood, including analysis of PD-1 expression.
- Analysis by multicolor flow cytometry of the functional effector responses of T cells elicited by different viral and non viral antigens.
- Determination of the *ex vivo* effect of durvalumab on baseline peripheral blood mononuclear cells (PBMCs):
 - To evaluate whether the *ex vivo* gain of lymphocyte effector function after durvalumab signaling blockade predicts anti-HIV function after *in vivo* therapy
 - To evaluate whether the effect of durvalumab signaling blockade on regulatory T cells restrains the enhancement in the lymphocyte effector function

In addition, the study will explore predictive factors of antitumoral activity in pretreatment tumor samples.

Tumor samples obtained by excisional or incisional biopsy (also EBUS samples in case of lung tumors) must be obtained. If it is not possible to obtain a new biopsy, the patients can be included if they have some archival tissue available (there must be analysed taking account if these samples have been performed more than 6 months before of starting durvalumab treatment)

To explore antitumoral effects according to immunohistochemical and molecular predictive markers, perform correlative studies with the objective of analyzing the expression of other biomarkers such as:

- mRNA expression (RT-PCR) of Interferon gamma, HLA-DR and PD-L1.
- Immunohistochemistry: PDL-1 and HLA-DR.

A set of immune response genes/proteins will be tested (both RT-PCR and immunohistochemistry).

3. STUDY DESIGN

3.1 Overview of study design

This is a multicenter, national, non-randomized, phase II study in HIV-1 infected patients with advanced solid tumors.

Twenty evaluable patients will be included in the trial. Patients will be included irrespective of number the previous line of treatments.

The clinical trial will be performed in 10 hospitals from the Spanish Lung Cancer Group in Spain with a competitive enrollment.

It is a single arm study. All patients included will received the treatment with durvalumab (MEDI4736). There is not placebo treated patients.

Patients must have stopped the previous treatments for cancer at least 30 days before starting study medication.

Clinical Study Protocol

Drug Substance Durvalumab (Medi4736)

Sponsor code: GECP 16/04_ Astra Zeneca Study number: **ESR 15-10869**

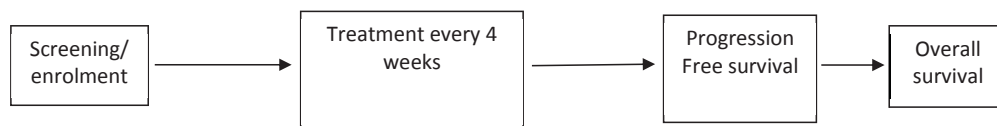
Version Number 4.0

Date 16th April 2018

3.2 Study schema

Clinical Study Protocol
Drug Substance Durvalumab (Medi4736)
Sponsor code: GECP 16/04_ Astra Zeneca Study number: ESR 15-10869
Version Number 4.0
Date 16th April 2018

Figure 1. Study flow chart



3.3 Study Oversight for Safety Evaluation

The whole trial may be discontinued prematurely in the event of any of the following situations:

- New information leading to unfavourable risk-benefit judgement of the trial drug, as inefficacy of the drug for this population, significant previously unknown adverse reactions or unfavourable safety findings.
- Sponsor's decision that continuation of the study is unjustifiable for medical or ethical reasons.

4. SUBJECT SELECTION

Only persons meeting the inclusion criteria and no exclusion criteria may be enrolled into the trial. Prior to performing any trial assessments not part of the routine medical care, the investigator will ensure that the subjects have provided written informed consent.

4.1 Inclusion criteria

For inclusion in the study subjects must fulfill all of the following criteria:

1. Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
2. Age \geq 18 years at time of study entry.
3. Eastern Cooperative Oncology Group (ECOG) 0-2.
4. Life expectancy of \geq 16 weeks.
5. Adequate normal organ and marrow function as defined below:
 - Haemoglobin \geq 9.0 g/dL
 - Absolute neutrophil count (ANC) \geq $1.5 \times 10^9/L$ (\geq 1500 per mm^3)
 - Platelet count \geq $100 \times 10^9/L$ (\geq 100,000 per mm^3)

- Serum bilirubin ≤ 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of hemolysis or hepatic pathology), who will be allowed only in consultation with their physician.
- AST (SGOT)/ALT (SGPT) ≤ 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be ≤ 5 x ULN
- Serum creatinine $CL > 40$ mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age}) \times 0.85}{72 \times \text{serum creatinine (mg/dL)}}$$

6. Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥ 60 years old and no menses for ≥ 1 year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.
7. Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
8. Subjects with histologically or cytologically-documented advanced/metastatic lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastroesophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity, refractory to standard treatment, intolerant

of standard treatment, or for which no standard therapy exists or who refuse the standard treatment.

9. Subjects may be included irrespectively of number of previous lines of treatment for advanced disease.
10. Prior palliative radiotherapy must have been completed at least 2 weeks prior to start the study treatment (subjects may receive localized palliative radiotherapy while receiving study drug).
11. Documented HIV-1 infection
12. Undetectable viral load in the last analysis.
13. Subjects with brain metastases are eligible if they are asymptomatic, are treated or are neurological stable for at least 2 weeks without the use of steroids or on stable or decreasing dose of < 10 mg daily prednisone or equivalent.
14. Subjects must be following an antiretroviral therapy at the moment of the inclusion.

4.2 Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study. Previous enrollment in the present study.
2. Participation in another clinical study with an investigational product during the last 4 weeks.
3. Other untreated coexisting HIV related malignancies.
4. Any previous treatment with a PD1, PD-L1 or PD-L2 inhibitor, including durvalumab.
5. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) 28 days prior to the first dose of study drug.

6. Mean QT interval corrected for heart rate (QTc) ≥ 470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.
7. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
8. Any unresolved toxicity (CTCAE grade 2) from previous anti-cancer therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy).
9. Any prior Grade ≥ 3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE $>$ Grade 1.
10. Active or prior documented autoimmune disease within the past 2 years
NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
11. Any syndrome that requires systemic corticosteroid/immunosuppressive medications EXCEPT for syndromes which would not be expected to recur in the absence of an external trigger (vitiligo, autoimmune thyroiditis, or type 1 diabetes mellitus are permitted to enroll).
12. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).
13. History of primary immunodeficiency.
14. History of allogeneic organ transplant.
15. History of hypersensitivity to durvalumab or any excipient.
16. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B or C, or psychiatric illness/social situations that would limit

compliance with study requirements or compromise the ability of the subject to give written informed consent.

17. Known history of active tuberculosis.
18. Any serious or uncontrolled medical disorder or active infection non HIV, that would impair the ability of the subject to receive the treatment of protocol therapy under treating physician criteria.
19. Subjects with previous malignances (except non melanoma skin cancer, and cancer in situ of: bladder, gastric, colon, cervical/dysplasia, melanoma, breast) are excluded unless a complete remission was achieved at least 5 years prior to study entry and no additional therapy is required or anticipated to be required during the study period.
20. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.
21. Female subjects who are pregnant, breast-feeding or male or female patients of reproductive potential who are not employing an effective method of birth control.
22. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
23. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
24. Subjects with uncontrolled seizures.
25. Patients with tumoral disease in the head and neck region, such as peritracheal or periesophageal lymph node involvement, with infiltration of structures of the digestive, aerea or vascular pathways that represent a risk of increased bleeding.
26. Patients with neuroendocrine tumors of pulmonary origin or pulmonary metastases with evidence of active bleeding.
27. Patients with digestive bleeding.

4.3 Withdrawal of Subjects from Study Treatment and/or Study

Permanent discontinuation of investigational product

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

1. Withdrawal of consent or lost to follow-up.
2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing.
3. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute asafety risk.
4. Pregnancy or intent to become pregnant.
5. Any AE that meets criteria for discontinuation as defined in Appendix 1, Section 10.1.3
6. Adverse event related to durvalumab of any Grade>3 ADRs or repetitive Grade 3 ADRs with the exception of toxicities that do not meet the criteria for discontinuation as defined in Section 10.1.3, Appendix 1
7. Grade ≥ 3 infusion reaction.
8. Subject non-compliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits.
9. Initiation of alternative anticancer therapy including another investigational agent.
10. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab.

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

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section10.3.1 and Appendix 3 or 4, including the collection of any

protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

4.4 Replacement of subjects

Subjects withdrawn from the study will not be replaced.

5. INVESTIGATIONAL PRODUCT(S)

5.1 Durvalumab

The sponsor will supply durvalumab to the site's pharmacies as a 500-mg vial solution for infusion after dilution.

5.1.1 Formulation/packaging/storage

Durvalumab will be supplied by AstraZeneca 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. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen. Durvalumab must be used within the individually assigned expiry date on the label.

The trial medication and its packaging will be labeled in accordance with annex 13 of EU Guidelines to Good Manufacturing Practice.

5.1.2 Durvalumab Doses and treatment regimens

Durvalumab 1500 mg IV commences on Day 1 following confirmation of eligibility into the study and continues on a Q4W schedule until confirmed PD (unless the investigator considers the subject to continue to receive benefit from treatment), initiation of alternative cancer therapy, unacceptable toxicity, withdrawal of consent, or if other reasons to discontinue study treatment occur.

5.1.3 Study drug preparation

For patients weighing > 30 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) (based on an average body WT of 75 kg) should be prepared. For subjects ≤30 kg body weight, dose is determined using body mass, calculating the stock volume of durvalumab (equivalent to 20 mg/kg Q4W) to achieve the accurate dose according to Appendix 2.

Preparation of durvalumab doses for administration with an IV bag

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

If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

No incompatibilities between durvalumab and polyvinylchloride or polyolefin IV bags have been observed. Dose of 1500 mg Q4W durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline 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.

Remove a volume of IV solution from the IV bag equal to the calculated volume of durvalumab to be added to the IV bag prior to addition of durvalumab. Next, the volume of durvalumab (ie, 15.0 mL for 750 mg) is added to the IV bag such that final concentration is within 1 to 20 mg/mL (IV bag volumes 100 to 1000 mL). Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

Patient weight at baseline should be used for dosing calculations in patients ≤30 kg unless there is a ≥10% change in weight. Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

For patients ≤ 30 kg, Calculate the dose volume of durvalumab and number of vials needed for the subject to achieve the accurate dose according to Appendix 2 (equivalent to 20 mg/kg Q4W).

Durvalumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump 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- μ m in-line filter. Less than 55 minutes is considered a deviation.

The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline) equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

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. The table below summarizes time allowances and temperatures.

Durvalumab hold and infusion times

Maximum time from needle puncture to start of administration	4 hours at room temperature, 24 hours at 2°C to 8°C
Maximum time for IV bag infusion, including interruptions	8 hours at room temperature

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

5.1.4 Monitoring of dose administration

Subjects will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Subjects are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

In the event of a \leq Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a \leq Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial 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. The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 4 hours at room temperature, with maximum total time at room temperature not exceeding 8 hours (otherwise requires new infusion preparation).

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 subjects to an intensive care unit if necessary.

5.1.5 Accountability and dispensation

The investigator is responsible for ensuring accountability for trial drug, including reconciliation of drugs and maintenance of drug records.

Upon receipt of trial drug, the investigator (or designee) will check for accurate delivery and acknowledge receipt by signing and dating the documentation provided by the sponsor and returning it to the sponsor. A copy will be retained for the investigator File.

The dispensing of durvalumab will be carefully recorded on the appropriate drug accountability forms provided by the sponsor and an accurate accounting will be available for verification by the sponsor's medical monitor at each monitoring visit.

Trial drug accountability records will include:

- confirmation of trial drug delivery to the trial site;
- the inventory at the site of trial drug provided by the Sponsor and prepared at the site;
- the use of each dose by each subject;
- the return to the Sponsor or alternative disposition of unused trial drug; and dates, quantities, batch numbers, expiry dates and (for trial drug prepared at the site)
- formulation, as well as the subjects' trial numbers.

The Investigator should maintain records that adequately document

- that the subjects were provided the doses specified by the clinical trial protocol /
- amendment(s); and
- That all trial drug provided by the Sponsor was fully reconciled.

Unused trial drug must not be discarded or used for any purpose other than the present trial. Any trial drug that has been dispensed to a subject must not be redispensed to a different subject.

The Sponsor's Monitor will periodically collect the trial drug accountability forms and will check all returns (both unused and used containers) before arranging for their return to the Sponsor or authorizing their destruction by the trial site.

At the conclusion or termination of this trial, trial site personnel and the Clinical Trial Monitor will conduct a final product supply inventory on the Investigational Drug Accountability Forms and all unused containers will be destroyed. Instructions for destruction of product will be provided to the site. The Clinical Trial Monitor will be supplied with a copy for filing of the Investigational Drug Accountability Forms. This documentation must contain a record of clinical supplies used, unused, and destroyed and shall include information on:

- all administered units,
- all unused units,
- all destroyed units (during the trial),
- all destroyed units at the end of the trial,
- date of destruction(s),
- name and signature of the Investigator / pharmacist.

It must be ensured at each trial site that the trial drug is not used:

- after the expiry date, and
- after the retest date unless the trial drug is reanalyzed and its retest date extended.

This is to be closely monitored by the Clinical Trial Monitor.

5.1.6 Disposition of unused investigational study drug

The site will account for all investigational study drug dispensed and also for appropriate destruction. Certificates of delivery and destruction must be signed.

6. TREATMENT PLAN

6.1 Subject enrollment

Only persons meeting all inclusion criteria and no exclusion criteria may be enrolled into the trial as subjects. Prior to performing any trial assessments not part of the subject's routine medical care, the investigator will ensure that the subject or his/her legal representative, has provided written informed consent following the procedure.

6.1.1 Procedures for handling subjects incorrectly enrolled

Subjects who are incorrectly enrolled or initiated on treatment should be withdrawn from the study.

6.2 Dosage and Administration

Subjects will receive an IV infusion of durvalumab at a dose of 1500 mg, once every four weeks.

When the patients weight is less than or equal to 30 kg, the dosage will be calculated based on the weight of the subject determined on the day prior to or the day of each drug administration (dosage equivalent to 20mg/kg Q4W).

Treatment may continue past the initial determination of disease progression per RECIST1.1. as long as the following criteria are met:

- Investigator assessed clinical benefit without any rapid disease progression.
- Tolerance of durvalumab.
- Stable ECOG PS.
- Treatment beyond progression will not delay an imminent intervention to prevent serious complications of disease progression

The decision to continue treatment should be discussed with the Medical Monitor and documented in the trial records.

A radiographic assessment should be performed within 6 weeks of original PD to determine whether there has been a decrease in the tumor size, or continued PD. The assessment of

clinical benefit should be balanced by clinical judgment as to whether the subject is clinically deteriorating and unlikely to receive any benefit from continued treatment with durvalumab.

If the Investigator feels that the subject continues to achieve clinical benefit by continuing treatment, the subject should remain on the trial and continue to receive monitoring according to the Schedule of Assessments.

6.3 Dose Modification and Toxicity Management

6.3.1 Durvalumab

For adverse events (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 the agent suspected of causing the toxicity where required).
- 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 (see Appendix 1).
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

In addition, there are certain circumstances in which durvalumab should be permanently discontinued.

Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed (see Appendix 1).

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects 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 enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions, for infusion-related reactions, and for non-immune-mediated reactions are detailed in Appendix 1.

In addition, management guidelines for adverse events of special interest (AESIs) are detailed in Section 10.1.3. All toxicities will be graded according to NCI CTCAE v4.03.

7. RESTRICTIONS DURING THE STUDY AND CONCOMITANT TREATMENT(S)

7.1 Restrictions during the study

Contraception

Females of childbearing potential who are sexually active with a non sterilised male partner must use effective contraception from screening, and must agree to continue using such precautions for at least 90 days following the last infusion of durvalumab; cessation of birth control after this point should be discussed with a responsible physician. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- Subjects must use acceptable methods of effective contraception as described in Table 2.
- Non-sterilised males who are sexually active with a female partner of childbearing potential must use acceptable methods of effective contraception (see Table 2) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Table 2. Effective methods of contraception

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

^a This is also considered a hormonal method.

Blood donation

As patients are HIV infected, they do not donate blood while participating in this study neither after its finalization.

7.2 Concomitant treatment(s)

7.2.1 Permitted concomitant medications

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed in Section 7.2.2.

Patients will continue their antiretroviral treatment during study time, following standard treatment recommendations.

7.2.2 Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy other than the protocol specified therapies.
2. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for non cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. NOTE: Local treatment of isolated lesions for palliative intent is acceptable (e.g., by local surgery or radiotherapy).

3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF- α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).
4. Live attenuated vaccines within 30 days of durvalumab dosing (ie, 30 days prior to the first dose, during treatment with durvalumab and for 30 days post discontinuation of durvalumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

In patients with head and neck cancer it is not yet known whether the risk of bleeding would increase with durvalumab. The principal investigator must ask the patients for any medications that might increase risk for example: aspirin; that they are taking. The physician must evaluate if it is possible to use alternative treatments. If it is not the case the therapeutic international normalized ratio (INR) must be monitored in the case of warfarin or similar drugs. Treatment with low molecular weight heparin (LMWH) is allowed.

Table 3. Prohibited and Rescue Medications	
Rescue/supportive medication/class of drug:	Usage:
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as “prohibited” as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, growth factor support, correction of metabolic disorders, optimal symptom control, and pain management [including palliative radiotherapy, etc])	Should be used when necessary for all patients

8. STUDY PROCEDURES

8.1 Schedule of study procedures

Before study entry, throughout the study, and following study drug discontinuation, various clinical and diagnostic laboratory evaluations are outlined. The purpose of obtaining these detailed measurements is to ensure adequate safety and tolerability assessments. Clinical evaluations and laboratory studies may be repeated more frequently if clinically indicated. The Schedules of Assessments during the screening and treatment period is provided following the Protocol Synopsis.

8.1.1 Screening Phase

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IEC-approved ICF before any study-specific screening procedures are performed. After signing the ICF, completing all screening procedures, and being deemed eligible for entry, subjects will be enrolled in the study. Procedures that are performed prior to the signing of the ICF and are considered standard of care may be used as screening assessments if they fall within the 28-day screening window.

The following procedures will be performed during the Screening Visit:

- Informed Consent.
- Assignment of subject identification number.
- Review of eligibility criteria.
- Medical and surgical history.
- HIV infection history.
- Demographics and history of tobacco and alcohol use.
- Review of prior/concomitant medications, including treatments for solid tumors.
- Complete physical exam.
- ECOG Performance Status.
- Vitals signs, weight and height.
- 12-lead ECG (in triplicate [2-5 minutes apart]).
- Tumor biopsy (archival tissue or resulting from a screening biopsy of the subject if no archival tissue is available).
- Imaging by PET-CT/CT/MRI. Tumor evaluation will be performed using CT scan or PET-CT or MRI (if MRI is used, CT of chest is mandatory). A brain MRI scan is required only following the investigator criteria.

- Blood samples for the translational study, will be collected before or on Day 1 before trial treatment starts.
- Clinical laboratory tests for:
 - Hematology (see Table 4).
 - Clinical chemistry (see Table 5).
 - TSH (and T3 and T4, if TSH is abnormal).
 - Coagulation (PT, APTT, INR).
 - Creatinine Clearance.
 - Serum pregnancy test (for women of childbearing potential only).
 - Hepatitis B and C, and HIV serologies.
 - Plasma viral load (PVL test)
 - Urinalysis (see Table 6), including, when applicable, urine hCG or serum β hCG (pre-menopausal female subjects of childbearing potential only)

8.1.2 Treatment Phase

Procedures to be conducted during the treatment phase of the study are presented in the Schedule of Assessments. Screening procedures performed within 72 hours of Cycle 1 Day 1 (C1D1) do not need to be repeated on C1D1.

In this trial the treatment will be given until PD, significant clinical deterioration (clinical progression), unacceptable toxicity, or any criterion of withdrawal from the trial or trial drug is fulfilled.

Treatment may continue past the initial determination of PD according to RECIST1.1 if the subject's ECOG PS has remained stable and in opinion of the Investigator, the subject will benefit from continued treatment.

Patients will be asked for to visit the trial site center once every 4 weeks.

A time window of up 3 days before or 1 day after the scheduled visit day (-3/+1) will be allowed for all trial procedures.

In addition, the tumor evaluation has a tumor assessment visiting time window of 5 days prior to the scheduled day (-5 days).

AEs and concomitant medications will be documented at each trial visit and between visits by weekly telephone contact.

ECOG PS will be assessed at Day 1 and every 4 weeks thereafter.

Vital signs will be performed at Day 1 and every 4 weeks thereafter. Subjects will have their blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (± 5 minutes)
- At the end of the infusion (at 60 minutes ± 5 minutes)

For the first infusion only and then for subsequent infusions as clinically indicated: In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (± 5 minutes).

If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should be collected every 30 minutes (± 5 minutes) and as described above or more frequently if clinically indicated

Physical examinations and body weight will be assessed in each visit.

The laboratory hematology serum chemistry tests will be assessed at Day 1 (if screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1) and every 4 weeks thereafter.

Liver enzyme panel will be assessed in each visit (if screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1).

Thyroid function tests will be assessed at Day 1 and every 4 weeks thereafter.

Urinalysis should be performed every 4 weeks.

Urine or serum β -HCG pregnancy tests are performed every 2 cycles and in the first follow up (pre-menopausal female subjects of childbearing potential only). Coagulation parameters are performed at screening and as clinically indicated.

Tumor evaluation (PET-CT, CT or MRI) will be performed every 8 weeks, with a tumor assessment visiting time window of 5 days prior to dosing until week 48. After that the tumor evaluation must be performed every 12 weeks (± 7 days).

Blood samples for the translational study, will be collected at week 2, 4, 12, 24. Patients that continue on treatment after 24 weeks will have peripheral blood samples every 12 weeks until disease progression or at least until week 72 in the absence of progression.

8.1.3 End of Treatment

End of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures may be completed within ± 7 days of the end of treatment visit. Repeat disease assessment is not required if performed within 28 days prior to the end of treatment visit.

Assessments for subjects who have discontinued durvalumab due to toxicity in the absence of confirmed progressive disease are provided in appendix 3.

Assessments for subjects who have discontinued durvalumab treatment due to confirmed PD are presented in appendix 4.

All subjects will be followed for survival until the end of the study regardless of further treatments, or until the sponsor ends the study.

8.2 Description of study procedures

8.2.1 Medical history and physical examination, electrocardiogram, weight and vital signs

Findings from medical history (obtained at screening) and physical examination shall be given a baseline grade according to the procedure for AEs. Increases in severity of pre-existing conditions during the study will be considered AEs, with resolution occurring when the grade returns to the pre-study grade or below.

Physical examinations will be performed on study days noted in the Schedule of Assessments.

A complete physical examination will be performed and will include an assessment of the following (as clinically indicated): general appearance, respiratory, cardiovascular, abdomen, skin, head and neck (including ears, eyes, nose and throat), lymph nodes, thyroid, musculo-skeletal (including spine and extremities), genital/rectal, and neurological systems and at screening only, height.

ECGs are required during screening, prior to starting study treatment on Cycle 1 Day 1, at 16 weeks after starting study treatment, as well as at any other time point when clinically indicated.

ECGs recorded during the screening period will be obtained in triplicate (with 2-5 minute lag time between each); ECGs recorded during the treatment phase will be single tracing. All 12-lead ECGs should be recorded while the subject is in the supine position. A 12-lead ECG will be recorded for all subjects on study days noted in Section 8.1. The same method of assessment should be used throughout the study. Twelve-lead ECGs will be obtained after the subject has been resting in a supine position for at least 5 minutes in each case. On Day 1 and Week 16, ECGs will be recorded within an hour prior to start of infusion and at least one time point 0 to 3 hours after the infusion.

Vital signs (temperature, blood pressure, pulse rate, and respiratory rate) will be measured on study days noted in the Schedule of Assessments. On durvalumab treatment day 1, vital signs will be measured within an hour prior to start of durvalumab administration, at 30 minutes during the infusion (± 5 minutes), at the end of infusion (+ 5 minutes), and at 30 minutes (± 5 minutes) and 60 minutes (± 5 minutes) post-infusion. If the infusion takes longer than 60 minutes, then blood pressure and pulse measurements should follow the principles described here, or more frequently if clinically indicated. For subsequent doses, the 1-hour observation period will not be required unless a subject experiences an infusion-related reaction.

8.2.2 Clinical laboratory tests

The following clinical laboratory tests will be performed (see the Schedule of Assessments, Appendix 3 and Appendix 4 for the time points of each test):

- Coagulation parameters: Activated partial thromboplastin time and International normalized ratio to be assessed at baseline and as clinically indicated
- Hematology test: hemogram with CD4 and CD8 count and plasma viral load (PVL)
- Pregnancy test (female subjects of childbearing potential only)
 - Urine human chorionic gonadotropin
 - Serum beta-human chorionic gonadotropin (at screening only)
- Thyroid Stimulating Hormone
 - free T3 and free T4 only if TSH is abnormal
- Other laboratory tests
 - Hepatitis B surface antigen, hepatitis C antibody

- HIV antibody

Table 4. Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular hemoglobin	Total white cell count
	CD4 T cells
Mean corpuscular hemoglobin concentration	CD8 T cells
	Plasma Viral Load (pVL)

Table 5. Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin ^a
Chloride	Total protein
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase ^b	Uric acid
Serum β hCG ^c	

^a If Total bilirubin is $\geq 2 \times$ ULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin.

^b At baseline and as clinically indicated.

^c Pre-menopausal female subjects of childbearing potential only.

Table 6. Urinalysis Tests^a

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance
Urine hCG ^b	

^a Microscopy should be used as appropriate to investigate white blood cells and use the high power field for red blood cells.

^b If applicable.

Table 7. Serology

Serology HIV, Hepatitis B, Hepatitis C

8.3 Biological sampling procedures

8.3.1 Biomarker/Pharmacodynamic sampling and evaluation methods

Immunohistochemistry Testing

PD-L1 testing

PD-L1 testing utilizes the Ventana SP263 assay. Testing should be restricted to the Ventana SP263 assay and should be performed in accordance with the package insert on the Ventana Benchmark platform (Ultra or XT).

The Ventana SP263 assay is fully analytically validated test characterized through to the completion of reader precision studies in the non-small cell lung cancer (NSCLC) and squamous cell carcinoma of the head & neck (SCCHN). For these tumors, the Ventana SP263 assay has a fully reproducibility data package supporting cut-off and scoring algorithm. Following completion of ATLANTIC and HAWK clinical trials, the assay will be associated with clinical utility. In other cancer types (bladder, pancreatic, gastric, hepatocellular, triple negative breast, ovarian, esophageal, nasopharyngeal, glioblastoma, soft tissue sarcoma, cholangiocarcinoma, small cell lung, melanoma and cervical HPV+ cancers), the Ventana SP263 assay has only limited clinical performance data.

Other immunohistochemistry tests:

A panel of putative markers including molecular and cellular markers may be analyzed in tumor tissue to investigate a possible correlation with clinical efficacy and analyzed markers.

PK-L1 and HLA-DRRNA expression analysis

A set of immune response genes/proteins will be tested for RNA expression techniques (both RT-PCR and immuno-histochemistry).

Sample collection for immunohistochemistry/ RNA expression testing

- The preferred tumor sample for translational is the one taken following the completion of the most recent prior line of therapy. Samples taken at this time reflect are considered clinically most relevant.
- The sample for translational testing was less than or equal to 6 months old. In cases where a sample a less than 6 months old was not available, patients were asked to undergo a new biopsy if considered clinically appropriate by their treating physician.
- Samples should be collected via a core needle of 18 gauge or larger or be collected by an incisional or excisional tumor biopsy. Where institutional practice uses a smaller gauge needle, samples should be evaluated for tumor cell quantity (i.e. >100 tumor cells) to allow for adequate immunohistochemistry analyses.
- When the collection of a new sample is not clinically appropriate, archival samples may be utilized provided the specimen it is not older than 3 years of age. When archival samples are used, the age of the sample / date of collection should be captured.
- Samples submitted for immunohistochemistry/RNA expression testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for immunohistochemistry analysis.

Sample data collection for translational study testing

The following fields of data should be collected from the site/institution collecting and if, indicated shipping of the samples:

- Patient identifier (ecode or unique identifier)
- Specimen identifier (written on the specimen)

- Site identifier
- Specimen collection date
- Type of specimen submitted
- Quantity of specimen
- Date of sectioning
- Archival of fresh tumor
- Tumor type
- Primary tumor location
- Metastatic tumor location (if applicable)
- Fixative

The following fields of data should be collected from translational study:

- Are the negative and positive controls stained correctly
- Is the H&E material acceptable
- Is morphology acceptable
- Total percent positivity of PD-L1 in tumor cells
- PD-L1 status (positive, negative or NA) in tumor cells
- Total percent positivity of PD-L1 in infiltrating immune cells

The Ventana SP263 and the other assays in tumors are experimental. As with all tests, there is a chance of false positive (for example, the test shows high PD-L1 when it is not there) or false negative (for example, the test does not show PD-L1 when it is there) results may occur.

Sample processing and if indicated submission process for translational study

Preparing Stored samples for testing

- Where samples already exist, they should be retrieved from the Bio-Bank storage location. These blocks should undergo quality review, prior to evaluation or shipment. Where it is not possible or indicated to ship the block to a testing laboratory, unstained slides should be prepared from the paraffin-embedded tumor sample block (described below) prior to evaluation or shipment.

Preparing newly acquired samples for testing

- If patients are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample should be used. Where clinically acceptable, a minimum of 2 core biopsies should be collected and processed to FFPE in a single

block. The provision of 2 cores is advised in order to provide sufficient tissue for immunohistochemistry assessment.

- It is recommended that core needle tumor biopsies are collected using an 18 gauge or larger needle and the process should be image-guided. Excisional or incisional samples are also adequate. If this is not per the institutions normal practice and a smaller gauge needle is used then the number of cores collected should be increased to allow sufficient material for successful PD-L1 testing (>100 tumor cells) and embedded in the same block. If available, a single excisional biopsy of at least 4 mm in diameter may substitute for all core biopsies.

Fixation of biopsy samples for testing

- Previously frozen tissue is not acceptable for processing to FFPE for testing. To fix newly acquired tissue, place immediately (within 30 min of excision) into an adequate volume of 10% v/v neutral buffered formalin (NBF). Samples should remain in fixative for 24 – 48 hours at room temperature.
- It is vital that there is an adequate volume of fixative relevant to the tissue (at least a 10 volume excess) and that large specimens (if any) are incised prior to fixation to promote efficient tissue preservation.

Embedding in paraffin for testing

- An overnight processing schedule into paraffin wax is recommended
- Below is the suggested routine overnight processing schedule:

Storage of tumor blocks for testing

- FFPE blocks should be stored at ambient temperature and protected from light until shipment by courier at ambient temperature. FFPE blocks are stable under these conditions for an indefinite period.

Quality control of samples to be used for testing

- Tissue should be assessed by the site pathologist prior to testing.
- Each sample should be reviewed for:

- Adequate fixation
- Good preservation of morphology
- Presence of tumor tissue
- Histopathology consistent with indication
- Greater than 100 tumor cells are required to determine PD-L1 status – tumor cell content must be reviewed prior to testing in order for PD-L1 obtain a valid result.

Shipping samples to a testing laboratory

- When submitting sample to for testing the recommendation is to ship the block in order for sectioning to occur at the laboratory. Blocks should be shipped - containing enough material to be provided to allow a minimum of 5, and preferably 10, sections to be cut (each 4 micron thick) to be used for testing.

Sectioning instructions

- Where it is not possible or indicated to ship the block to laboratory for testing, unstained slides should be prepared from the paraffin-embedded tumor sample block as described below:
 - A minimum of 5-10 x 4 micron (μm) thick, unstained sections should be provided for testing
 - A new disposable microtome blade must be used for each block to prevent contamination between Slides are stable under these conditions for 6 months.
 - patient samples
 - Apply one section per slide to positively-charged Superfrost glass slides
 - The sections should be dried overnight between room temperature and 37°C. Do not dry sections at temperatures above 37°C.

Sections should be stored at ambient temperature and protected from light until use or shipment to testing lab by courier at ambient temperature. It is recommended that slides are cut freshly prior to testing and they are used within 90 days of being cut.

8.3.2 Estimate of volume of blood to be collected

The total volume of blood that will be drawn from each subject in this study is as follows:

Table 8. Volume of Blood to Be Drawn From Each Subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	Clinical chemistry	10	1	10
	Hematology with CD4 count	5	1	5
	Viral load	5	1	5
Biomarker		8 Ml	8	64 Ml
Total				

For the Biomarker analysis in blood, 60-80 mL will be required. They must be sent in EDTA tubes (8-10ml per tube, 8 tubes) as a whole blood at temperature ambient. Samples must arrived to the lab before eight hours from the extraction. If it is not possible arriving in less than 8 hour, samples will be processed at the local lab and the products will be frozen.

8.3.3 Withdrawal of informed consent for donated biological samples

If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented. As collection of the biological samples is an integral part of the study, then the subject is withdrawn from further study participation.

The Principal Investigator:

- Ensures that biological samples from that subject, 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/destroyed, the action documented and the signed document returned to the study site
- Ensures that the subject is informed about the sample disposal.

9. DISEASE EVALUATION AND METHODS

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
- SD while on immunotherapy may be durable and represent clinical benefit.

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 anti-cancer compounds, the study may wish to implement the following in addition to standard RECIST 1.1 criteria:

- 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 durvalumab would continue between the initial assessment of progression and confirmation for progression.
- In addition, subjects may continue to receive durvalumab beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that subjects continue to receive benefit from treatment.

Modification of RECIST as described may discourage the early discontinuation of durvalumab and provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on RECIST 1.1 criteria.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anti-cancer therapy other than durvalumab or with symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to tumor compression, spinal cord compression).

9.1.1 ORR and PFS rate

Subjects who are withdrawn from durvalumab treatment for reasons other than confirmed PD will continue to have objective tumor assessments (see Appendix 4).

For the endpoint of BOR according to RECIST1.1, the ORR in terms of having a confirmed BOR of CR or PR will be calculated. Also it will be recoded the ORR by ir RECIST criteria.

Tumor shrinkage will be summarized as the percent change in target lesions per time point from baseline.

Duration of response will be analyzed descriptively. The Kaplan-Meier estimate of median time along with its 95% CI, as well as estimates the survival function at 12 months will be calculated for duration of response.

PFS time according to RECIST 1.1 by Kaplan-Meier analysis.

PFS at 6 months will be the efficacy variable.

9.1.2 OS

Kaplan-Meier estimates will be presented with a summary of associated statistics including the median survival time with two-sided 95% CIs. In particular the survival rate at 12 months will be estimated with corresponding two side 95% CIs. The CIs for median will be calculated according to Kaplan-Meier.

10. ASSESSMENT OF SAFETY

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

10.1.1 Safety Parameters

10.1.1.1 Definition of adverse events

The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

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

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or non serious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

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

10.1.2 Definition of serious adverse events

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity
- Is a congenital abnormality or birth defect in offspring of the subject
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.
 - Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug abuse.

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s) and communicated to AstraZeneca.

10.1.3 Definition of adverse events of special interest (AESI)

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

AESIs for 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 immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. 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 adverse event (AE) being an irAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab include:

- Diarrhea / Colitis
- Pneumonitis/ ILD
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis/ Blood creatinine increases
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)
- Bleeding

- Other inflammatory responses that are rare with a potential immune-mediated aetiology include, but are not limited to, myocarditis, pericarditis, and uveitis.

Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator Brochure.

All the AESI must be reported as a SAE to the promoter of the study in order to monitor properly these adverse events.

10.1.4 Pneumonitis

Adverse events of pneumonitis are of interest for AstraZeneca/Medimmune, as pneumonitis has been reported with anti-PD-1 MAb (Topalian et al, NEJM 2012). Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

Guidelines for the management of subjects with immune-mediated events including pneumonitis are outlined in Appendix 1.

10.1.5 Hypersensitivity Reactions

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

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Appendix 1.

10.1.6 Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies (Brahmer et al 2012). Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea

and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than $3 \times \text{ULN}$ and concurrent increase in total bilirubin to be greater than $2 \times \text{ULN}$. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in Appendix 1.

Cases where a subject shows an AST **or** ALT $\geq 3 \times \text{ULN}$ **or** total bilirubin $\geq 2 \times \text{ULN}$ may need to be reported as SAEs, These cases should be reported as SAEs if, after evaluation they meet the criteria for a Hy's Law case or if any of the individual liver test parameters fulfill any of the SAE criteria.

10.1.7 Gastrointestinal disorders

Diarrhea/colitis is the most commonly observed treatment emergent SAE when tremelimumab is used as monotherapy. In rare cases, colon perforation may occur that requires surgery (colectomy) or can lead to a fatal outcome if not properly managed. Guidelines on management of diarrhea and colitis in patients receiving durvalumab are provided in Appendix 1.

10.1.8 Endocrine disorders

Immune-mediated endocrinopathies include hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism. Guidelines for the management of patients with immune-mediated endocrine events are provided in Appendix 1.

10.1.9 Pancreatic disorders

Immune-mediated pancreatitis includes autoimmune pancreatitis, and lipase and amylase elevation. Guidelines for the management of patients with immune-mediated pancreatic disorders are provided in Appendix 1.

10.1.10 Neurotoxicity

Immune-mediated nervous system events include encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Appendix 1.

10.1.11 Nephritis

Consult with Nephrologist. Monitor for signs and symptoms that may be related to changes in renal function (e.g. routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc).

Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc).

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event. Guidelines for the management of patients with immune-mediated neurotoxic events are provided in Appendix 1.

10.1.12 Bleeding

Bleeding has been reported in up to 10% or greater in patients with head and neck cancer. Reports of bleeding, including fatal reports, have been received from head and neck cancer patients enrolled in MAH clinical trials with durvalumab as monotherapy or in combination. It is not yet known whether the risk of bleeding would be higher or lower with the experimental treatment than with standard chemotherapy. Monitor bleeding as an AESI.

Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo.
- Among trial subjects showing such aminotransferase elevations, often with aminotransferases much greater than 3 x ULN, one or more also show elevation of serum total bilirubin to >2 x ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase).
- No other reason can be found to explain the combination of increased aminotransferases and total bilirubin, such as viral hepatitis A, B, or C; pre-existing or acute liver disease; or another drug capable of causing the observed injury.

10.2 Assessment of safety parameters

10.2.1 Assessment of severity

Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v4.03.

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.

Grade 2 (moderate) An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3 (severe) An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.

Grade 4 (life threatening) An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).

Grade 5 (fatal) Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a non-serious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.2.2 Assessment of relationship

Investigators must systematically assess the causal relationship of AEs to the trial treatment using the following definitions. Decisive factors for the assessment of causal relationship of an

AE to trial treatment include, but may not be limited to, temporal relationship between the AE and treatment administration, known side effects of trial treatment, medical history, concomitant medication, course of the underlying disease, trial procedures.

Not related: Not reasonably related to the trial. The AE could not medically (pharmacologically / clinically) be attributed to the trial treatment in this clinical trial protocol. A reasonable alternative explanation must be available.

Related: Reasonably related to the trial treatment The AE could medically (pharmacologically / clinically) be attributed to the trial treatment.

TEAEs defined as possibly related to trial treatment will be summarized by Preferred Term and System Organ Class, and described in terms of intensity and relationship to treatment. Treatment emergent AEs are those events with onset dates occurring during the on-treatment period or if the worsening of an event is during the on-treatment period. Any AEs with an onset or worsening date after the on-treatment period will be reported separately.

All premature terminations will be summarized by primary reason for treatment discontinuation/withdrawal.

10.3 Recording of adverse events and serious adverse events

Adverse events will be recorded in the eCRF using a recognized medical term or diagnosis that accurately reflects the event. Adverse events will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety.

In cases of surgical or diagnostic procedures, the condition / illness leading to such a procedure is considered as the AE rather than the procedure itself.

According to the Sponsor's convention, any clinical AE with severity of Grade 4 or 5 must also be reported as an SAE; however, a laboratory abnormality of Grade 4, such as anemia or neutropenia, is considered serious only if the condition meets one of the serious criteria described below. If death occurs, the primary cause of death (or event leading to death) should be recorded and reported as an SAE. "Fatal" will be recorded as the outcome of this respective event; death will not be recorded as a separate event. Only if no cause of death can be reported (for example, sudden death, unexplained death), the death per se might be reported as an SAE.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against durvalumab (yes or no)
- Action taken with regard to durvalumab
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to<<criteria>>
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)

Events, which are unequivocally due to disease progression, should not be reported as an AE during the study.

10.3.1 Study recording period and follow-up for adverse events and serious adverse events

Adverse events and serious adverse events will be recorded from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab).

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

If a subject 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.

The investigator is responsible for following all SAEs until resolution, until the subject returns to baseline status, or until the condition has stabilized with the expectation that it will remain chronic, even if this extends beyond study participation.

Follow-up of unresolved adverse events

Any AEs that are unresolved at the subject's last visit in the study are followed up by the investigator for as long as medically indicated, but without further recording in the eCRF. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety.

AstraZeneca/MedImmune retains the right to request additional information for any subject with ongoing AE(s)/SAE(s) at the end of the study, if judged necessary.

Post study events

After the subject has been permanently withdrawn from the study, there is no obligation for the investigator to actively report information on new AE or SAEs occurring in former study subjects after the 90-day safety follow-up period for patients treated with durvalumab. However, if an investigator learns of any SAEs, including death, at any time after the subject has been permanently withdrawn from study, and he/she considers there is a reasonable possibility that the event is related to study treatment, the investigator should notify the study sponsor and AstraZeneca/MedImmune Drug Safety.

10.3.2 Reporting of serious adverse events

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The Sponsor is responsible for informing the Regulatory Authorities of the SAE as per local requirements.

The sponsor must inform local Health Authorities, via a CIOMS form, of any serious or unexpected adverse events that occur, and will concurrently forward all such reports to AstraZeneca. A copy of the CIOMS report must be faxed to AstraZeneca at the time the event is reported to local Health Authorities. It is the responsibility of the sponsor to compile all necessary information and ensure that the local Health Authorities receives a report according to the local reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

* A **cover page** should accompany the CIOMS form indicating the following:

- “Notification from an Investigator Sponsored Study”
- The EudraCT Number
- The sponsor’s name and address
- The trial name/title and ESR reference number (ESR-##-#####)

* Sponsor must also indicate, either in the SAE report or the cover page, the **causality** of events **in relation to all study medications** and if the SAE is **related to disease progression**, as determined by the principal investigator.

* ***Send SAE report and accompanying cover page by way of email to AstraZeneca’s designated mailbox:*** AEMailboxClinicalTrialTCS@astrazeneca.com

If a non-serious AE becomes serious, this and other relevant follow-up information must also be provided to AstraZeneca and the local Health Authorities.

Serious adverse events that do not require expedited reporting to local Health Authorities still need to be reported to AstraZeneca preferably using the MedDRA coding language for serious adverse events. This information should be reported on a monthly basis and under no circumstance less frequently than quarterly.

10.3.3 Reporting of deaths

All deaths that occur during the study, or within the protocol-defined 90-day post-last dose of durvalumab safety follow-up period must be reported as follows:

- Death that is clearly the result of disease progression should be documented but 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 as a SAE within **24 hours** (see Section 10.3.2 for further details). The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

Deaths that occur following the protocol-defined 90-day post-last-dose of durvalumab safety follow-up period will be documented as events for survival analysis, but will not be reported as an SAE.

10.3.4 Other events requiring reporting

10.3.5 Overdose

An overdose is defined as a subject receiving a dose of durvalumab in excess of that specified in the Investigator's Brochure, unless otherwise specified in this protocol.

Any overdose of a study subject with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox(see Section 10.3.2 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE (see Section 10.3). 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 10.1.2 and Section 10.3.2). There is currently no specific treatment in the event of an overdose of durvalumab.

The investigator will use clinical judgment to treat any overdose.

10.3.6 Hepatic function abnormality

Hepatic function abnormality (as defined in Section 10.1.3.3) in a study subject, with or without associated clinical manifestations, is required to be reported as “hepatic function abnormal” *within 24 hours of knowledge of the event* to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox (see Section 10.3.2 for contact information), unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to investigational product has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.
- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

Each reported event of hepatic function abnormality will be followed by the investigator and evaluated by the sponsor.

10.3.7 Pregnancy

10.3.8 Maternal exposure

If a patient becomes pregnant during the course of the study, the IPs 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 appropriate AstraZeneca representatives within 1 day, ie, immediately, but **no later than 24 hours** of when he or she becomes aware of it.

The same timelines apply when outcome information is available.

10.3.9 Paternal exposure

Male patients should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab monotherapy.

Pregnancy of the patient's partner is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, ectopic pregnancy, normal birth, or congenital abnormality) occurring from the date of the first dose until 90 days after the last dose should, if possible, be followed up and documented.

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the patient's partner. Therefore, the local study team should adopt the generic ICF template in line with local procedures and submit it to the Ethics Committees (ECs) prior to use.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

The screening analysis set includes all subjects who signed the ICF.

ITT Analysis set: the ITT analysis set will include all subjects who were included into the trials.

Per-protocol analysis set will include all ITT subjects who do not have major protocol violations.

11.1.1 Safety analysis set

The safety analysis set will include all subjects who were administered at least 1 dose of the trial drug. Analysis performed on the Safety analysis set will considered subjects as treated.

11.1.2 Efficacy analysis set

Analysis of efficacy variables will also be performed on subgroups of interest as PD-L1+ on tumor and on TILs, Also as an exploratory endpoint efficacy in terms of antiretroviral activity of the drug will be performed. It will be recorded as number of CD4, viral load along the treatment, and viral reservoir (HIV integrated in resting T cells).

11.2 Methods of statistical analyses

In general descriptive summaries will be presented for the efficacy and safety variables collected. Continuous variables will be summarized using mean, standard deviation, minimum, median, and maximum. Categorical variables will be summarized using frequency counts and percentages.

Unless otherwise specified, the calculation of proportions will be based on the sample size of the population of interest. Count missing observations will be included in the denominator and presented in a separate category.

11.2.1 Safety Analyses

Analysis of safety endpoint(s)

The extent of exposure to trial drug will be characterized by duration (weeks), number of administrations, cumulative dose (mg/kg), dose intensity (mg/kg/week), relative dose intensity (actual dose given/planned dose) and number of dose delays.

Safety analysis will be performed on the Safety analysis set. The safety endpoints will be tabulated using descriptive statistics.

Safety assessments will be based on review of incidence of AEs including AESIs, ADRs, and changes in vital signs, ECGs, body weight, and laboratory values (hematology, serum chemistry).

The on-treatment period is defined as the time from the first trial drug administration to the last drug administration date +29 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated.

11.2.2 Efficacy Analyses

Analysis of efficacy endpoint(s)

Kaplan Meier method will be used to estimate the survival function. Secondary measurements will be PFS rate at 6 months and OS rate at 12 months.

11.2.3 Exploratory Analyses

Analysis of immunohistochemistry

Immunohistochemistry results (defined as positive or negative) in the pretreatment sample with their relation to response and survival.

Analysis of gene expression

Analysis of gene expression in relation to response and survival.

Analysis of anti HIV activity in blood

Analysis by digital droplet PCR (ddPCR) of HIV-1 DNA associated to CD4+ T cells obtained from peripheral blood.

Analysis of residual plasma viremia

Using an ultrasensitive single copy assay (these patients would be on antiretroviral treatment, so standard techniques for determine viral load with not be useful).

Analysis of HIV-1 RNA expression

Analysis by ddPCR of HIV-1 RNA expression on CD4+ T cells obtained from peripheral blood.

Analysis of 2LTR

Change in 2LTR mean levels in CD4+ T cells.

Analysis of CD4+ and CD8+ T-cell subsets in peripheral blood

Analysis by multicolor flow cytometry of the percentage of naïve, memory and activated CD4+ and CD8+ T-cell subsets in peripheral blood, including analysis of PD-1 expression.

Analysis of functional effector responses of T cells

Analysis by multicolor flow cytometry of the functional effector responses of T cells elicited by different viral and non viral antigens.

Analysis of predictive factors of antitumoral activity in pretreatment tumor samples

mRNA expression (RT-PCR) of Interferon gamma, HLA-DR and PD-L1.

Immunohistochemistry: PDL-1 and HLA-DR.

A set of immune response genes/proteins will be tested (both RT-PCR and immunohistochemistry).

11.2.4 Interim analyses

No interim analyses are planned in this study.

11.3 Determination of sample size

Feasibility will be defined based on the rate of patients that will complete at least 4 treatment cycles. One cycle is four weeks with infusions every four weeks. It is assumed that at least 50% of patients must be complete four cycles for considering feasible the treatment with durvalumab (MEDI4736).

Sample size calculation for an estimated proportion of 50% with a level of confidence of 95% and an accuracy of 22%: 20 patients must be included in this study.

12. ETHICAL AND REGULATORY REQUIREMENTS

12.1 Ethical conduct of the study

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

12.2 Ethics and regulatory review

The Investigator is responsible for the conduct of the trial at his site. He/she will ensure that the trial is performed in accordance with the clinical trial protocol and with the ethical principles that have their own origin in the Declaration of Helsinki, as well as with the ICH Note for Guidance on GCP (ICH Topic E6, 1996) and applicable regulatory requirements. In

particular the investigator must ensure that only patients who have their informed consent are included in the trial.

12.3 Informed consent

An unconditional prerequisite for a subject's participation in the trial is his/her written informed consent. The subject's written consent to participate in the trial must be given before any trial-related activities are carried out. A separate specific PGx ICF will be provided to subjects who are willing to participate in the procedure, which refers to the extraction and analysis of DNA/RNA from blood and /or tumor biopsy in order to better understand how genes may affect the efficacy of durvalumab.

Adequate information must therefore be given to the subject by the Investigator before informed consent is obtained (a person designated by the Investigator may give the information, if permitted by local regulations). A subject information sheet in the local language and prepared in accordance with the Note for Guidance on GCP (IHC Topic E6, 1996) will be provided by the Sponsor for the purpose of obtaining informed consent. In addition to providing this written information to a potential subject, the Investigator or his /her designate will inform the subject verbally of all aspects of the trial. The language used in doing so must be chosen so that the information can be fully and readily understood by lay persons.

The ICF must be signed and personally dated by the Investigator and the subject.

The signed and dated declaration of informed consent will remain at the Investigator's site, and must be safely archived. A copy of the signed and dated information and ICF should be provided to the subject prior to participation.

Data protection and privacy regulations will be observed in capturing, forwarding, processing, and storing subject data. Subjects will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

A unique subject number will be assigned to each subject at inclusion by IVRS system, immediately after informed consent has been obtained. This number will serve as the subject's identifier in the trial as well as in the clinical trial database. The subject's data will be stored under this number. Only the investigator will be able to link the subject's identity with the subject's trial data via an identification list kept at the site. The medical data that are reviewed at the site during the source data verification by the Clinical Trial Monitor, audits, and Health Authority inspections will be kept strictly confidential.

Subjects will be informed accordingly and will be requested to give their consent on data handling procedures in accordance with national regulations.

12.4 Changes to the protocol and informed consent form

Any change in the approved protocol will require a Protocol amendment. The Investigator must not make any change in the study without favorable opinion from the Ethics Committee and authorization from the Health Authorities, except as necessary to eliminate an impending and obvious risk for the subjects except when necessary to remove an apparent, immediate hazard to subjects. Protocol changes introduced to eliminate an impending and obvious risk may be implemented immediately, but must subsequently be documented in an amendment, reported to the Ethics Committee and be submitted to the relevant Health Authorities within the required timeframe.

Any substantial amendments to the protocol must be submitted in writing to the Investigator's Ethics Committee and the Health Authorities for approval before the changes proposed in the amendment are implemented. Depending on the magnitude of the change, the recruitment may be temporally halted.

The sponsor does not have to notify non-substantial amendments to the Health Authorities or the Ethics Committee. However, any non-substantial amendments will be recorded and contained in the documentation when it is subsequently submitted, for example in the subsequent notification of a substantial amendment. Documentation of any non-substantial amendments will be available on request for inspection at the trial site or the sponsor premises as appropriate.

Whenever important new information becomes available that may be relevant to the subject's consent, the written subject information sheet and any other written information provided to subjects will be revised by the Sponsor or designee and be submitted again to the IEC/IRB for review and favorable opinion. The agreed, revised information will be provided to each subject in the trial for signing and dating. The Investigator will explain the changes to the previous version.

12.5 Audits and inspections

This trial will be monitored in accordance with the ICH Note for Guidance on GCP (ICH Topic E6, 1996). The clinical Trial Monitor will perform visits to the trial site at regular intervals.

Representatives of the Sponsor's Quality Assurance unit or a designated organization, as well as Health Authorities, must be permitted to inspect all trial-related documents and other materials at the site, including the Investigator Site File, the completed eCRFs, the trial drug, and the subject's original medical records/files.

The clinical trial protocol, each step of the data capture procedure, and the handling of the data, including the final clinical trial report, will be subject to independent quality assurance activities. Audits may be conducted at any time during or after the trial to ensure the validity and integrity of the trial data.

12.6 Insurance

The sponsor contracts an insurance policy to cover the responsibilities of the investigator and other parties participating in the study, according to the applicable Spanish legislation.

Insurance company: HDI Global SE

- Policy number: **08057681-14129**,

12.7 Publications

The sponsor commits to responsible publication of both the positive and negative results from its clinical trials as required by all governing regulatory and health authorities.

Investigators will not publish the global study results (all sites) unless the sponsor has not done so in a suitable time period after the clinical study report (CSR) has been available. Should the Investigator(s) independently seek to publish results of this study which occur at their study site(s), they must inform the study sponsor of any/all drafts (including, but not limited to papers, manuscripts or abstracts) at least 60 days before submission to the congress, meeting or journal.

The sponsor and Investigator(s) will agree with all aspects related to any proposed publications with regards to the following: 1) any proposed publications will be drafted in

agreement with international recommendations, such as those from the International Committee of Medical Journal Editors (ICMJE) and all elements of the Consort Statement (2010), to maintain integrity of the trial results in all communications; 2) any proposed publications will state the Clinical Research Ethics Committees which approved the trial and the funding sources of the trial; 3) any proposed publications will occur before disclosure of results to lay people; 4) any proposed publications will not report premature or partial data prior to completion of the analysis of the overall results of the trial.

13. STUDY MANAGEMENT

13.1 Training of study site personnel

The principal investigator will maintain a record of all center staff involved in the clinical trial (doctors, nurses and other staff involved) ensuring that they receive appropriate training to perform the study, and that any new information of relevance to the study will be transmitted to them.

Researchers will be instructed about the procedures of the trial in the investigator meeting and/or initiation visits made by monitors at each participating center prior to the study start.

13.2 Monitoring of the study

Spanish Lung Cancer Group is the company responsible for monitoring the study (see appendix 5). The clinical monitors have the obligation to follow the trial closely so that all aspects of the trial are carefully monitored for compliance with applicable government regulations and with ICH E6 (R1) guidelines.

The clinical monitors will visit the study sites and Investigators at intervals as defined in the monitoring plan, in addition to maintaining necessary contact through telephone, e-mail, and letter. The clinical monitors will maintain current personal knowledge of the trial through observation, review of trial records and source documentation, and discussion of the conduct of the trial with the study site Investigators and staff.

13.2.1 Source data

Source documents are all documents used by the Investigator or hospital that relate to the subject's medical history, that verify the existence of the subject, the inclusion and exclusion criteria, and all records covering the subject's participation in the study. They include enrolment log, investigational product accountability log, laboratory notes, memoranda, material dispensing records, subject files, etc. The eCRF is essentially considered a data entry

form and should not constitute the original (or source) medical records unless otherwise specified.

Each Investigator is responsible for maintaining source documents. These will be made available for inspection by the study monitor at each monitoring visit. All supportive documentation submitted with the eCRF, such as laboratory data should be clearly identified with the study, visit and subject number. Any personal information (e.g., subject name, initials) should be removed or rendered illegible to preserve individual confidentiality.

13.2.2 Study documentation

The Investigator will be provided with an Investigator Site File upon initiation of the trial. This file will contain all documents necessary for the conduct of the trial and will be updated and completed throughout the trial. It must be available for review by the Monitor, and must be ready for Sponsor audit as well as for inspection by Health Authorities during and after the trial, and must be safely archived for at least 25 years after the end of the trial. The documents to be archived include the Subject Identification List and the signed subject ICFs. If archiving of the Investigator Site File is no longer possible at the site, the Investigator must notify the Sponsor.

All original subject files (medical records) must be stored at the site (hospital, research institute, or practice) for the longest possible time permitted by the applicable regulations, and / or as per ICH GCP guidelines, whichever is longer. In any case, the Investigator should ensure that no destruction of medical records is performed without the written approval of the Sponsor.

13.3 Study timetable and end of study

End of study is defined as Last Subject Last Visit.

- Recruitment period will be 12 months
- Research Agreement executed: April, 2016
- Projected IRB/IEC approval: March, 2017
- First Subject In: April, 2017
- 50% Enrollment: September, 2017
- Last Subject In (100% enrollment): April 2018

- Last Subject Last Visit (Treatment end): April 2019
- Publication: June, 2020

14. DATA MANAGEMENT

The Investigator or designee will be responsible for entering trial data in the eCRF provided by the CRO and follow the data entry guidelines. It is the Investigator's responsibility to ensure the accuracy of the data entered in the eCRFs and to sign the case report forms.

The data will be entered into a validated database. The CRO will be responsible for data review and processing, in accordance with the CRO's data management procedures.

The principal CRO functions in data management are CRF tracking and query generation, tracking and resolution as well as to perform Eligibility, Treatment, AE, Response checks and inform Medical Reviewers if any doubt regarding eligibility comes up.

Data Manager (DM) will check the database twice a week or when necessary, depending on the recruitment of the Study.

Queries issued by the DM will show up in the eCRF.

DM will send an e-mail to the investigators according the quantity of queries to be solved requesting their resolution as soon as possible. If there would be a lot of queries at the same center, DM will send an e-mail/reminder once a week.

DM have to access to the eCRF in regular intervals to check if any queries have been solved. The participant centers have to access to the eCRF to check if any queries have been issued in their patients.

The data review will be done from the first patient included until the last follow of the last patient reported in the eCRF.

The data cleaning consists of the exhaustive review of data from the baseline to the end of the follow up of the patient, performing queries when necessary.

DM reviewers will follow the most current version of the SLCG's Data Management SOP.

The field which have to be reviewed by DM will be detailed in the eCRF Data Management Manual.

Database lock will occur once quality control procedures and quality assurance procedures (if applicable) have been completed.

Clinical Study Protocol

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Copies of the eCRFs will be provided to the Investigators at the completion of the trial.

The Investigator must keep a subject file (medical file, original medical records) on paper or electronically for every subject included in the trial. This file will contain the available demographic and all medical information for the subject, and should be as complete as possible.

14.1 Study governance and oversight

The safety of all AstraZeneca products is closely monitored on an ongoing basis by AstraZeneca 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.

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Appendix 1 Appendix 1. Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion- Related, and Non-Immune-Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) 1 November 2017 Version

General Considerations

Dose Modifications	Toxicity Management
<p>Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v4.03.</p>	<p>It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table:</p>
<p>In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions:</p> <ul style="list-style-type: none"> • Inability to reduce corticosteroid to a dose of ≤ 10 mg of prednisone per day (or equivalent) within 12 weeks after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing 	<ul style="list-style-type: none"> – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥ 3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper).
<p>Grade 1 No dose modification</p>	
<p>Grade 2 Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1.</p>	
<p>If toxicity worsens, then treat as Grade 3 or Grade 4.</p>	
<p>Study drug/study regimen can be resumed once event stabilizes to Grade ≤ 1 after completion of steroid taper.</p>	
<p>Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions:</p>	
<ol style="list-style-type: none"> 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating 	

Appendix 1 Appendix 1. Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion- Related, and Non-Immune-Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy With Tremelimumab or Tremelimumab Monotherapy) 1 November 2017 Version

General Considerations

Dose Modifications	Toxicity Management
<p>physician’s clinical judgement.</p> <p>3. Doses of prednisone are at ≤10 mg/day or equivalent.</p> <p>Grade 3 Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.</p> <p>Grade 4 Permanently discontinue study drug/study regimen.</p> <p>Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed.</p> <p>Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines.</p> <p>Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper</p> <p>Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).</p>	<ul style="list-style-type: none"> – More potent immunosuppressives such as TNF inhibitors (e.g., infliximab) (also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for <i>Pneumocystis jirovecii</i> pneumonia (PJP, formerly known as <i>Pneumocystis carinii</i> pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

AE Adverse event; CTC Common Toxicity Criteria; CTCAE Common Terminology Criteria for Adverse Events; imAE immune-mediated adverse event; IV intravenous; NCI National Cancer Institute; PO By mouth.

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Pediatric Considerations

Dose Modifications

The criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity is the same for pediatric patients as it is for adult patients, as well as to permanently discontinue study drug/study regimen if unable to reduce corticosteroid \leq a dose equivalent to that required for corticosteroid replacement therapy **within 12 weeks** after last dose of study drug/study regimen

Toxicity Management

- All recommendations for specialist consultation should occur with a pediatric specialist in the specialty recommended.
 - The recommendations for dosing of steroids (i.e., mg/kg/day) and for IV IG and plasmapheresis that are provided for adult patients should also be used for pediatric patients.
 - The infliximab 5 mg/kg IV dose recommended for adults is the same as recommended for pediatric patients \geq 6 years old. For dosing in children younger than 6 years old, consult with a pediatric specialist.
 - For pediatric dosing of mycophenolate mofetil, consult with a pediatric specialist.
 - With long-term steroid and other immunosuppressive use, consider need for PJP prophylaxis, gastrointestinal protection, and glucose monitoring.
-

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Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	Any Grade	General Guidance	For Any Grade: <ul style="list-style-type: none">– Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below.– Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	For Grade 1 (radiographic changes only): <ul style="list-style-type: none">– Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated.– Consider Pulmonary and Infectious disease consult.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade \leq 1. <ul style="list-style-type: none">• If toxicity worsens, then treat as Grade 3 or Grade 4.• If toxicity improves to Grade \leq1, then the decision to reinstate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	For Grade 2 (mild to moderate new symptoms): <ul style="list-style-type: none">– Monitor symptoms daily and consider hospitalization.– Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent).– Reimage as clinically indicated.– If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started– If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors

			(e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
			<ul style="list-style-type: none"> Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])^a Consider pulmonary and infectious disease consult. Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	<p>For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):</p> <ul style="list-style-type: none"> Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. Hospitalize the patient. Supportive care (e.g., oxygen). If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a
Diarrhea/Colitis	Any Grade	General Guidance	<p>For Any Grade:</p> <ul style="list-style-type: none"> Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis,

		<p>peritoneal signs, and ileus).</p> <ul style="list-style-type: none"> - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. - Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event. - Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
<p>Grade 1</p> <p>(Diarrhea: stool frequency of <4 over baseline per day)</p> <p>(Colitis: asymptomatic; clinical or diagnostic observations only)</p>	<p>No dose modifications.</p>	<p>For Grade 1:</p> <ul style="list-style-type: none"> - Monitor closely for worsening symptoms. - Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
<p>Grade 2</p> <p>(Diarrhea: stool frequency of 4 to 6 over baseline per day)</p> <p>(Colitis: abdominal pain; mucus or blood in stool)</p>	<p>Hold study drug/study regimen until resolution to Grade \leq1</p> <ul style="list-style-type: none"> • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade \leq1, then study drug/study regimen can be resumed after completion of steroid taper. 	<p>For Grade 2:</p> <ul style="list-style-type: none"> - Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. - Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. - If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks^a. Caution: it

			is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab.
			<ul style="list-style-type: none"> – Consider, as necessary, discussing with study physician if no resolution to Grade ≤ 1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a
	<p>Grade 3 or 4 (Grade 3 diarrhea: stool frequency of ≥ 7 over baseline per day; Grade 4 diarrhea: life threatening consequences) (Grade 3 colitis: severe abdominal pain, change in bowel habits, medical intervention indicated, peritoneal signs; Grade 4 colitis: life-threatening consequences, urgent intervention indicated)</p>	<p>Grade 3 Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤ 1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper.</p> <p>Grade 4 Permanently discontinue study drug/study regimen.</p>	<p>For Grade 3 or 4:</p> <ul style="list-style-type: none"> – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a
<p>Hepatitis (elevated LFTs)</p>	<p>Any Grade</p>	<p>General Guidance</p>	<p>For Any Grade:</p> <ul style="list-style-type: none"> – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).

<p>Infliximab should not be used for management of immune-related hepatitis.</p> <div style="border: 1px solid black; padding: 5px; width: fit-content;"> <p>PLEASE SEE shaded area immediately below this section to find guidance for management of “Hepatitis (elevated LFTS)” in HCC patients</p> </div>	<p>Grade 1 (AST or ALT >ULN and $\leq 3.0 \times \text{ULN}$ and/or TB > ULN and $\leq 1.5 \times \text{ULN}$)</p>	<ul style="list-style-type: none"> No dose modifications. If it worsens, then treat as Grade 2 event. 	<p>For Grade 1:</p> <ul style="list-style-type: none"> Continue LFT monitoring per protocol.
	<p>Grade 2 (AST or ALT >3.0×ULN and $\leq 5.0 \times \text{ULN}$ and/or TB >1.5×ULN and $\leq 3.0 \times \text{ULN}$)</p>	<ul style="list-style-type: none"> Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1. If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤ 1 or baseline, resume study drug/study regimen after completion of steroid taper. 	<p>For Grade 2:</p> <ul style="list-style-type: none"> Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. If no resolution to Grade ≤ 1 in 1 to 2 days, consider, as necessary, discussing with study physician. If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).^a Discuss with study physician if mycophenolate mofetil is not available. Infliximab should NOT be used. Once the patient is improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a
	<p>Grade 3 or 4 (Grade 3: AST or ALT >5.0×ULN and $\leq 20.0 \times \text{ULN}$ and/or TB >3.0×ULN and</p>	<p>For Grade 3: For elevations in transaminases $\leq 8 \times \text{ULN}$, or elevations in bilirubin $\leq 5 \times \text{ULN}$:</p> <ul style="list-style-type: none"> Hold study drug/study regimen dose until resolution to Grade ≤ 1 or 	<p>For Grade 3 or 4:</p> <ul style="list-style-type: none"> Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if

<p>≤10.0×ULN)</p> <p>(Grade 4: AST or ALT >20×ULN and/or TB >10×ULN)</p>	<p>baseline</p> <ul style="list-style-type: none"> Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days <p>For elevations in transaminases >8 × ULN or elevations in bilirubin >5 × ULN, discontinue study drug/study regimen.</p> <p>Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3 × ULN + bilirubin >2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause.^b</p> <p>For Grade 4:</p> <p>Permanently discontinue study drug/study regimen.</p>	<p>mycophenolate is not available. Infliximab should NOT be used.</p> <ul style="list-style-type: none"> Perform hepatology consult, abdominal workup, and imaging as appropriate. Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a
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Hepatitis (elevated LFTs)	Any Grade	General Guidance	For Any Grade:
			<ul style="list-style-type: none"> Monitor and evaluate liver function test: AST, ALT, ALP, and TB. Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]).

<p>Infliximab should not be used for management of immune-related hepatitis.</p> <div style="border: 1px solid black; padding: 5px; margin: 10px 0;"> <p>THIS shaded area is guidance <i>only</i> for management of “Hepatitis (elevated LFTs)” in HCC patients</p> </div>	<ul style="list-style-type: none"> - For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg - For HCV+ patients: evaluate quantitative HCV viral load - Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml - Consider consulting hepatologist/Infectious disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥ 2-fold - For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
<p>See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation</p>	<ul style="list-style-type: none"> • No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as Grade 2 event. <p>For all grades, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either increasing bilirubin or signs of DILI/liver decompensation</p>
<p>(Isolated AST or ALT $>5.0 \times \text{ULN}$ and $\leq 8.0 \times \text{ULN}$, if normal at baseline)</p> <p>(Isolated AST or ALT</p>	<ul style="list-style-type: none"> • Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤ 1 or baseline. • If toxicity worsens, then treat as Grade 3 or Grade 4. If toxicity improves to Grade ≤ 1 or baseline, resume study drug/study regimen after completion of steroid taper. <p>For Grade 2:</p> <ul style="list-style-type: none"> - Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. - Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. - Consider, as necessary, discussing with study physician. - If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

<p>>2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline)</p>	<ul style="list-style-type: none"> – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).^a Discuss with study physician if mycophenolate mofetil is not available. Infliximab should NOT be used. 	
<p>Grade 3 (Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline) (Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)</p>	<ul style="list-style-type: none"> • Hold study drug/study regimen dose until resolution to Grade ≤1 or baseline • Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade ≤1 or baseline within 14 days <p>Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.^b</p>	<p>For Grade 3:</p> <ul style="list-style-type: none"> – Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. Infliximab should NOT be used. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a
<p>Grade 4</p>	<p>Permanently discontinue study drug/study</p>	<p>For Grade 4:</p>

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	(Isolated AST or ALT >20×ULN, whether normal or elevated at baseline)	regimen.	Same as above (except would recommend obtaining liver biopsy early)
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin ($\geq 1.5 \times \text{ULN}$, if normal at baseline; or $2 \times \text{baseline}$, if $> \text{ULN}$ at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR):			
<ul style="list-style-type: none">- Manage dosing for Grade 1 transaminase rise as instructed for Grade 2 transaminase rise- Manage dosing for Grade 2 transaminase rise as instructed for Grade 3 transaminase rise- Grade 3-4: Permanently discontinue study drug/study regimen			
Nephritis or renal dysfunction (elevated serum creatinine)	Any Grade	General Guidance	For Any Grade: <ul style="list-style-type: none">- Consult with nephrologist.- Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria).- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections).- Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.
	Grade 1 (Serum creatinine > 1 to $1.5 \times \text{baseline}$; > ULN to $1.5 \times \text{ULN}$)	No dose modifications.	For Grade 1: <ul style="list-style-type: none">- Monitor serum creatinine weekly and any accompanying symptoms.<ul style="list-style-type: none">• If creatinine returns to baseline, resume its regular monitoring per study protocol.

		<ul style="list-style-type: none"> If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4.
		<ul style="list-style-type: none"> Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics.
<p>Grade 2 (serum creatinine >1.5 to 3.0 × baseline; >1.5 to 3.0 × ULN)</p>	<p>Hold study drug/study regimen until resolution to Grade ≤1 or baseline.</p> <ul style="list-style-type: none"> If toxicity worsens, then treat as Grade 3 or 4. If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper. 	<p>For Grade 2:</p> <ul style="list-style-type: none"> Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. Consult nephrologist and consider renal biopsy if clinically indicated. If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
<p>Grade 3 or 4 (Grade 3: serum creatinine >3.0 × baseline; >3.0 to 6.0 × ULN; Grade 4: serum</p>	<p>Permanently discontinue study drug/study regimen.</p>	<p>For Grade 3 or 4:</p> <ul style="list-style-type: none"> Carefully monitor serum creatinine on daily basis. Consult nephrologist and consider renal biopsy if clinically indicated. Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV

creatinine >6.0 × ULN)

methylprednisolone 2 to 4 mg/kg/day started.

- Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a

Rash (excluding bullous skin formations)	Any Grade (refer to NCI CTCAE v 4.03 for definition of severity/grade depending on type of skin rash)	General Guidance	For Any Grade:
	Grade 1	No dose modifications.	For Grade 1: - Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. <ul style="list-style-type: none"> • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper. 	For Grade 2: - Obtain dermatology consult. - Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). - Consider moderate-strength topical steroid. - If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. - Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.

Grade 3 or 4	For Grade 3: Hold study drug/study regimen until resolution to Grade \leq 1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade \leq 1 or baseline within 30 days, then permanently discontinue study drug/study regimen. For Grade 4: Permanently discontinue study drug/study regimen.	For Grade 3 or 4: <ul style="list-style-type: none"> - Consult dermatology. - Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. - Consider hospitalization. - Monitor extent of rash [Rule of Nines]. - Consider skin biopsy (preferably more than 1) as clinically feasible. - Once the patient is improving, gradually taper steroids over \geq28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a - Consider, as necessary, discussing with study physician.
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Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased also included in this section)	Any Grade (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	For Any Grade: <ul style="list-style-type: none"> - Consider consulting an endocrinologist for endocrine events. - Consider, as necessary, discussing with study physician. - Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. - Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). - Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose
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		and ketone levels, HgA1c).
		<ul style="list-style-type: none"> - For modest asymptomatic elevations in serum amylase and lipase, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. - If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
Grade 1	No dose modifications.	<p>For Grade 1 (including those with asymptomatic TSH elevation):</p> <ul style="list-style-type: none"> - Monitor patient with appropriate endocrine function tests. - For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). - If TSH < 0.5 × LLN, or TSH > 2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
Grade 2	<p>For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable.</p> <ul style="list-style-type: none"> • If toxicity worsens, then treat as Grade 3 or Grade 4. <p>Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.</p> <p>Patients with endocrinopathies who may require prolonged or continued steroid</p>	<p>For Grade 2 (including those with symptomatic endocrinopathy):</p> <ul style="list-style-type: none"> - Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. - For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). - Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. - Isolated Type 1 diabetes mellitus (DM) may be treated with

	<p>replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions:</p> <ol style="list-style-type: none"> 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤ 10 mg/day or equivalent. 	<p>appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids.</p> <ul style="list-style-type: none"> – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).³ – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
<p>Grade 3 or 4</p> <p>For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled.</p> <p>Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper.</p> <p>Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions:</p> <ol style="list-style-type: none"> 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤ 10 mg/day or equivalent. 		<p>For Grade 3 or 4:</p> <ul style="list-style-type: none"> – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥ 28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections

[Category 2B recommendation].^a

Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Any Grade (depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)	General Guidance	For Any Grade:
			<ul style="list-style-type: none"> - Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). - Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). - Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). - Perform symptomatic treatment with neurological consult as appropriate. -
	Grade 1	No dose modifications.	For Grade 1:
			<ul style="list-style-type: none"> - See “Any Grade” recommendations above.
	Grade 2	<p>For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1.</p> <p>For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1.</p> <p>If toxicity worsens, then treat as Grade 3 or 4.</p> <p>Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.</p>	For Grade 2:
			<ul style="list-style-type: none"> - Consider, as necessary, discussing with the study physician. - Obtain neurology consult. - Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). - Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. - If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	Grade 3 or 4	<p>For Grade 3:</p> <p>Hold study drug/study regimen dose until</p>	For Grade 3 or 4:
			<ul style="list-style-type: none"> - Consider, as necessary, discussing with study physician. - Obtain neurology consult.

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		resolution to Grade ≤ 1 . Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤ 1 within 30 days.	<ul style="list-style-type: none">- Consider hospitalization.- Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.- If no improvement within 3 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG).- Once stable, gradually taper steroids over ≥ 28 days.
		For Grade 4: Permanently discontinue study drug/study regimen.	
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	Any Grade	General Guidance	For Any Grade: <ul style="list-style-type: none">- The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability.- Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult.- Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation.- It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV

IG and followed by plasmapheresis if not responsive to IV IG.

Grade 1	No dose modifications.	For Grade 1: <ul style="list-style-type: none">- Consider, as necessary, discussing with the study physician.- Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.- Obtain a neurology consult.
Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤ 1 . Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤ 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	For Grade 2: <ul style="list-style-type: none">- Consider, as necessary, discussing with the study physician.- Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above.- Obtain a neurology consult- Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). <p><i>MYASTHENIA GRAVIS:</i></p> <ul style="list-style-type: none">o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist.o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient.o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. <p><i>GUILLAIN-BARRE:</i></p> <ul style="list-style-type: none">o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not

			typically considered effective.
			○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4	For Grade 3:		
	Hold study drug/study regimen dose until resolution to Grade ≤1.		
	Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.		
	For Grade 4:		
	Permanently discontinue study drug/study regimen.		
		For Grade 3 or 4 (severe or life-threatening events):	
		– Consider, as necessary, discussing with study physician.	
		– Recommend hospitalization.	
		– Monitor symptoms and obtain neurological consult.	
		<i>MYASTHENIA GRAVIS:</i>	
		○ Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist.	
		○ Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG.	
		○ If myasthenia gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis.	
		<i>GUILLAIN-BARRE:</i>	
		○ It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective.	
		○ Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.	

Myocarditis	Any Grade	General Guidance	For Any Grade:
		Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	– The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function.
			– Consider, as necessary, discussing with the study physician.

- Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures.
- Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed.
- Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)

Grade 1
(asymptomatic with laboratory (e.g., BNP) or cardiac imaging abnormalities)

No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.

For Grade 1 (no definitive findings):

- Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated.
- Consider using steroids if clinical suspicion is high.

Grade 2, 3 or 4
(Grade 2: Symptoms with mild to moderate activity or exertion)

(Grade 3: Severe with symptoms at rest or with minimal activity)

- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinstitute study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not

For Grade 2-4:

- Monitor symptoms daily, hospitalize.
- Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy.
- Supportive care (e.g., oxygen).
- If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start

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or exertion; intervention indicated) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	rapidly improve, permanently. discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). ^a
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Myositis/Polymyositis ("Poly/myositis")	Any Grade	General Guidance	For Any Grade:
			<ul style="list-style-type: none"> – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e.,

consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia.

Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).

Grade 1 (mild pain)	- No dose modifications.	For Grade 1: <ul style="list-style-type: none">- Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated.- Consider Neurology consult.- Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade \leq 1. <ul style="list-style-type: none">- Permanently discontinue study drug/study regimen if it does not resolve to Grade \leq1 within 30 days or if there are signs of respiratory insufficiency.	For Grade 2: <ul style="list-style-type: none">- Monitor symptoms daily and consider hospitalization.- Obtain Neurology consult, and initiate evaluation.- Consider, as necessary, discussing with the study physician.- If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids <u>along with receiving input</u> from Neurology consultant- If clinical course is <i>not</i> rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day- If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.- Once the patient is improving, gradually taper steroids over

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Grade 3 or 4
(pain associated with severe weakness; limiting self-care ADLs)

For Grade 3:
Hold study drug/study regimen dose until resolution to Grade \leq 1.

Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade \leq 1 within 30 days or if there are signs of respiratory insufficiency.

For Grade 4:
- Permanently discontinue study drug/study regimen.

\geq 28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a

For Grade 3 or 4 (severe or life-threatening events):

- Monitor symptoms closely; recommend hospitalization.
- Obtain Neurology consult, and complete full evaluation.
- Consider, as necessary, discussing with the study physician.
- Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant.
- If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.
- Consider whether patient may require IV IG, plasmapheresis.
- Once the patient is improving, gradually taper steroids over \geq 28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).^a

^aASCO Educational Book 2015 “Managing Immune Checkpoint Blocking Antibody Side Effects” by Michael Postow MD.

^bFDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation.

AChE Acetylcholine esterase; ADL Activities of daily living; AE Adverse event; ALP Alkaline phosphatase test; ALT Alanine aminotransferase; AST Aspartate aminotransferase; BUN Blood urea nitrogen; CT Computed tomography; CTCAE Common Terminology Criteria for Adverse Events; ILD Interstitial lung disease; imAE immune-mediated adverse event; IG Immunoglobulin; IV Intravenous; GI Gastrointestinal; LFT Liver function tests; LLN Lower limit of normal; MRI Magnetic resonance imaging; NCI National Cancer Institute; NCCN National Comprehensive Cancer Network; PJP *Pneumocystis jirovecii* pneumonia (formerly known as *Pneumocystis carinii* pneumonia); PO By mouth; T3 Triiodothyronine; T4 Thyroxine; TB Total bilirubin; TNF Tumor necrosis factor; TSH Thyroid-stimulating hormone; ULN Upper limit of normal.

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Date 16th April 2018

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	<p style="text-align: center;">For Any Grade:</p> <ul style="list-style-type: none"> - Manage per institutional standard at the discretion of investigator. - Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	<p style="text-align: center;">For Grade 1:</p> <p>The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event.</p> <p style="text-align: center;">For Grade 2:</p> <p>The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event.</p> <p>Subsequent infusions may be given at 50% of the initial infusion rate.</p>	<p style="text-align: center;">For Grade 1 or 2:</p> <ul style="list-style-type: none"> - Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator. - Consider premedication per institutional standard prior to subsequent doses. - Steroids should not be used for routine premedication of Grade ≤ 2 infusion reactions.
Grade 3 or 4	<p>For Grade 3 or 4:</p> <p>Permanently discontinue study drug/study regimen.</p>	<p style="text-align: center;">For Grade 3 or 4:</p> <ul style="list-style-type: none"> - Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

CTCAE Common Terminology Criteria for Adverse Events; IM intramuscular; IV intravenous; NCI National Cancer Institute.

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Non-Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to \leq Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to \leq Grade 1 or baseline. For AEs that downgrade to \leq Grade 2 within 7 days or resolve to \leq Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

Note: As applicable, for early phase studies, the following sentence may be added: "Any event greater than or equal to Grade 2, please discuss with Study Physician."
AE Adverse event; CTCAE Common Terminology Criteria for Adverse Events; NCI National Cancer Institute.

Appendix 2 Durvalumab dose calculations

Durvalumab Dosing

The durvalumab dosing should be done depending on subject weight (if subject is ≤ 30 kg):

1. Cohort dose: X mg/kg (An equivalent dose of 20 mg/kg should be administered for patients weighting ≤ 30 kg)

2. Subject weight: Y kg

3. Dose for subject: XY mg = X (mg/kg) \times Y (kg)

4. Dose to be added into infusion bag:

$$\text{Dose (mL)} = \text{XY mg} / 50 \text{ (mg/mL)}$$

where 50 mg/mL is durvalumab nominal concentration

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

5. The theoretical number of vials required for dose preparation is the next greatest whole number of vials from the following formula:

$$\text{Number of vials} = \text{Dose (mL)} / 10 \text{ (mL/vial)}$$

Example:

1. Cohort dose: 20 mg/kg

2. Subject weight: 30 kg

3. Dose for subject: 600 mg = 20 (mg/kg) \times 30 (kg)


4. Dose to be added into infusion bag:

$$\text{Dose (mL)} = 600 \text{ mg} / 50 \text{ (mg/mL)} = 12.0 \text{ mL}$$

5. The theoretical number of vials required for dose preparation:

$$\text{Number of vials} = 12.0 \text{ (mL)} / 10.0 \text{ (mL/vial)} = 2 \text{ vials}$$

Appendix 3 Schedule of study procedures: follow-up for subjects who have completed durvalumab treatment and achieved disease control (until confirmed progression of disease) and subjects who have discontinued durvalumab due to toxicity in the absence of confirmed progression of disease

Evaluation	Time Since Last Dose of durvalumab							
	Day (± 3)	Months (± 1 week)						12 Months and Every 6 Months (± 2 weeks)
	30	2	3	4	6	8	10	
Physical examination ^a	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Weight	X							
Urine hCG or serum β hCG	X			x				
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated 							
ECOG performance status	X	X	X		X (and month 9)			X
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Hematology	X	X	X					X
Serum chemistry	X	X	X					
Thyroid function tests (TSH, and fT3 and fT4) ^b	X							

Appendix 3 Schedule of study procedures: follow-up for subjects who have completed durvalumab treatment and achieved disease control (until confirmed progression of disease) and subjects who have discontinued durvalumab due to toxicity in the absence of confirmed progression of disease


Evaluation	Time Since Last Dose of durvalumab						
	Day (± 3)	Months (± 1 week)					12 Months and Every 6 Months (± 2 weeks)
	30	2	3	4	6	8	
Tumour assessment (CT or MRI)	<p>For subjects who achieve disease control following 12 months of treatment, tumour assessments should be performed every 12 weeks (± 1 week) relative to the date of first infusion thereafter until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Table 1: schedule of assessments for timings of confirmatory scans.</p> <p>For subjects who discontinue durvalumab due to toxicity (or symptomatic deterioration), tumour assessments should be performed relative to the date of first infusion as follows: every 8 weeks (± 1 week) for the first 48 weeks, then every 12 weeks (± 1 week) until confirmed PD by RECIST 1.1 by investigational site review. Please refer to Table 1: schedule of assessments for timings of confirmatory scans.</p> <p>Upon confirmed PD, scans should be conducted according to local standard clinical practice and submitted for central review until a new treatment is started (these scans are optional).</p>						

^a Full physical exam

^b Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

^c For patient questionnaires different approaches based on indication and study design

Appendix 4 Schedule of study procedures: follow-up for subjects who have discontinued durvalumab treatment due to confirmed progression of disease at the discretion of the investigator

Evaluation	Time Since Last Dose of durvalumab							
	Day (± 3)	Months (± 1 week)						12 Months and Every 6 Months (± 2 weeks)
	30	2	3	4	6	8	10	
Physical examination ^a	X							
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X							
Weight	X							
AE/SAE assessment	X	X	X					
Concomitant medications	X	X	X					
Palliative radiotherapy	As clinically indicated 							
ECOG performance status ^b	X	X	X					
Subsequent anti-cancer therapy	X	X	X	X	X	X	X	X
Survival status: phone contact with subjects who refuse to return for evaluations and agree to be contacted		X	X	X	X	X	X	X (every 2 months)
Urine hCG or serum β hCG	X							
Hematology	X	X	X					
Serum chemistry	X	X	X					
Thyroid function tests (TSH, and fT3 and fT4) ^c	X							
Tumour assessment (CT or MRI)	<p>For subjects who continue on durvalumab post-confirmed progression at the investigator's discretion (following consultation with the sponsor), tumour assessments should be performed relative to the date of first infusion per schedule of assessments until durvalumab is stopped.</p> <p>For subjects who discontinue durvalumab following confirmed progression, scans should be conducted according to local clinical practice and submitted for central review until a new treatment is started (these scans are optional).</p>							

^a Full physical exam

^b PS to be collected if available at the 2 monthly calls to obtain subsequent anti-cancer therapy and survival status

^c Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

^d For patient questionnaires different approaches based on indication and study design

Appendix 5: Contact Details

Sponsor	Spanish Lung Cancer Group (SLCG) Villarroel, 251 principal 2 ^a 08036 Barcelona Phone Number. +34 93 430 20 06 Fax. +34 93 419 17 68 E-mail: gecp@gecp.org
Principal investigator	Dr. Rafael Rosell Instituto Oncológico Dr. Rosell Phone. +34935460135 Fax. +34935460196 E-mail: rrosell@iconcologia.net
Participating investigators	Dr. Maria Gonzalez-Cao Hospital Instituto Oncológico Dr. Rosell Department Oncology Department Address Sabino Arana 5 08028 Barcelona Phone Number: +34935460135 E-mail: mgonzalezcao@oncorosell.com Dr. Javier Martinez-Picado AIDS Research Institute -IrsiCaixa- Hospital Univ. Germans Trias i Pujol Address: Carretera Canyet s/n Badalona (Barcelona) Phone Number: 34 934656374 E-mail: jmpicado@irsicaixa.es Dr. Bartomeu Massuti Hospital General de Alicante Department Oncology Department Address Pintor Baeza, 11 03010 Alicante Phone Number: 34965933000 E-mail: bmassutis@seom.org Dr. Bonaventura Clotet AIDS Research Institute -IrsiCaixa- Hospital Univ. Germans Trias i Pujol Address: Carretera Canyet s/n Badalona (Barcelona) Phone Number: 34 934656374 E-mail: bclotet@irsicaixa.es

Clinical Study Protocol

Drug Substance Durvalumab (Medi4736)

Sponsor code: GECP 16/04_ Astra Zeneca Study number: **ESR 15-10869**

Version Number 4.0

Date 16th April 2018

CRO Spanish Lung Cancer Group (SLCG)
Villarroel, 251 principal 2^a
08036 Barcelona
Phone Number. +34 93 430 20 06
Fax. +34 93 419 17 68
E-mail: secretaria@gecp.org

Central lab oncology PangaeaBiotech
Sabino Arana 5
Phone Number: +34935460135
E-mail: mamolina@oncorosell.com

Central lab virology AIDS Research Institute -IrsiCaixa-
Hospital Univ. Germans Trias i Pujol
Address: Carretera Canyet s/n
Phone Number: +34 934656374
E-mail: jmpicado@irsicaixa.es



Grupo Español de Cáncer de Pulmón
Spanish Lung Cancer Group

STATISTICAL ANALYSIS PLAN

STUDY CODE: GEC 16/04_ ASTRA ZENECA STUDY NUMBER: ESR 15-10869

(VERSION PROTOCOL: 4.0, DATE: 16-APR-2018)

A PHASE II EXPLORATORY STUDY OF DURVALUMAB (MEDI4736) IN HIV-1 PATIENTS WITH ADVANCED SOLID TUMORS

Investigational product: Durvalumab (Medi4736).

Indication studied: HIV-1 PATIENTS WITH ADVANCED SOLID TUMORS

Name of Sponsor: Spanish Lung Cancer Group (SLCG/GEC)

EudraCT No.: 2016-004524-38

Phase of study: II

Principal investigator: Dr. Rafael Rosell

Instituto Oncológico Dr. Rosell

Oncology Department

Study Coordinator: Dr. Maria Gonzalez Cao

Instituto Oncológico Dr. Rosell

Oncology Department

Date: 16 April 2018

Version: 1.0

Pages No.: 34

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2 ABBREVIATIONS

The following abbreviations and special terms might be used in this Statistical Analysis Plan

ADA anti-drug antibody	IL interleukin
AE adverse event	irAE immune-related adverse event
AESI adverse event of special interest	IV intravenous(ly)
ALP alkaline phosphatase	Mab monoclonal antibody
ALT alanine aminotransferase	MDSC Myeloid derived suppressor cells
APC antigen-presenting cells	miRNA micro ribonucleic acid
AST aspartate aminotransferase	MRI magnetic resonance imaging
AUC area under the concentration-time curve	mRNA messenger ribonucleic acid
CDCC complement dependent cytotoxicity	MTD maximum tolerated dose
CI confidence interval	NCI CTCAE National Cancer Institute Common Terminology Criteria for Adverse Events
CL clearance	NK natural killer
C _{max} peak concentration	NOAEL no-observed-adverse-effect level
C _{max,ss} peak concentration at steady state	NSCLC non-small cell lung cancer
C _{min} trough concentration	OR objective response
C _{min,ss} trough concentration at steady state	ORR objective response rate
CNS central nervous system	OS overall survival
CR complete response	PD progressive disease
CT computed tomography	PD-1 programmed cell death 1
CTLA-4 cytotoxic T-lymphocyte-associated antigen-4	PD-L1 programmed cell death ligand 1
DCR disease control rate	PD-L2 programmed cell death ligand 2
DLT Dose limiting toxicity	PFS progression-free survival
DNA deoxyribonucleic acid	PK pharmacokinetic(s)
DoR duration of response	PR partial response
ECG electrocardiogram	PRO patient-reported outcome
ECOG Eastern Cooperative Oncology Group	PVC polyvinyl chloride
EDTA disodium edetate dihydrate	Q2W every 2 weeks
Fc fragment crystallizable	Q3M every 3 months
FFPE formalin fixed paraffin embedded	Q3W every 3 weeks
FSH follicle-stimulating hormone	Q4W every 4 weeks
FTIH first-time-in-human	Q12W every 12 weeks
HCl hydrochloride	QoL quality of life
HIV human immunodeficiency virus	QTc the time between the start of the Q wave

ICH International Conference on Harmonization	and the end of the T wave corrected for heart rate
IEC Independent Ethics Committee	QTcF QT interval on ECG corrected using the Frederica's formula
IFN interferon	RCC renal cell carcinoma
IGF insulin-like growth factor	RECIST Response Evaluation Criteria in Solid Tumors
IgG1 immunoglobulin G1	RNA ribonucleic acid
IgG2 immunoglobulin G2	SAE serious adverse event
IGSF immunoglobulin superfamily	SD stable disease
IHC immunohistochemistry	SID subject identification
	sPD-L1 soluble programmed cell death ligand 1
	SOCS3 suppressor of cytokine signaling 3
	SUSAR suspected unexpected serious adverse reaction
	t ^{1/2} half-life
	TEAE treatment-emergent adverse event
	TIL tumor infiltrating lymphocyte
	Tmax time to peak concentration
	Tmax ss time to peak concentration at steady state
	TNF-α tumor necrosis factor alpha
	TSH thyroid stimulating hormone
	ULN upper limit of normal
	WFI water for injection

3 INTRODUCTION

3.1 PREFACE

PD-1/ PD-L1 coinhibitory pathway plays a significant role in the regulation of the immune response in both chronic infectious diseases and cancer. Preclinical and animal data support the safety and promising activity of anti-PD-1 antibody in HIV-1 infection. It has been demonstrated anticancer activity and safety profile of durvalumab (MEDI4736) in cancer clinical trials. Drug interactions of durvalumab (MEDI4736) and antiretroviral treatments are unlikely

A phase II clinical study is proposed, designed to assess the feasibility of durvalumab (MEDI4736) in HIV-1-infected individuals with solid tumors. Additionally, we hope to obtain data that let us understand the possible benefit of this treatment in cancer patients and HIV infection, exploring if activity of durvalumab (MEDI4736) could be higher in cancer that has been produced at least in part due to the chronic immunosuppression. Simultaneously, it will allow us to investigate the effect of disrupting this immunoregulatory pathway might have in reversing cancer pathways and HIV-specific T-cell function during persistent chronic HIV infection in humans.

In this regard, our hypothesis is:

HIV patients with cancer have a similar outcome in terms of tolerability when treated with durvalumab (MEDI4736) monotherapy at the recommended dose than HIV uninfected patients.

3.2 RATIONALE FOR CONDUCTING THIS STUDY

HIV-1-infected patients with cancer have been systematically excluded from clinical trials of anti cancer drugs because of concerns related to drug interactions and the unknown effect of the underlying HIV infection on the safety and activity of the investigational drugs. Anti PD-L1 antibody durvalumab (MEDI4736) could be an active treatment both for cancer and for HIV infection, with non-expected drugs interactions

3.3 PURPOSE OF THE ANALYSIS

This Statistical Analysis Plan (SAP) describes the methodology and statistical analyses that will be performed for reporting purposes of the study DURVAST, and it is based on the study protocol version 4.0 , dated 16 april, 2018.

These analyses will assess the feasibility, efficacy and safety of Durvalumab in HIV-1 patients with advanced solid tumors.

4 **STUDY OBJECTIVES AND ENDPOINTS**

4.1 STUDY OBJECTIVES

The following objectives/endpoints for this phase II study may be assessed:

4.1.1 **Primary objective**

To explore the feasibility of durvalumab (MEDI4736) monotherapy at the recommended dose of 1500 mg every 4 weeks in solid tumors in HIV-1-infected patients.

4.1.2 **Secondary objectives**

- To assess ORR (RECIST 1.1) and duration of response.
- To evaluate the PFS rate at 6 months
- To evaluate the OS rate at 12 months

4.1.3 **Exploratory Objectives**

- To measure the activity of durvalumab (MEDI4736) in terms of antiviral activity, exploring:
 - o Changes in the viral reservoir.
 - o Changes in residual viral replication.
 - o Changes in the composition and function of circulating T lymphocytes.
- To explore molecular predictive factors of antitumoral activity in pretreatment tumor samples.

5 STUDY METHODS

5.1 GENERAL STUDY DESIGN AND PLAN

5.1.1 Study Design

This is a multicenter, national, nonrandomized, open label trial, phase II trial in subjects with advanced solid tumors and HIV-1 infection. Twenty patients will receive durvalumab.

Patients have to be diagnosed of advanced (metastatic or locally advanced disease without cure options with surgery or radiotherapy) cancer of any of these types: lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastro-esophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity.

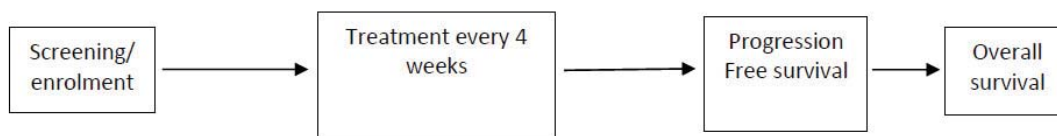
Adverse events (AEs) will be assessed throughout and evaluated using National Cancer Institute (NCI) Common Technology Criteria version of Adverse Events version 4.03 (CTCAE v 4.03).

Tumor measurements by PET-CT, CT scan or MRI will be performed every 8 weeks to determine response to treatment. Response will be evaluated using Response Evaluation Criteria in Solid Tumors version 1.1 (RECIST 1.1) and immune related response criteria (irRECIST).

Treatment will continue until disease progression, significant clinical deterioration, unacceptable toxicity, any criterion for withdrawal from the trial or trial drug is fulfilled. Treatment may continue past the initial determination of disease progression per RECIST1.1 if the subject`s performance status has remained stable, and if the opinion of the Investigator, the subject will benefit from continued treatment and if other criteria are fulfilled as outline in the protocol.

5.1.2 Study schema

Figure1.- Study flow chart



5.1.3 **Duration of the study**

- Recruitment period will be 12 months
- First subject in: Q1, 2017
- Last subject out: Q1, 2018

5.1.4 **Inclusion-Exclusion Criteria**

All patients must fulfil ALL inclusion criteria and NONE exclusion criteria. To avoid the inclusion of ineligible patients, any doubts should be discussed with the Sponsor. If a patient does not fulfil eligibility criteria and is included inadvertently in the study, the Sponsor should be notified.

The Sponsor will decide whether the patient should continue in the study by evaluating the risks and benefits for the patient and guaranteeing the patient's maximum safety

Inclusion criteria

Patients must meet all the following inclusion criteria to be eligible for study entry:

- 1) Written informed consent obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
- 2) Age > 18 years at time of study entry.
- 3) Eastern Cooperative Oncology Group (ECOG) 0-2
- 4) Life expectancy of > 16 weeks
- 5) Adequate normal organ and marrow function as defined below:
 - a) Haemoglobin \geq 9.0 g/dL
 - b) Absolute neutrophil count (ANC) \geq $1.5 \times 10^9/L$ (> 1500 per mm³)
 - c) Platelet count \geq $100 \times 10^9/L$ (>100,000 per mm³)
 - d) Serum bilirubin \leq 1.5 x institutional upper limit of normal (ULN). This will not apply to subjects with confirmed Gilbert's syndrome (persistent or recurrent hyperbilirubinemia that is predominantly unconjugated in the absence of haemolysis or hepatic pathology), who will be allowed only in consultation with their physician
 - e) AST (SGOT)/ALT (SGPT) \leq 2.5 x institutional upper limit of normal unless liver metastases are present, in which case it must be \leq 5x ULN
 - f) Serum creatinine $CL > 40$ mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance

Males:

Creatinine CL (mL/min) = $(\text{Weight(kg)} \times (140 - \text{Age})) / (72 \times \text{serum creatinine (mg/dL)})$

Females:

Creatinine CL (mL/min)=(Weight (kg) x (140 – Age) x0.85)/(72 x serum creatinine (mg/dL))

- 6) – Female subjects must either be of non-reproductive potential (ie, post-menopausal by history: ≥ 60 years old and no menses for $\cdot 1$ year without an alternative medical cause; OR history of hysterectomy, OR history of bilateral tubal ligation, OR history of bilateral oophorectomy) or must have a negative serum pregnancy test upon study entry.
- 7) – Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.
- 8) – Subjects with histologically or cytologically advanced/metastatic-documented lung cancer, head and neck cancer, cervical cancer, melanoma, anal cancer, pancreatic cancer, gastroesophageal cancer, triple negative breast cancer, bladder cancer, renal cancer, Cholangiocarcinoma, Kaposi sarcoma, lymphomas, ovarian cancer, Merkel cell carcinoma or any other tumor type in which anti PD-1 or anti PD-L1 antibodies have demonstrated antitumoral activity, refractory to standard treatment, intolerant of standard treatment, or for which no standard therapy exists or who refuse the standard treatment..
- 9) – Subjects may be included irrespectively of number of previous lines of treatment for advanced disease.
- 10) – Prior palliative radiotherapy must have been completed at least 2 weeks prior to start the study treatment (subjects may receive localized palliative radiotherapy while receiving study drug).
- 11) Documented HIV-1 infection
- 12) Undetectable viral load in the last analysis.
- 13) Subjects with brain metastases are eligible if they are asymptomatic, are treated or are neurological stable for at least 2 weeks without the use of steroids or on stable or decreasing dose of < 10 mg daily prednisone or equivalent.
- 14) Subjects must be following an antiretroviral therapy at the moment of the inclusion. Life expectancy of ≥ 3 months.

Exclusion criteria

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

1. Involvement in the planning and/or conduct of the study. Previous enrollment in the present study.

2. Participation in another clinical study with an investigational product during the last 4 weeks.
3. Other untreated coexisting HIV related malignancies.
4. Any previous treatment with a PD1, PD-L1 or PD-L2 inhibitor, including durvalumab.
5. Receipt of the last dose of anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) 28 days prior to the first dose of study drug
6. Mean QT interval corrected for heart rate (QTc) ≥ 470 ms calculated from 3 electrocardiograms (ECGs) using Fridericia's Correction.
7. Current or prior use of immunosuppressive medication within 28 days before the first dose of durvalumab, with the exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.
8. Any unresolved toxicity (CTCAE grade 2) from previous anti-cancer therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy).
9. Any prior Grade ≥ 3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE $>$ Grade 1.
10. Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.
11. Any syndrome that requires systemic corticosteroid/immunosuppressive medications EXCEPT for syndromes which would not be expected to recur in the absence of an external trigger (vitiligo, autoimmune thyroiditis, or type 1 diabetes mellitus are permitted to enroll)
12. Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).
13. History of primary immunodeficiency.
14. History of allogeneic organ transplant.
15. History of hypersensitivity to durvalumab or any excipient
16. Patients with second primary cancer, except: adequately treated non-melanoma skin cancer, curatively treated in situ cancer of the cervix, or other solid tumours curatively treated with no evidence of disease for ≥ 5 years.
17. Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses including any subject known to have evidence of acute or chronic hepatitis B or C, or

psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent..

18. Known history of active tuberculosis.
19. Any serious or uncontrolled medical disorder or active infection non HIV, that would impair the ability of the subject to receive the treatment of protocol therapy under treating physician criteria
20. Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab.
21. Female subjects who are pregnant, breast-feeding, male, or female patients of reproductive potential who are not employing an effective method of birth control.
22. Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.
23. Symptomatic or uncontrolled brain metastases requiring concurrent treatment, inclusive of but not limited to surgery, radiation and/or corticosteroids.
24. Subjects with uncontrolled seizures.
25. Patients with tumoral disease in the head and neck region, such as peritracheal or periesophageal lymph node involvement, with infiltration of structures of the digestive, aerea or vascular pathways that represent a risk of increased bleeding.
26. Patients with neuroendocrine tumors of pulmonary origin or pulmonary metastases with evidence of active bleeding.
27. Patients with digestive bleeding.

5.1.5 **Withdrawal of subjects from study treatment and/or Study criteria**

Permanent discontinuation of study treatment

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

1. Withdrawal of consent or lost to follow-up.
2. Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing.
3. Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
4. Pregnancy or intent to become pregnant.
5. Any AE that meets criteria for discontinuation as defined in Appendix 1, Section 10.1.3
6. Adverse event related to durvalumab of any Grade>3 ADRs or repetitive Grade 3 ADRs with the exception of toxicities that do not meet the criteria for discontinuation as defined in Section 10.1.3, Appendix 1 of the study protocol

7. Grade \geq 3 infusion reaction.
8. Subject non-compliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits.
9. Initiation of alternative anticancer therapy including another investigational agent.
10. Confirmation of PD and investigator determination that the subject is no longer benefiting from treatment with durvalumab.

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

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 10.3.1 and Appendix 3 or 4, of the study protocol, including the collection of any protocol-specified blood specimens, unless consent is withdrawn or the subject is lost to follow-up or enrolled in another clinical study. All subjects will be followed for survival. Subjects who decline to return to the site for evaluations will be offered follow-up by phone every 3 months as an alternative.

Withdrawal of consent

If consent is withdrawn, the subject will not receive any further investigational product or further study observation.

6 STATISTICAL METHODS

6.1 SAMPLE SIZE

Feasibility was defined based on the rate of patients that will complete at least 4 treatment cycles. One cycle is four weeks with infusions every four weeks. It is assumed that at least 50% of patients must be complete four cycles for considering feasible the treatment with durvalumab (MEDI4736).

Sample size calculation for an estimated proportion of 50% with a level of confidence of 95% and an accuracy of 22%: 20 patients must be included in this study.

6.2 STUDY VARIABLES

6.2.1 Safety variables

- **Incidence of Adverse Events** the incidence of AEs including AESIs, ADRs, and changes in vital signs, ECGs, body weight, and laboratory values (hematology, serum chemistry)
- **Extent of exposure to trial drug:** The extent of exposure to trial drug will be characterized by duration (weeks), number of administrations (cycles) and number of dose delays.
- **Time on treatment:** The on-treatment period is defined as the time from the first trial drug administration to the last drug administration date +29 days or the earliest date of subsequent anticancer drug therapy minus 1 day, whichever occurs first, unless otherwise stated.
- **Changes in Vital signs:** Change from baseline of ECG's and body weight.
- **Change in laboratory values:** Change from baseline of laboratory values (hematology, serum chemistry, Thyroid function tests)

6.2.2 Efficacy variables

- **Feasibility** is the **primary objective** and is defined based on the **rate of patients that receive at least 4 treatment cycles**. It should happen in, at least 50% of the patients in the efficacy population.
- **Tumor response rate:** Tumor response evaluation will be classified according to RECISTV1.1
- **Duration of response.** It will be computed for patients with Complete response, Partial response or Stable Disease assessed.
- **Progression free survival**
- **Overall survival**
- **As secondary analysis: Progression free survival** at 6 months
- **As secondary analysis: Overall survival** at 12 months

6.3 DERIVED VARIABLES

- **Age:** is defined as the time, in years, between the birth date and the informed consent date.
- **Time from diagnosis:** is defined as the elapsed time (in months) from the date of the diagnosis of the disease to the informed consent date.
- **Best global response:** will be computed as the best response achieved, according to RECIST criteria v1.1, during all assessments.
- **Clinical Benefit** A patient has a Clinical Benefit if his best overall response is Complete Response, Partial Response or Stable Disease that remains for more than 24 weeks.
- **Duration of response** it is defined as the time, in weeks, from the first date when Complete Response, Partial Response or Stable Disease is assessed to the first Progressive Disease date, death date or end of the study date, whichever happens first.
- **Overall response rate** is defined as the proportion of patients with complete or partial response, evaluated according to RECIST criteria v1.1, from the total of patients with response evaluation.
- **Duration of study treatment:** is defined as the time, in weeks between the first and the last administration/dose of the study treatment date.
- **On-treatment period:** is defined as the elapsed time, in weeks, between the first and the last administration/dose + 29 days or the earliest date of subsequent anticancer drug therapy minus 1 day, or the withdrawal date, whichever occurs first, unless otherwise stated.
- **Sign and Symptoms:** is any AE with onset date previous to the start of the on treatment period that is resolved before the first administration of the study drug or that did not worsen during the on-treatment period.
- **Treatment emergent adverse event:** treatment-emergent is defined as any AE that occurs after administration of the first dose of study drug and through 29 days after the

last dose of study drug, any event that is considered drug-related regardless of the start date of the event, or any event that is present at baseline and continues after the first dose of study treatment but worsens in intensity

- **Non Treatment emergent adverse event:** a non treatment emergent adverse event is defined as any AE with onset date or worsening date after the on treatment period, that is not drug related according to the investigator criteria
- **Adverse events of special interest:** An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring and rapid communication by the investigator to the sponsor. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this investigational product. AESIs for Durvalumab are specified in section 101.3 of the study protocol.

6.4 MISSING DATA

Missing data will not be imputed, and it will be considered as missing values for the analysis. Only in case of any incomplete dates (missing day) necessary for the analysis, first day of the month and year indicated in each case will be imputed.

Just in case the previous imputation generated an incoherence considering the rest of dates reported for any patient, the day imputed would be the corresponding day according to the rest of dates for the same patient.

6.5 SUMMARY OF DATA ANALYSIS

Since this clinical trial has only one treatment arm, statistics will be mainly descriptive.

Continuous variables will be summarized using the number of cases, mean, standard deviation (SD), mean 95% CI, median, Q1, Q3, minimum and maximum. Shapiro-Wilk test will be used to contrast if the continuous measure follows a normal distribution.

Categorical variables will be summarized in contingency tables that show the number and percentage of cases in each category. If applicable, a two-sided 95% confidence intervals may be provided.

Fisher's exact test (2-sided) or Chi-squared test will be used to explore associations of categorical data. For continuous variables, these comparisons will be done using the parametric t-Student test (or ANOVA if there are more than 2 categories) if the variable follows a normal distribution or the non-parametric Wilcoxon-test (Mann-Whitney test)(or Kruskal-Wallis for more than 2 categories) otherwise.

To explore the change in value of a variable, between baseline and any other time point, a t-test for paired data or the Wilcoxon signed rank test will be used, based on the distribution followed by the corresponding variable.

Survival analysis (PFS and OS) will be evaluated using the Kaplan-Meier model. The results of the survival analysis will include the survival curves, the values of the median with its corresponding 95% confidence interval, the distribution of the number of events and censored cases and the related statistics derived from Long rank test. A proportional hazard Cox regression will be adjusted in order to control prognostic factors, the corresponding hazard ratio (HR) and its 95% CI will be displayed. Thereafter, the probability of estimated survival, as well as the corresponding 95% CI by time intervals will be presented.

6.6 REPORTING CONVENTIONS

The minimum, maximum, mean, standard deviation, median and lower and upper quartiles will be reported to 2 decimal places.

P-values ≥ 0.0001 will be reported to 4 decimal places; p-values less than 0.0001 will be reported as "<0.001".

The AEs will be graded using version NCI 4.03 (CTCAE v 4.03)..

6.7 TECHNICAL DETAILS

The study protocol v4.0 (16 APR 18) has been used as a reference for this document. Statistical programs, logs and outputs generated during the creation of the Statistical Report will be archived in the Study File System.

6.8 SOFTWARE DOCUMENTATION

All analysis and reporting will be undertaken using SPSS V26 and SAS® for Windows Version 9.4 or later release.

7 STATISTICAL RESULTS

7.1 ANALYSIS POPULATIONS

The following analysis populations will be used:

7.1.1 **Efficacy population**

The efficacy population will be the primary population for efficacy analysis. This population is defined as those patients that are included in the study and who have received at least one dose of study treatment. Responserate will be calculated over the total of patients with response evaluation.

Analysis of efficacy variables will also be performed on subgroups of interest as PD-L1 expression in tumor tissue samples.

Exploratory efficacy analysis, in terms of the anti viral activity of Durvakumab, will be performed in a separate analysis.

7.1.2 **Safety Population**

The safety population will be the primary population for safety analysis. This population is defined as those patients included in the study and who received at least one dose of study treatment. An incorrect treatment schedule or drug administration, or an early termination of treatment, will not result in exclusion of patients from this population.

The number and percentage of patients included in each of these populations will be tabulated. Patients excluded of these populations will be described in a listing, specifying the cause of exclusion.

7.2 PATIENTS' DISPOSITION ANALYSIS

The analysis of patients' disposition will be performed on the Safety/Efficacy **population**. Disposition of subjects will be summarized overall. The number of subjects who discontinue from the study or from study treatment will be summarized along with the reason for discontinuation.

7.3 DEMOGRAPHIC AND BASELINE VARIABLES

Demographic and baseline data analyses will be performed on the Safety/Efficacy **population**. The following items and variables will be analysed and summarized in accordance with section 6.5

7.3.1 Demographic data

- Demographic data includes: Age (years), gender, and race

7.3.2 Anthropometrics, ECOG and vital signs

- Weight (kg), height (cm), temperature (°C), blood pressure systolic (mmHg) and diastolic (mmHg), respiratory rate (breath spm) and pulse rate (beats pm)
- Smoking history
- Physical Examination
- ECOG performance status
- Comorbidities.

As appendix, a listing with the information of the abnormal findings details during the physical examination will be included. Also, a listing of comorbidities by patient will be generated

7.3.3 Cancer history

The following parameters will be analyzed generating summary tables

- Type of cancer.
- Current TNM
- Time from histological diagnosis to informed consent date.
- Current disease stage

As appendix, a listing by patient of the complete cancer history information will be generated.

This listing will include patient-id, type of cancer, time from diagnosis, TNM, and Stage.

7.3.4 **HIV-1 Infection history**

The following parameters will be analyzed generating summary tables

- Time from primary diagnosis of HIV.1 to the inclusion in the study.
- Risk group
- Previous and current ART treatments.
- Nadir CD4-T cell count
- Viral load zenith.

As appendix, a listing by patient of the complete HIV-1 infection history information will be generated.

This listing will include patient-id, detail of the last viral load determination before starting the ART, detail of the previous and current ART treatments, detail of the first undetectable viral load determination after ART start.

7.3.5 **Previous treatment- Chemotherapy/Immunotherapy/Oral targeted therapy**

The number and percentage of patients with, any previous treatment will be analysed. Also a summary table of the type of previous treatments will be generated

As appendix, a listing with all previous treatment by patient will be included. This listing will contain the following variables: patient id, Type of Therapy, schema, start and stop date, best response, number of cycles.

7.3.6 **Previous Radiotherapy**

The number and percentage of patients with Previous Radiotherapy Treatment will be summarized.

As appendix, a listing with information regarding prior Radiotherapy treatment will be included, it will contain the following variables: patient id, start and stop date, Total Dose (Gy) intention, Type of radiotherapy, Irradiated area

7.3.7 **Laboratory tests and other analytics**

Baseline values of haematology, coagulation, biochemistry, Urinalysis tests, Thyroid function, Pregnancy test and ECG will be summarized.

Also, a listing by patient of Laboratory tests and other analytics will be generated and included as part of the appendix

7.3.8 **Current Signs and Symptoms**

The number and percentage of patients with, at least one sign or symptom (prior to onset study treatment) will be tabulated.

As appendix, a listing with the information related to Signs and Symptoms reported will be included. This listing will contain the following variables: patient id, Sign/Symptom description and its NCI CTCAE v4.03 code, toxicity grade, start and stop date and ongoing indicator.

7.4 EFFICACY ANALYSES

Efficacy analysis will be performed on the **Efficacy/Safety population**

7.4.1 **Feasibility**

Feasibility is defined based on the rate of patients that will complete at least 4 treatment cycles. One cycle is four weeks with infusions every four weeks. It is assumed that at least 50% of patients must be complete 4 cycles for considering feasible the treatment with durvalumab.

A summary table with the number and percentage of patients who complete at least 4 treatment cycles will be generated.

7.4.2 **Overall Response Rate**

Best Global Response will be summarized by dose cohort using a contingency table that will include the 95% confidence interval of the percentage. In addition Overall Response Rate will be analysed from the total of patients that have a tumor response evaluation, percentage and 95% confidence interval of the percentage will be reported

7.4.3 **Progression Free Survival**

Progression free survival is defined as the time between informed consent date and the date of first progressive disease or death, whatever happen first and irrespective of the cause of death. Patients who did not progress or are still alive at the time of analysis will be censored at the date of the last tumor assessment or last contact known to be alive.

A Kaplan Meier model will be applied to estimate the PFS distribution function. Median and the 95% confidence limits will be estimated using Kaplan-Meier survival methodology.

Plots of the Kaplan-Meier estimates will also be produced

7.4.4 **Overall Survival**

Overall survival (OS) is defined as the time between informed consent date and the date of death, irrespective of the cause of death. Patients still alive at the time of analysis will be censored at the date they were last known to be alive.

A Kaplan Meier model will be applied to estimate the OS distribution function. Median and the 95% confidence limits will be estimated using Kaplan-Meier survival methodology.

Plots of the Kaplan-Meier estimates will also be produced

7.4.5 **Exploratory efficacy analysis**

An exploratory endpoint efficacy in terms of anti viral activity of the drug will be performed. It will be recorded as measurements in the viral reservoir, viral replication and changes in the function and phenotype of circulating lymphocytes. These analyses will be performed in a separated report. Also, exploratory analysis about possible predictive factors of antitumoral response will be performed on tumor tissue and tumor blood samples (cfDNA). For this exploratory analysis a patient will be classified as having Clinical Benefit or no, following the definition in section 6.3 of this document.

A patient without a response evaluation will be classified as NA. Analysis will be performed on the the subpopulation of patients with at least one tumor assessment and response evaluated.

Analysis of immunohistochemistry

Immunohistochemistry results of PD-L1 (defined as positive or negative) in the pretreatment sample with their relation to response and survival.

Relation of response to Immunohistochemistry results will be analyzed as categorical parameters. Chi-square test or Fisher test, as applicable will be used.

A Cox proportional hazards regression model will be used to analyze the effect of the inmuno histochemistry results in the Overall Survival probability distribution function.

Analysis of gene expression

Analysis of gene expression, will be analysed , in relation to tumor response and survival.

Gene expression will be analyzed as a continuous parameter. Parametric t-test or the non-parametric Wilcoxon test will be used to analyze the potential association between gene expression and response.

Finding a cutting point of the gene expression value will be done, as applicable, in order to better identify the potential association between response and gene expression value. In this case Chi-square or Fisher exact test , as applicable, will be used.

A Cox proportional hazards regression model will be used, if applicable, to analyze the effect of the gene expression value on the Overall Survival distribution function. Also, for the PFS distribution function.

If a cutting point was found for the gene expression value, a Kaplan Meier model and the Log-rank test will be used to identify the potential effect of the gene expression value on the Overall survival distribution function, and on the PFS distribution function. It will allow to compare between groups where the gene expression is above or below the cutting point.

Raw reporter counts were preprocessed using the nSolver Analysis Software version 4.0 (NanoString Technologies Inc., Seattle, WA, USA). An initial quality control step was performed for each sample, and counts were then normalized for technical assay variation, using the geometric mean of the positive control targets. Lane-specific gene counts were then multiplied by the obtained normalization factor. Data were normalized for sample input variability using the geometric mean of the most stable set of housekeeping genes and lane-specific normalization factors were calculated. A second quality control step was implemented, where samples with a positive-normalization or content-normalization factor outside of the predefined minimum and maximum threshold (0.3-3.0 and 0.1-10.0, respectively), were excluded from analysis. Data analysis was performed on \log_2 -transformed data with the nCounter Advanced Analysis Software version 2.0 (NanoString Technologies Inc., Seattle, WA, USA) and R and R-studio version 3.5.3. Fold change in expression of each gene between the two groups was calculated based on the average gene expression of each group. Appropriate statistical testing was performed within the software to determine differentially expressed genes (DEGs) between groups, and nominal p-values and false discovery rate (FDR) adjusted p-values, have been reported. Fold changes and p-values were depicted in volcano plots for visualization, where a fold change of 2 and nominal p-value of <0.05 was used to define DEGs. For the pathway signatures average expression of all genes in one pathway were used to calculate a pathway score. Differences in pathway signature scores were then determined using a Mann-Whitney U test.

7.4.6 **Other exploratory analysis**

Any other complementary analyses needed to satisfy the objectives of the clinical trial or to obtain information interesting from a clinical point will be added to the statistical report

7.5 SAFETY ANALYSES

Safety evaluations will be based on the incidence, intensity and type of AEs, and clinically significant changes in the patient's vital signs and clinical laboratory results. Exposure to study drug and reasons for discontinuation of study treatment will be tabulated. Laboratory toxicity grades will be calculated for the appropriate laboratory parameters according to NCI CTCAE v4.0.3, and the baseline and worst post-baseline values observed for each patient will be summarized.

Safety analysis will be performed on the **safety population**.

The following items and variables will be analysed and summarized in accordance with section 6.5.

7.5.1 **Study treatment administration**

Exposure to Durvalunab treatment (definition in section 6.3) and Total cumulative dose administered (definition in section 6.3) will be calculated and summarized.

Number of cycles administered per patient of the study treatment will be summarized, also the number and percentage of patients with each number of cycles received will be shown.

Number and percentage of patients with delays, reductions, interruptions and withdrawals will be tabulated. The total number of cycles affected, and reasons given by each of these actions will be analyzed.

A listing with all information about study treatment administration will be included in the appendix. This listing will contain the following variables: patient id, total number of cycles, duration of treatment, type of modification if exist, and reason of the modification.

7.5.2 **Adverse Events (TEAEs)**

In the adverse event analysis, The term AE will refer to TEAEs as defined previously. The analysis will produce the following results

Summary of Adverse events

The following summary of safety will be described for the safety population during the on-treatment period:

- Number (%) of patients who have presented at least one TEAE.
- Number (%) of patients who have presented at least one grade 3/4 TEAE.
- Number (%) of patients who have study discontinuation due to TEAEs.
- Number (%) of patients who have study discontinuation due to TEAEs.

- Number (%) of patients who have presented at least one TEAE that the investigator considers treatment-related.
- Number (%) of patients who have presented at least one grade 3/4 TEAE that the investigator considers treatment-related.
- Number (%) of patients who have presented at least one grade 3/4 TEAE that the investigator considers treatment-related
- Number (%) of patients who have left the clinical study for a TEAE that the investigator considers treatment-related.
- Number (%) of patients who have presented at least one AE with outcome death (*).
- Number (%) of patients who have presented at least one TEAE that the investigator considers treatment-related, with outcome death (*).
- Number (%) of patients who have presented at least one SAE.
- Number (%) of patients who have presented at least one SAE that the investigator considers treatment-related.

(*) A brief patient narrative will be included for all TEAEs G=5 and/or outcome "death", related or not with the study treatments.

As presented in the study protocol the relationship of an AE with the study drug must be classified as one of the following

- Unrelated: The AE is clearly not related to the study medication
- Unlikely Related: The AE is not likely to be related to the study medication
- Possibly Related: The AE may be related to the study medication
- Probably Related: The AE is most likely related to the study medication
- Definitely Related: The AE is clearly related to the study medication

An adverse event that has a causal relation with the study drug "Possible", "Probable" or "Definitive" should be considered a related Adverse Event.

Reporting of adverse events Tables of maximum toxicity by patient

Summary tables of maximum reported intensity by patient and preferred term will be generated for each treatment arm, grouped by System Organ Class (SOC), and Preferred term (PT)

Incidence of adverse events will be tabulated by System Organ Class (SOC) and Preferred Term (PT), sorted by decreasing total incidence of SOC and PT within SOC.

When calculating the incidence of adverse events, or any sub-classification, there of causality, severity, etc, each Adverse Event will only be counted once (corresponding to the maximum

toxicity grade by patient and AE) and any repetitions of adverse events will be ignored; the denominator will be the corresponding total population size. Incidence of severe AE related with the study drug will be tabulated.

The following tables of maximum reported intensity by patient and preferred term will be generated.

All TEAEs

TEAEs grade 3,4,5

..Related TEAEs

Serious TEAEs

.. Related Serious TEAEs

..Adverse Events of special interest

As appendix, a listing with all adverse events will be included. This listing will contain the following variables: patient id, SOC term, PT term, grade, seriousness indicator, onset date, end date, ongoing indicator, relationship with study drug, action taken and outcome.

7.5.3 Anthropometrics and Vital signs

Weight (kg), will be summarized by visit, following the specifications in section 6.5

Vital signs variables include temperature (°C), blood pressure systolic (mmHg) and diastolic (mmHg), They will be summarized by time point, following the specifications in section 6.5.

7.5.4 Laboratory test

Laboratory assessments include hematology, coagulation, serum chemistry, urinalysis, Thyroid function tests, plasma viral load and pregnancy test (if applicable). For each time point laboratory tests results will be summarized as continuous variables, following the specifications in section 6.5.

Also safety in terms of HIV infection will be assessed. It will be recorded as total number of CD4⁺ T cells, CD8⁺ T cells and plasma viral load along the treatment

7.5.5 ECOG PS

ECOG PS will be measured at different time points during the study, from the screening visit, baseline during the treatment and follow up periods.

ECOG PS measurements will be summarized as a categorical variable by time point, following the specifications in section 6.5

7.5.6 Electrocardiogram

ECGs are required during screening, prior to starting study treatment on Cycle 1 Day 1, at 16 weeks after starting study treatment, as well as at any other time point when clinically indicated.

Results will be summarized as a categorical variable by time point, following the specifications in section 6.5

7.5.7 **Physical examination**

Physical examination is performed during screening, prior to first dose of study treatment and on Day 1 of each cycle

Results will be summarized by time point, following the specifications in section 6.5

7.5.8 **Exitus**

The number and percentage of patients who die during the study will be tabulated.

Afterwards, cause of death will be also be tabulated.

A detailed listing of deaths ordered by patient will be generated.

7.5.9 **Other Analysis**

Any complementary analyses needed to satisfy the objectives of the clinical study or to obtain information of interest from a clinical point of view will be made.

Any deviation from the original statistical plan will be justified and detailed in the final study report