Investigational Drug Substance(s)	Durvalumab (MEDI4736)
Study Number	ESR-15-11576
Version Number	5
Date	05/23/16

Pilot Study to Evaluate the Anti-tumor Effect of Durvalumab (MEDI4736) in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN), Human Papilloma Virus (HPV) Positive versus Negative, when Treated Before Surgery

CLINICALTRIALS.GOV: NCT02827838

PROTOCOL SYNOPSIS

Clinical Protocol CCCWFU 60116

Study Title: Pilot Study to Evaluate the Anti-tumor Effect of Durvalumab (MEDI4736) in Patients with Squamous Cell Carcinoma of the Head and Neck (SCCHN), Human Papilloma Virus (HPV) Positive versus Negative, when Treated Before Surgery
Protocol Number:
Clinical Phase: Pilot Study
Study Duration: 18 mo
Investigational Product 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 We hypothesize that immunotherapy with PD-L1 antibody will lead to more intense and efficient specific immune activation against the SCCHN tumor in HPV + patients compared with HPV - patients. We also hypothesize that an extensive analysis of the blood and saliva might lead to identification of markers predictive of a more efficient response to PD-L1 inhibition. Lastly, we hypothesize that a corresponding increase in the immune response with an increase in the number of infiltrative activated immune cells could be associated with an increase in metabolic activity measured by PET SUV. Similarly, an effective anti-tumor activity of the activated immune response could lead to decreased metabolic activity. We are interested in evaluating the dynamic in the metabolic activity early in the treatment and to attempt to detect potential consistency that could be used in future therapeutic paradigms.
Objectives:

Primary Objectives:

The primary objective of this study is to investigate the effect of Durvalumab on local and systemic immune activation by HPV status in patients with oral cavity and oropharynx SCCHN. This will be done by:

a) Examining the effects of Durvalumab on systemic immune response to HPV and tumor associated antigens
b) Examining the effects of Durvalumab on immune regulatory mechanisms.
c) Exploring the association between levels of immune-regulatory miR in plasma and saliva and immune response.

Results will be compared between HPV positive and negative patients to identify a possible differential effect of treatment with Durvalumab. Level of local immune response in the primary tumor and in the regional lymph nodes will be compared whenever possible.

Secondary Objectives:

Investigate the effect of the treatment with Durvalumab on the CT scan and PET scan response.

Evaluate the safety of a short induction treatment with Durvalumab.

Study Design:

This is a non-randomized, open label, uncontrolled, single group assignment study, to evaluate the anti-tumor effect of Durvalumab in patients with SCCHN when given in a short treatment course before surgery.

10 HPV positive and 10 HPV negative patients will be enrolled, who have an interval longer then 3 weeks between the time of diagnosis and time of surgery.

Two administrations of Durvalumab will be given with an interval of 3 to 17 days between the last administration of drug and surgery. Patients will then undergo surgery as scheduled. After surgery the patients may proceed with adjuvant treatment as indicated by the stage of their disease and by the surgical pathology findings. A Radiation Oncologist is included in the study team in order to address and to include in the therapeutic algorithm the impact of the potential cytoreduction by Durvalumab therapy on the final surgical and pathologic staging.

The primary goal of this pilot study is to make use of biopsy tissue obtained before treatment and of the surgical tissue specimen obtained after treatment with durvalumab, in order to assess tissue biomarkers. Saliva and blood will be collected before each treatment, one week after the treatment and before surgery, and will be analyzed in the same time with tumor tissue.

CT scan or MRI and whenever possible PET scan will be performed before treatment with Durvalumab and before surgery.

The clinical trial will be considered completed as soon as the last patient has completed his last follow up visit, at 1 month after surgical treatment.

Number of Centers: 1

Number of Subjects:

20 patients, 10 patients with HPV positive and 10 patients with HPV negative.

Study Population:

HNSCC of the oral cavity or oropharynx

Inclusion Criteria:

- Histologically or cytologically confirmed SCCHN of the oral cavity (OC; more than 90% patients have HPV negative cancer) or oropharynx (about 60-70% of patient have HPV positive cancer).
- Presence of radiologically or clinically documented disease. All radiology studies must be performed within 28 days prior to registration.
- Any stage, considered candidates for surgery and scheduled for surgery either by robotic or by standard surgical technique.
- Documentation of HPV tested by PCR.
- Willing to provide consent for an additional tissue biopsy for research purposes, to allow a part of their surgical tumor tissue to be utilized for research, and to donate samples of blood and saliva collected before and after treatment.
- All patients must have provided informed consent for correlative studies.
- ECOG performance status of 0 or 1.
- Previous surgery is permitted provided that a minimum of 28 days (4 weeks) have elapsed between any major surgery and date of registration, and that wound healing has occurred.
- Organ and marrow function as defined below:
    - Absolute neutrophil count (ANC) $\geq 1.5 \times 10^9$/L;
    - Platelet count $\geq 100 \times 10^9$/L;

- Hemoglobin ≥ 9.0 g/dL;
- Serum bilirubin ≤ 1.5 x ULN (institutional upper limit of normal). Total Bilirubin is less than or equal to ULN, except the case in which the elevated total bilirubin is not a sign of liver disease, such as the Gilbert Syndrome, in which case a Total Bilirubin less than or equal to 2X ULN is acceptable;
- AST and ALT ≤ 2.5 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:

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

- 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.
- In accordance with NCIC CTG policy, protocol treatment is to begin within 2 working days of patient registration
- Written informed consent and any locally-required authorization (e.g., HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
- Age ≥ 18 years at time of study entry.
- 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.

Exclusion Criteria:

- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). Previous enrolment in the present study.

- Participation in another clinical study with an investigational product during the last 3 mo
- Any previous treatment with a PD1 or PD-L1 inhibitor, including Durvalumab
- Any anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) within the last 3 months before the first dose of Durvalumab.
- Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction
- 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
- 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).
- Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1
- 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.
- Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
- History of primary immunodeficiency
- History of allogeneic organ transplant
- History of hypersensitivity to durvalumab or any excipient
- History of pneumonitis or interstitial lung disease
- Subjects with uncontrolled seizures
- 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, hepatitis C or human immunodeficiency

virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent

- Known history of active tuberculosis
- Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving durvalumab
- 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
- Patients with body weight < 30kg
- Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results

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

Durvalumab, 750 mg Q2W (equivalent of 10 mg/kg Q2W) IV infusion x 2 administrations. In exceptional cases in which the window time to surgery is longer than 4 weeks, a third dose of Durvalumab of 750 mg IV infusion is allowed.

Study Assessments and Criteria for Evaluation:

Immune Response Assessments:

a) Peripheral blood mononuclear cell interferon-γ production *in vitro* (ELISA) in response to commercially available peptide pools corresponding to HPV, p53, Mage-A3, Her2/neu, and survivin will be determined. Responses of patients whose tumor are HPV+ will be compared to those that are HPV−.

b) PD-1+CD4+, PD 1+CD8+, PD-1L+, and Foxp3+CD4+ tumor-infiltrating cells will be quantified (0 to 3+) using standing immunofluorescence techniques.

c) The following immune effector and regulatory responses will be assessed in blood using standard flow cytometric techniques: CD4+, CD8+, CD4+FoxP3+ Treg, and CD45RO+CD4+ memory T cells; CD3−CD56+ NK cells, and CD14−HLA-DR−CD15+ MDSC. The results of patients whose tumor are HPV+ will be compared to those that are HPV−.

d) The relationship between levels of the miRs and the immune response to HPV, immune response to tumor associated antigens, and immune regulatory molecules/cells will be assessed.

Safety Assessments:

a) Clinical toxicity per NCI Common Terminology Criteria for Adverse Events version 4.0 and

b) Any delays in planned surgery.

Efficacy Assessments:

Response to Durvalumab using CT scan and PET scan

Statistical Methods and Data Anlaysis:

For this pilot study our goal is to get preliminary descriptive data for a series of measures taken using blood, saliva and tumor tissue pre- and post- immunotherapy. With a sample size of 10 patients in each group (i.e. 10 with HPV+ and 10 HPV-) we will be able to estimate a 95% confidence interval for each group with confidence limits +/- 0.72 standard deviations. We can also examine the change in each measure (pre- versus post- therapy) to see whether any confidence intervals show a significant change from baseline (i.e., the measure increased (or decreased) by more than 0.72 standard deviations). This data would provide useful preliminary information concerning the potential mean value and variability for each measure of interest. It may also provide information about which possible measures are most impacted by the intervention within each group (HPV+/HPV-). Furthermore, if we were to compare groups, we would have 80% power to detect a difference in measures equal to 1.3 standard deviations of the measure of interest using a 2-sample t-test with alpha=0.05.

SCHEDULE OF STUDY ASSESSMENTS

Schedule of study assessments: Screening and Treatment Period

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Pre-screening for PD-L1 status ONLY**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**					
			Baseline First drug administration	**Follow up**	**Second Drug Administration**	**Follow up**	**Before Surgery** (3-17 days from last drug adm.)	**Surgery**
Day	**-42 to -1**	**-28 to -1**	**Day 1 of the week (±3 days)**					
Week	**-6 to -1**	**-4 to -1**	**1**	**2**	**3**	**4**		
Written informed consent/assignment of subject identification number	X							
Preliminary eligibility fulfilment (investigator's opinion)	X							
Demography and history of tobacco and alcohol use		X						
Previous treatments for SCCHN		X						
HPV by PCR in FFPE	X[a]							
Obtain archived or fresh tumour biopsy for PD-L1 assay, if applicable	X							
Formal verification of eligibility criteria		X						
Medical and surgical history		X						
Hepatitis A antibody Hepatitis B surface Ag, Hepatitis C antibody and HIV		X						
Urine hCG or serum βhCG[b]		X	As clinically indicated					
Durvalumab administration (monotherapy)			X		X			
Physical examination[c]		X	X	X	X	X	X	

Schedule of study assessments: Screening and Treatment Period

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Pre-screening for PD-L1 status ONLY**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**					
			Baseline First drug administration	**Follow up**	**Second Drug Administration**	**Follow up**	**Before Surgery** (3-17 days from last drug adm.)	**Surgery**
Day	**-42 to -1**	**-28 to -1**	**Day 1 of the week (±3 days)**					
Week	**-6 to -1**	**-4 to -1**	**1**	**2**	**3**	**4**		
Vital signs (pre- during and post-infusion vital signs assessments)[d]		X	X	X	X	X	X	
Weight		X	X	X	X	X	X	
Electrocardiogram[e]		X	X				X	
Adverse event/serious adverse event assessment	X[l]	X	X	All visits				
Concomitant medications		X	X	All visits				
ECOG performance status		X	X	X	X	X	X	
Liver enzyme panel[f]		X	X	X	X	X	X	
Serum Chemistry		X	X	X	X	X	X	
Magnesium[f]		X	X	As clinically indicated				
Uric Acid[f]		X	X	As clinically indicated				
LDH		X	X	X	X	X	X	
Amilase, Lipase		X	X	X	X	X	X	
Thyroid function tests (TSH and fT3 and fT4)[g]		X	X	X	X	X	X	
Hematology[f]		X	X					

Schedule of study assessments: Screening and Treatment Period

Assessments to be performed at the times stipulated in the table and as clinically required in the management of the subject.	**Pre-screening for PD-L1 status ONLY**	**Screening**	**All assessments to be performed pre-infusion unless stated otherwise**					
			Baseline First drug administration	**Follow up**	**Second Drug Administration**	**Follow up**	**Before Surgery** (3-17 days from last drug adm.)	**Surgery**
Day	**-42 to -1**	**-28 to -1**	**Day 1 of the week (±3 days)**					
Week	**-6 to -1**	**-4 to -1**	**1**	**2**	**3**	**4**		
Urinalysis[h]		X	As clinically indicted					
Coagulation parameters[i]		X	As clinically indicted					
Tumor assessment (CT or MRI)[j]		X					X	
Tumor Assessment PET scan[k]		X					X	
Immune response assessment (blood)			X	X	X	X	X	
Blood collection for miRNA			X	X	X	X	X	
Saliva collection for miRNA			X	X	X	X	X	
Whole blood collection for flow cytometry			X				X	
Collect fresh tumor tissue by biopsy and store in Tumor Tissue Bank		X						
Collect fresh tumor tissue from surgical specimen and store in Tumor Tissue Bank								X
sPD-L1 concentration (to assess target engagement), if applicable (if additional funding secured)			X		X		X	

[a] Should be obtained from the initial diagnostic biopsy. In exceptional cases when not enough tissue is available, it can be performed on tissue obtained with research biopsy or on the surgical specimen. This option is not available when one of the study arms completed accrual. HPV status must be known before at time of screening.
[b] Pre-menopausal female subjects of childbearing potential only

[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 and at Day1 –baseline. Thereafter as clinically indicated. Baseline and abnormal ECG at any time in triplicate others single. 1 ECG is needed while on treatment, and as clinically indicated. 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. Creatinine clearance, gamma glutamyltransferase, magnesium, and uric acid testing are to be performed at screening, on Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1), and if 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, 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 but not more than 14 days prior to first treatment.

[k]PET scan will be performed in all cases if reimbursed by Medical Insurance or funded. It will be performed as close to the initiation of treatment but not more than 28 days prior to treatment.

[l] For AEs/SAEs reported during prescreening additional information such as medical history and concomitant medications may be needed. AEs/SAEs will continue to be collected by PI (from medical records or by phone) up to 90 days from the last administration of Durvalumab. Follow up visit will be scheduled whenever possible.

TABLE OF CONTENTS PAGE

LIST OF FIGURES

LIST OF APPENDICES

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
Cmax	peak concentration
Cmax,ss	peak concentration at steady state
Cmin	trough concentration
Cmin,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
DCR	disease control rate
DLT	dose-limiting toxicity
DNA	deoxyribonucleic acid
DoR	duration of response

Abbreviation or special term	Explanation
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
IL	interleukin
irAE	immune-related adverse event
IRB	Institutional Review Board
IV	intravenous(ly)
MAb	monoclonal antibody
MDSC	Myeloid derived suppressor cells

Abbreviation or special term	Explanation
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
PBMC	peripheral blood mononuclear cell
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)
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

Abbreviation or special term	Explanation
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
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SUSAR	suspected unexpected serious adverse reaction
t½	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
USA	United States of America
WFI	water for injection
WHO	World Health Organization

1. INTRODUCTION

1.1 Disease Background

Oropharynx cancer (OPC), a subset of squamous cell carcinoma of the head and neck (SCCHN), is often associated with human papillomavirus (HPV) infection. It has been proposed that the favorable prognosis observed in HPV+ vs. HPV− OPC may be due to immune responses directed against viral antigens. Tumor-infiltrating CD4+ and CD8+ T cells in OPC are associated with a favorable prognosis. HPV-specific T cells can also be grown from tumor biopsies, suggesting that at least some of the infiltrating T cells are HPV-specific. Immune responses to several tumor-associated determinants have also been implicated in HPV+ and HPV− HNSCC, including p53, Mage-A3, Her2/neu, and survivin.

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 (Mu et al, 2011), renal (Thompson et al, 2005; Thompson et al, 2006; Krambeck et al, 2007), pancreatic (Nomi et al, 2007; Loos et al, 2008; Wang et al, 2010), ovarian cancer (Hamanishi et al, 2007), and hematologic malignancies (Andorsky et al, 2011; Brusa et al, 2013) 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 (Keir et al, 2008; Park et al, 2010). 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 (Zou and Chen, 2008).

1.2 Durvalumab Background

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 (IgG1κ) 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 (Fcγ) receptors involved in triggering effector function.

1.2.1 Summary of non-clinical experience

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 (t1/2) 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.

Finally, 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.

1.2.2 Summary of clinical experience

As of the DCO dates (15Apr2015 to 18Sept2015, Durvalumab IB Version 9.0), a total of 1910 subjects have been enrolled and treated in 30 ongoing Durvalumab clinical studies, including 20 sponsored and 10 collaborative studies. Of the 1,910 subjects, 1,279 received Durvalumab monotherapy, 454 received Durvalumab in combination with Tremelimumab or other anticancer agents, 14 received other agents (1 Gefitinib, 13 MEDI6383), and 163 have been treated with blinded investigational product. No studies have been completed or terminated prematurely due to toxicity.

Pharmacokinetics and Product Metabolism

Study CD-ON-durvalumab-1108: As of 09 Feb2015, 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 µg/mL throughout the dosing interval.

As of 09 Feb2015, 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 07 May2015, 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 ≥ 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 ≥ Grade 3 events occurring in 65 subjects (9.4%). Treatment-related ≥ Grade 3 events reported in 3 or more subjects (≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 ≥ 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 (5^{th}, median and 95^{th} percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~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 [3]. 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 750 mg Q2W Durvalumab (equivalent to 10 mg/kg Q2W), 1500 mg Q4W Durvalumab (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.

1.3 Research hypothesis

Based on preliminary data showing that the presence of HPV antigens is contributing to increased anti-tumor T cell activity in patients with SCCHN, we hypothesize that immunotherapy with PD-L1 antibody will lead to more intense and efficient specific immune activation against the SCCHN tumor in HPV + patients compared with HPV - patients. We also hypothesize that an extensive analysis of the blood and saliva might lead to identification of markers predictive of a more efficient response to PD-L1 inhibition. Lastly we would like to test the ability of PET scan to detect an increased immune response. One can hypothesize that a corresponding increase in the immune response with an increase in the number of infiltrative activated immune cells could be associated with an increase in metabolic activity measured by PET SUV. Similarly, an effective anti-tumor activity of the

activated immune response could lead to decreased metabolic activity. We are interested in evaluating the dynamic in the metabolic activity early in the treatment and to attempt to detect potential consistency that could be used in future therapeutic paradigms.

1.4 Rationale for conducting this study

While the beneficial effect of activating an anti-cancer immune response is well-recognized, one emerging mechanism for negative regulation of immune responses in cancer is the Programmed Death-1 (PD-1) receptor, expression of which on T cells is associated with the impaired cell-mediated immunity. Blockade of PD-1 or its ligand, PD-L1, has demonstrated promise in several cancers including SCCHN. However, detailed mechanistic evaluations in patient tissue are missing. Moreover, the critical question regarding differences in efficacy of releasing the immune inhibition by cancer in HPV positive vs HPV negative patients has not been addressed.

Methods to predict and monitor cancer immunotherapy response are needed. Many of the laboratory assessments currently applied are cumbersome. MicroRNAs (miRs), small non-coding RNAs that regulate multiple processes at the post-transcriptional level, are emerging as important biomarkers. Because of incorporation in microparticles and exosomes, miRs are stable and can be measured in several body fluids, including plasma/serum and saliva. The ability of miR expression profiling to classify tumors has been well-described, and miR profiles that may identify HPV+ HNSCC have been reported. miR profiling of plasma and saliva may be useful diagnosing HNSCC. Changes in specific miRs in plasma and saliva have also been observed after therapy. Recent studies have demonstrated roles for a number of miRs in immune development and function. Specific miRs have been shown to regulate T-cell responses, the development and activation of myeloid cells, and dendritic cell function. Changes in specific immune-regulatory miRs have been associated with changes circulating immune effector and regulatory cells in patients with melanoma.

The scientific rationale of the proposed clinical study is to identify parameters of clinical and tissue response to cancer immunotherapy with the PDL-1 inhibitor Durvalumab and to compare the degree of response in HPV + vs HPV - patients. This pilot study will provide preliminary data to address important questions in designing future therapeutic strategies in patients with SCCHN such as: 1) potential role of immunotherapy in early treatment of patients with SCCHN; 2) differential role of immunotherapy in HPV + vs HPV - patients; 3) identification of possible predictors of response to immunotherapy and particular to PDL-1 inhibitors in blood and saliva in HPV + and - patients.

In order to answer these significant questions, we would like to take advantage of the window of opportunity time between the diagnosis by biopsy and primary surgical treatment in operable patients with SCCHN and to treat them with the immunotherapy drug Durvalumab. The tissue biopsy obtained at the time of diagnosis, before treatment, and the surgical pathology tissue collected after treatment with Durvalumab, as well as blood and saliva samples collected before and after treatment will be analyzed to answer critical mechanistic questions and to compare level of response in HPV+ vs HPV - patients.

1.5 Benefit/risk and ethical assessment

1.5.1 Potential risks

The important potential risks, based on the mechanism of action of Durvalumab and reported toxicities include immune-mediated reactions such as enterocolitis, dermatitis, hepatitis/hepatotoxicity, endocrinopathy, pneumonitis, nephritis, pancreatitis (elevated amylase/lipase), and neuropathy or neurologic events. Additional important potential risks include infusion-related reactions, hypersensitivity, and anaphylaxis or serious allergic reactions. Other potential/theoretical risks include serious infections and immune complex disease. The most common treatment-related toxicities included fatigue, nausea, and diarrhea with <1% of cases of colitis or pneumonitis.

Adverse events resulted in the discontinuation of treatment in 10.8% of patients, were serious in 30.6%, and were Grade ≥3 in 34.3% of patients treated with Durvalumab monotherapy.

Recent data are available for patients with SCCHN in the expansion cohort of a PhaseI/II ongoing study (Segal et al 2015).Drug-related AEs were observed in 60% of pts; the most frequent were fatigue (11%), diarrhea, (8%), and nausea (7%). Grade ≥ 3 related AEs were reported in 7% of pts: rash (2 pts), and increased GGT, fatigue, and tumor inflammation (1 pt each). No drug-related AEs led to discontinuation or death. No colitis or grade ≥ 3 pneumonitis was observed.

1.5.2 Potential benefits

Patients are being enrolled in 5 ongoing clinical studies of Durvalumab as monotherapy in patients with SCCHN. No studies have yet been completed. An ongoing phase I/II, multicenter, open-label study (NCT01693562) is evaluating the safety and efficacy of Durvalumab in multiple solid tumor types including SCCHN (Segal et al 2015). Sixty-two SCCHN patients were treated with Durvalumab as monotherapy at 10 mg/kg q2w and evaluable for disease assessments as of the data cut-off date of 7 April 2015. Tissue samples were retrospectively tested for PD-L1 expression using an immunohistochemistry (IHC) assay using the Ventana SP263 clone. Of 62 SCCHN patients, an ORR of 11% was observed in the PD-L1-unselected population and in 18% and 8% of patients with PD-L1-positive (n=22) and PD-L1-negative disease (n=37), respectively, with DCR at 24 weeks achieved in 18% and 11% of patients with PD-L1-positive and –negative disease, respectively. DoRs ranged from 41 to 53 weeks in patients with PD-L1 positive disease and 16 to 54 weeks in patients with PD-L1-negative disease, with responses noted in both HPV-positive and -negative patients and in smokers and non-smokers.

1.5.3 Overall benefit/risk and ethical assessment

Durvalumab has demonstrated expected clinical activity and durable response in heavily pretreated patients. Advancing research for use of Durvalumab in earlier treatment stages represents the next step in exploiting this immunotherapeutic agent.

Little is known about effect of Durvalumab on previously untreated tumors, specifically HNSCC.

HPV+ patients, have better prognosis and response to treatment, however they currently undergo the same aggressive and highly toxic regimens as the HPV- patients. There remains a significant unmet medical need for additional, less toxic treatment options for these patients. Preliminary studies show increased presence of immune effector cells in the HPV+ tumor, potentially indicative of increased susceptibility to immunotherapeutic agents such as Durvalumab.

Our study addresses fundamental mechanistic questions about the tumor effect of Durvalumab in previously untreated patients with HNSCC and addresses the potential difference between HPV + and HPV- tumor response. The study designs takes advantage of the window of opportunity for first line drug treatment between the time of diagnosis and time of surgery in patients with SCCHN scheduled for primary surgical resection.

We recognize the importance of safety trial design in this patient population with potential curable disease. The study design aims to minimize potential risks, with intensive, weekly monitoring and safety assessments. The second administration of Durvalumab will be considered prudently with consideration for upcoming surgery. It is recognized, however, that few side-effects are expected with such a short course of treatment.

The overall benefit/risk assessment supports the proposed study design.

2. STUDY OBJECTIVES

2.1 Primary objectives

2.1.1 The primary objective of this study is to investigate the effect of Durvalumab on local and systemic immune activation by HPV status in patients with oral cavity and oropharynx HNSCC. This will be done by:

a) Examining the effects of Durvalumab on systemic immune response to HPV and tumor associated antigens
b) Examining the effects of Durvalumab on immune regulatory mechanisms.
c) Exploring the association between levels of immune-regulatory miR in plasma and saliva and immune response.

Results will be compared between HPV positive and negative patients to identify a possible differential effect of treatment with Durvalumab. Level of local immune response in the primary tumor and in the regional lymph nodes will be compared whenever possible.

2.2 Secondary objective(s)

2.2.1 Investigate the effect of the treatment with Durvalumab on the CT scan and PET scan response.

2.2.2 Evaluate the safety of a short induction treatment with Durvalumab.

3. STUDY DESIGN

3.1 Overview of study design

This is a non-randomized, open label, uncontrolled, single group assignment study, to evaluate the anti-tumor effect of Durvalumab in patients with HNSCC when given as a short treatment course before surgery.

A schematic diagram of the overall study design is shown below.

Patients must be scheduled for surgery and have a window of at least 3 weeks between the time of diagnosis and time of surgery.

In order to be eligible for this clinical study, the patients must have fresh tumor tissue frozen and saved in our Tumor Tissue Bank or need to consent for an additional biopsy procedure to obtain a tumor tissue sample for the clinical protocol that will be saved in our Tumor Tissue Bank for the correlative studies. Patients will undergo an assessment on their tumor tissue sample to determine HPV status.

10 HPV+ and 10 HPV- patients will be initially enrolled and need to complete the study. If any patient does not complete the study treatment and investigations, the patient will be replaced.

First administration of Durvalumab will be given with the first visit after registration with the clinical study. Second administration of Durvalumab will be given 2 weeks later. An interval of 3 to 17 days must be ensured for all patients between the last administration of drug and surgery. A 7-14 days interval will be strongly considered and attempted in each case. In the rare circumstances in which surgery was scheduled or delayed at more than 2 weeks after second administration of Durvalumab, a third administration of drug must be given in order to ensure the proposed interval between the last dose of Durvalumab and surgery.

After surgery the patients may proceed with adjuvant treatment as indicated by the stage of their disease and by the surgical pathology findings. A Radiation Oncologist is included in the study team in order to address and to include in the therapeutic algorithm the impact of the potential cytoreduction by Durvalumab therapy on the final surgical and pathologic staging.

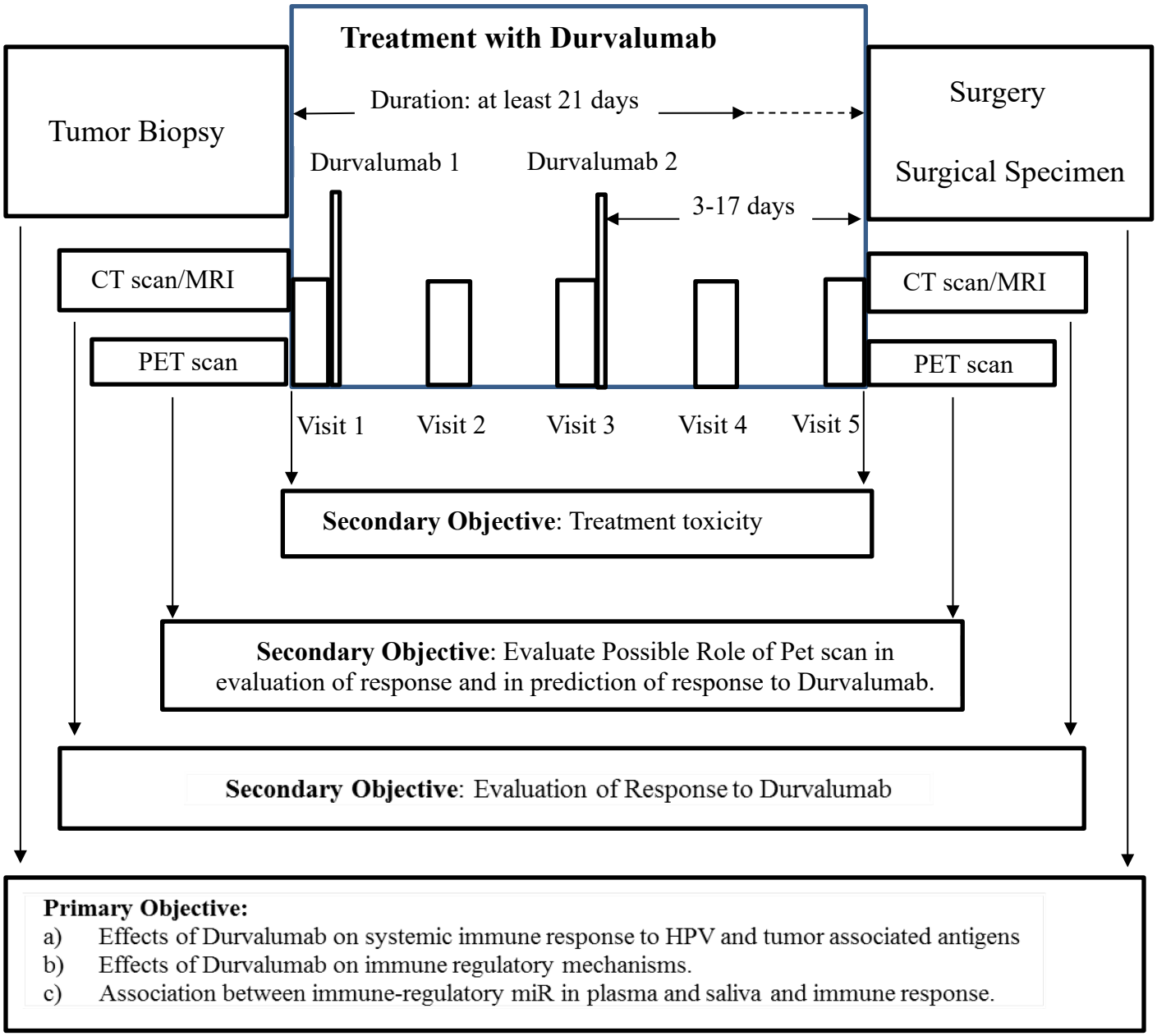
Study ends for each patients with the last visit before surgery. However follow up visits will be scheduled monthly after surgery whenever possible and laboratory tests and clinical data will be collected to assess for any adverse events. Subjects who decline to return to the site for evaluations will be offered follow-up by phone up to 3 months as an alternative and the PI will make every effort to collect toxicity data from medical records.

The primary goal of this pilot study is to make use of biopsy tissue obtained before treatment and of the surgical tissue specimen obtained after treatment with durvalumab, in order to assess tissue biomarkers.

Saliva and blood will be collected before each treatment, one week after the treatment and before surgery, and will be analyzed in the same time with tumor tissue.

CT scan or MRI and whenever possible PET scan will be performed before treatment with Durvalumab and before surgery.

3.2 Study schema



3.3 Study Oversight for Safety Evaluation

Although no interim analysis is planned, each study patient will be very carefully monitored for safety and treatment toxicity. Strict Durvalumab treatment discontinuation rules will apply. The study team will ensure that patients do not develop consistently toxicities of ≥ grade III that exposes them to unnecessary and unjustified risks, including but not limited to the risk to delay or compromise the curative surgical intervention.

Should more than 3 patients develop toxicity ≥ grade III (except infusion reaction) or have delays in surgical treatment due to toxicities related to treatment with Durvalumab, the study will be discontinued.

4. SUBJECT SELECTION

4.1 Inclusion criteria

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

- Histologically or cytologically confirmed HNSCC of the oral cavity (OC; more than 90% patients have HPV negative cancer) or oropharynx (about 60-80% of patient have HPV positive cancer).
- Presence of radiologically or clinically documented disease. All radiology studies must be performed within 28 days prior to registration.
- Any stage, considered candidates for surgery and planned for surgery either by robotic or by standard surgical technique.
- Documentation of HPV tested by PCR (resulted or pending).
- Willing to provide consent for an additional tissue biopsy for research purposes, to allow a part of their surgical tumor tissue to be utilized for research (in case tumor tissue has not already been saved in the Tumor Tissue Bank), and to donate samples of blood and saliva collected weekly through the treatment.
- All patients must have provided informed consent for correlative studies.
- ECOG performance status of 0, 1 or 2.
- Patients must have no prior exposure to immune-mediated therapy, including anti-CTLA-4, anti-PD-1, anti–PD-L1, or anti–programmed cell death ligand 2 antibodies, excluding therapeutic anticancer vaccines.
- At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥15 mm) with CT or MRI or clinical measurement and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.
- Previous surgery is permitted provided that a minimum of 28 days (4 weeks) have elapsed between any major surgery and date of registration, and that wound healing has occurred.

- Organ and marrow function as defined below:
    - Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L;
    - Platelet count ≥ 100 x 10^9/L;
    - Hemoglobin ≥ 9.0 g/dL;
    - Serum bilirubin ≤ 1.5 x ULN (institutional upper limit of normal)
        - Total Bilirubin is less than or equal to ULN, except the case in which the elevated total bilirubin is not a sign of liver disease, such as the Gilbert Syndrome, in which case a Total Bilirubin less than or equal to 2X ULN is acceptable.
    - AST and ALT ≤ 2.5 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:

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

- 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.
- In accordance with NCIC CTG policy, protocol treatment is to begin within 2 working days of patient registration
- Written informed consent and any locally-required authorization (e.g., HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations.
- Age ≥ 18 years at time of study entry.

- 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.

4.2 Exclusion criteria

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

- Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). Previous enrolment in the present study
- Participation in another clinical study with an investigational product during the last 6 mo.
- Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab
- Receipt of any anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) within the last 6 mo. (before the first dose of Durvalumab).
- Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Frediricia's Correction
- 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
- 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)
- Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1
- 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.
- Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)
- History of primary immunodeficiency
- History of allogeneic organ transplant
- History of hypersensitivity to Durvalumab or any excipient

- History of pneumonitis or interstitial lung disease
- Subjects with uncontrolled seizures
- 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, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent
- Known history of previous clinical diagnosis of tuberculosis
- Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving Durvalumab
- 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
- Patients with body weight < 30 kg
- Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results

4.3 Withdrawal of Subjects from Study Treatment and/or Study

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. Alterations in treatment, biological samples collection or other study guided investigations that in the opinion of the investigator or the sponsor affects the integrity of the study data collection and analysis
4. 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
5. Pregnancy or intent to become pregnant
6. Any AE that meets criteria for discontinuation as defined in Section 6.2.1 and Appendix 1.

7. Grade ≥ 3 infusion reaction

8. Subject noncompliance 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

11. Surgical treatment is cancelled for any reasons and a tumor biopsy in lieu of surgical specimen cannot be obtained.

12. Patients who do not complete at least two administrations of Durvalumab and/or do not submit the biological samples required per protocol.

13. Patients who require treatment with steroids for a period longer than 5 days or who receive any steroids within 3 days before surgery.

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 discontinued from the study treatment and/or from the study will be replaced.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety per Section 10.3.1 and Appendix 2, 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. Subjects who decline to return to the site for evaluations will be offered follow-up by phone up to 3 months as an alternative.

Withdrawal of consent

Patients are free to withdraw from the study at any time without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further study drug or further study observation. Patient will be asked for permission to use surgical specimen if deemed useful by the investigator.

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

The patient will be replaced in the study.

5. INVESTIGATIONAL PRODUCT

5.1 Durvalumab

The Investigational Products Supply section of AstraZeneca/MedImmune will supply durvalumab to the investigator 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.

5.1.2 Durvalumab Doses and treatment regimens

Durvalumab every 2 weeks x 2 administrations. A third dose will be allowed in the exceptional cases in which the window time to surgery is longer than 4 weeks. Surgery will follow 3-17 days after the last administration of Durvalumab.

5.1.3 Study drug preparation

For patients weighing ≥ 30 kg, a fixed dose of 750 mg Q2W durvalumab (equivalent to 10 mg/kg Q2W), should be prepared.

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 750mg durvalumab for patients >30 kg will be administered using an IV bag containing 0.9% (w/v) saline or dextrose with a final durvalumab concentration ranging from 1 to 20 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

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 or 30.0 mL for 1500 mg of durvalumab) 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.

Dosing day weight can be used for dosing calculations instead of baseline weight per institutional standard.

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-µm 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 ≤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 ≤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 4 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

Drug accountability logs will be maintained for the investigative agent used under this protocol. These logs shall record quantities of study drug received and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the medication.

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

All patients entered on any CCCWFU trial, whether treatment, companion, or cancer control trial, **must** be registered with the CCCWFU Protocol Registrar or entered into WISER Screening Log within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix 3)
2. Complete the Protocol Registration Form (Appendix 4)
3. Complete the Race and Ethnicity Verification Form (Appendix 5)
4. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

5.

Contact Information:

Protocol Registrar PHONE (336) 713-6767

Protocol Registrar FAX (336) 713-6772

Protocol Registrar E-MAIL (registra@wakehealth.edu)

*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

6. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

6.2 Dosage and Administration

Patients will receive Durvalumab 750 mg (equivalent of 10 mg/kg) every 2 weeks, two administrations. In exceptional cases of a longer than 17 days interval between the last administration of Durvalumab and surgery, a third dose of Durvalumab will be considered.

Dose Modification and Toxicity Management

6.2.1 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. Otherwise, Durvalumab should be permanently discontinued. If the patient received only one dose of Durvalumab, patient will be removed from the protocol. Dose reductions are not permitted.

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.

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 nonsterilised male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for 90 days after the final dose of investigational product, or for at least 90 days following the last infusion of durvalumab <<or until after 4-5X the half-life of <<insert additional investigational agent>> or until the time specified in the prescribing information of <<insert approved agent>>, whichever occurs longest>>.; 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 2 acceptable methods of effective contraception as described in Table 1.

- Nonsterilised males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 1) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Table 1. Effective methods of contraception (two methods must be used)

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

Subjects should not donate blood while participating in this study and for at least 90 days following the last infusion of durvalumab.

7.2 Concomitant treatments

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.

7.2.2 Excluded Concomitant Medications

The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy

2. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.

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, 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.

Table 2. 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, correction of metabolic disorders, optimal symptom control, and pain management.	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

The procedures for the pre-screening, screening, and treatment periods in this study presented in the Schedule of Assessments table.

Screening procedures will be performed up to 28 days before Day 1, unless otherwise specified. All subjects must first read, understand, and sign the IRB/REB/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
- Review of eligibility criteria
- Medical history and demographics
- Complete physical exam
- ECOG Performance Status
- Vitals signs, weight and height
- 12-lead ECG (in triplicate [2-5 minutes apart])
- Tumor biopsy
- HPV by PCR in tumor tissue (can be pending at the time of enrollment if none of the arms have met the 10 patients enrollment requirement)
- Review of prior/concomitant medications
- Imaging by CT or MRI (+/- PET)
- Clinical laboratory tests for:
    - Hematology (see Table 3)
    - Clinical chemistry (see Table 4)
    - TSH
    - Coagulation (PT, PTT, INR)
    - Creatinine Clearance
    - Serum pregnancy test (for women of childbearing potential only)
    - Hepatitis serologies
    - Urinalysis (see Table 5)

8.1.2 Treatment Phase

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

8.1.3 End of Treatment

End of treatment is defined as the last planned visit before surgery. For subjects who discontinue durvalumab prior to the last scheduled treatment, the end of treatment is considered the last visit where the decision is made to discontinue treatment. All required procedures should be completed before surgery.

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, and at the end of 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 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 days, 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 (at dose levels of 10 mg/kg or less), 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 and Appendix 2 for the timepoints of each test):

- Coagulation parameters: Activated partial thromboplastin time and International normalised ratio to be assessed at baseline and as clinically indicated

- 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 A antibody, hepatitis B surface antigen, hepatitis C antibody
    - HIV antibody

Table 3. Hematology Laboratory Tests

Basophils	Mean corpuscular volume
Eosinophils	Monocytes
Hematocrit	Neutrophils
Hemoglobin	Platelet count
Lymphocytes	Red blood cell count
Mean corpuscular haemoglobin	Total white cell count
Mean corpuscular haemoglobin concentration	

Table 4. Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Alkaline phosphatase	Lactate dehydrogenase
Alanine aminotransferase	Lipase
Amylase	Magnesium[b]
Aspartate aminotransferase	Potassium
Bicarbonate	Sodium
Calcium	Total bilirubin[a]
Chloride	Total protein

Table 4. Clinical chemistry (Serum or Plasma) Laboratory Tests

Albumin	Glucose
Creatinine	Urea or blood urea nitrogen, depending on local practice
Gamma glutamyltransferase[b]	Uric acid[b]

[a] If Total bilirubin is ≥2xULN (and no evidence of Gilbert's syndrome) then fractionate into direct and indirect bilirubin
[b] At baseline and as clinically indicated

Table 5. Urinalysis Tests[a]

Bilirubin	pH
Blood	Protein
Glucose	Specific gravity
Ketones	Colour and appearance

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

8.3 Biological sampling procedures

8.3.1 Immunogenicity sampling and evaluation methods

Blood and saliva will be collected pre- and post-treatment with Durvalumab.

Blood (20 ml) will be drawn into EDTA tubes. Samples will be labelled and transported at rrom temperature within one hour to Dr. Triozzi laboratory in Hanes building 5th floor. Peripheral blood mononuclear cells (PBMC) are isolated from whole blood by density gradient centrifugation using Lymphocyte Separation Medium (Mediatech) and Leucosep tubes (Greiner Bio-one). Whole blood is centrifuged at 410 × g for 10 minutes and the plasma layer is collected, centrifuged for 10 minutes at 885 × g, and the supernatant frozen at −80°C for subsequent experiments. The whole blood is diluted 1:1 with RPMI (Mediatech) and the PMBCs isolated per manufacturer's guidelines. Cells at the interface are harvested and washed once with RPMI, and red blood cells are lysed with ammonium chloride lysis buffer. Cells are washed, counted, and immediately used fresh for staining and flow cytometry analysis, or 10 million PBMCs are frozen per milliliter of freezing solution (10% DMSO 10% FBS-supplemented RPMI) per NUNC cryovial. PBMCs are frozen in a Nalgene Cryo 1°C freezing container per manufacturer's instructions and stored in liquid nitrogen thereafter.

PBMC and plasma will be used for the following assays:

1. Examine the effects of Durvalumab on systemic immune response to HPV and tumor associated antigens. Peripheral blood mononuclear cell interferon-γ production in vitro in response to commercially available peptide pools corresponding to HPV, p53, Mage-A3, Her2/neu, and survivin will be determined.

PBMC that have been separated by gradient centrifugation and cryopreserved are thawed at 37 ºC, diluted in 5 ml RPMI, and incubated at 37 ºC for 1 hour. Cells are then pelleted at 200g, resuspended in complete medium, counted with trypan blue, and suspended at 4x106/ml and plated in 100 µl in 96 well conical wells. PBMC are then cultured with 20 µg/ml of WT-1, p53, Her2/neu, Mage-A3, telomerase, and survivin peptide mixtures ProMix Peptide Pools (Proimmune Inc.). As a control PBMC are also stimulated with anti-CD3 plus anti-CD28 antibody (BD Pharmingen). After 3 days, culture supernatants are collected and assayed using commercially available ELISA kits according to the recommendation of the manufacturer. Results are expressed as a concentration.

2. Examine the effects of Durvalumab on immune regulatory mechanisms. The following immune effector and regulatory responses will be assessed in blood using standard flow cytometric techniques: CD4+, CD8+, CD4+FoxP3+ Treg, and CD45RO+CD4+ memory T cells; CD3−CD56+ NK cells, and CD14−HLA-DR−CD15+ MDSC.

Antibodies that will be used for flow cytometry analysis include CD4-BV421 (eBiosciences), CD8-PE (BD Pharmingen), CD14-APC (eBiosciences), HLA-DR-FITC (BD Pharmingen), lineage (CD3/CD16/CD19/CD20/CD56) cocktail FITC (BD Pharmingen), ICOS-efluro660 (eBiosciences), and FoxP3-Alexa480 (eBioscience). Isotype controls include the appropriate fluorochrome-conjugated mouse IgG1, IgG 1k, IgG2a, or IgG2b k (BD Pharmingen; Beckman Coulter; R&D Systems). Triplicate samples will be analyzed using the FACSCanto II (Becton Dickinson). Data will be analyzed using the BD FACSDiva software. Gates are set according to appropriate isotype controls. Absolute lymphocyte counts will also be determined. Frequency (%) of the following phenotypes will be determined.

3. Levels of immune-regulatory miRs will be quantified in plasma using PCR-based techniques.

microRNAs (miRs) are important regulators of immune response miRs negatively regulate gene expression by base pairing with the 3′ untranslated region of their target mRNAs. Most cellular processes, both physiological and pathological, are affected. These include differentiation, development, metabolism, proliferation, death, viral infection, and malignant transformation. Recent studies have shown that miRs play a critical role in regulating the development of immune cells and in modulating innate and adaptive immune responses. Several miRs, referred to as “immunomiRs,” have been identified. miR-125b, 155, 181a, and miRs of the 17-92 complex play central roles in T-cell [1]; miR 146a and 155, in NK cell [2]; miR-155 and 146a, in dendritic cell [3]; miR 125b, 146a, 155, and miRs of the 17-92 complex, in T regulatory cell [4,5]; and miR-223, in myeloid derived suppressor cell [6] development and function. Because of their low complexity (when compared to proteins), their stability, and highly sensitive detection methods, miRs are attractive biomarkers [7]. Because of incorporation in microparticles and exosomes, miRs are stable and can be measured in blood and several other body fluids, including saliva [8]. We will examine plasma and salivary immune-regulatory miRs as biomarkers of immune response.

Total RNA will be isolated from plasma and saliva using the miRNeasy Mini Kit (Qiagen). Reverse transcription reactions are performed using a TaqMan MicroRNA Reverse Transcription Kit (Applied

Biosystems) according to the manufacturer's instructions. qRT-PCR will be performed using the reverse transcription reaction product, TaqMan MicroRNA Assay kits, and TaqMan Universal PCR Master Mix (Applied Biosystems. Data are normalized to a C. elegans synthetic miR sequence, cel miR-39 (Qiagen), which is spiked in as a control during RNA isolation.

Remaining samples will be retained for future research after the study report has been finalized if agreed by patients in the ICF. Otherwise it will be disposed.

8.3.1.2 Saliva collection for miRNA testing.

Saliva will be collected weekly (at each visit) through the duration of the study.

Two common, well-documented methods of saliva collection are: (1) the passive drool technique, and (2) the absorbent device technique. In order to maintain consistency in the type of sample collected, we prefer to use the unstimulated, whole saliva that pools on the floor of the mouth, collected by the passive drool technique. On the other hand, use of an absorbent device that can be placed in the mouth often allows for studies with individuals that have difficulty with the passive drool technique. For the purpose of this study the the passive drool technique is preferred. We will target collection of 5 ml saliva from each patient.

Recommendations:

1. Participants should not brush their teeth within 45 minutes prior to sample collection.
2. Dental work should not be performed within 24 hours prior to sample collection.
3. Saliva samples visibly contaminated with blood should be discarded and recollected. Contamination that is not visible is not of concern for this study.

For saliva sample collection we will use 50 ml Falcon tube kept on ice. 5 mL of saliva will be collected.

Instructions for Collecting Saliva:

1. Remove cap from tube. We will use laboratory tubes with large diameter.

3. Instruct participants to allow saliva to pool in the mouth. Some find it helpful to imagine eating their favorite food.

4. With head tilted forward, participants should drool through the SCA to collect saliva in the tube.

5. Replace cap onto tube.

6. Place label immediately.

7. Place tube in refrigerator and transport as soon as possible in an ice box.

Samples will be transported within one hour to Dr. Triozzi's laboratory in Hanes building. Saliva samples will be processed immediately after collection. They will be centrifuged at 2,600 g for 15 min at 4°C. Supernatant will be separated and an RNase inhibitor (Ambion) is added. All samples are aliquoted and stored at −80°C until further use.

Levels of immune-regulatory miRs will be quantified in saliva collected before and after treatment with Durvalumab using PCR-based techniques.

We would like to collect three additional saliva samples (week 2, 3 and 4) for future research, if agreed by the patient in ICF.

8.3.2 Biomarker/Pharmacodynamic sampling and evaluation methods – if additional funding will be secured

PD-L1 Testing

To ensure comparability of data across all studies of durvalumab and to gain real world experience on the performance of this assay, it is strongly encouraged that all studies that include PD-L1 testing utilize 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.

Sample collection for PD-L1 testing

- The preferred tumor sample for the determination of a patient's PD-L1 status is the one taken following the completion of the most recent prior line of therapy. Samples taken at this time reflect the current PD-L1 status of the tumor and considered clinically most relevant.

- In AstraZeneca studies, the preferred sample for PD-L1 testing was less than or equal to 3 months old. In cases where a sample a less than 3 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 PD-L1 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 to assess PD-L1 status, the age of the sample / date of collection should be captured.

- Samples submitted for PD-L1 testing should be formalin fixed and embedded in paraffin. Samples from fine needle aspirates (FNA) or decalcified bone are not appropriate for PD-L1 analysis.

Sample data collection for PD-L1 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 PD-L1 testing laboratory:

- 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 assay to measure PD-L1 in tumors is experimental. As with all tests, there is a chance of false positive (the test shows high PD-L1 when it is not there) or false negative (the test does not show PD-L1 when it is there) results may occur.

Sample processing and if indicated submission process for PD-L1 testing

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 PD-L1 testing

- If patients are undergoing a biopsy procedure that provides the option to submit newly acquired samples, this sample should be used to determine PD-L1 status. 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 PD-L1 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 PD-L1 testing

- Previously frozen tissue is not acceptable for processing to FFPE for PD-L1 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 PD-L1 testing

- An overnight processing schedule into paraffin wax is recommended

- Below is the suggested routine overnight processing schedule:

Storage of tumor blocks for PD-L1 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 PD-L1 testing

- Tissue should be assessed by the site pathologist prior to PD-L1 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.

If indicated, shipping samples to a PD-L1 testing laboratory

- When submitting sample to for PD-L1 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 PD-L1 testing.

Sectioning instructions

- Where it is not possible or indicated to ship the block to laboratory for PD-L1 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 PD-L1 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 PD-L1 testing and they are used within 90 days of being cut to obtain PD-L1 status

8.3.3 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 6. Volume of Blood to Be Drawn From Each Subject

Assessment		Sample volume (mL)	No. of samples	Total volume (mL)
Safety	**Clinical chemistry**	10	9	90
	Hematology	5	9	45
Immune Studies		20	2	40
Additional Research Samples (with patient's consent per ICF)		20	3	60
Total: 235 ml				

8.3.4 Fresh tumor biopsies

Procurement of a fresh tumor sample before treatment is mandatory for enrolling the patient in this study, unless a tumor sample has already been banked in our Tumor Tissue Bank at the time of initial diagnostic biopsy, under Wake Forest University IRB approved and monitored Protocol Number BG98-391.

A separate consent for banking tumor tissue is available for all patients undergoing biopsies and surgeries at our institution.

Due to tumor location in the study patient population (oral cavity and oropharynx) biopsies will be performed in the office. However, if needed in exceptional cases, procedure will be scheduled in OR. One tumor sample and one normal tissue sample will be collected by incisional biopsy under local anaesthesia by our co-PI investigator, Dr. Waltonen of ENT or his designee.

Biopsy tissue will be placed immediately in special tubes containing transporting media, readily available and Libby McWilliams, tissue procurement officer, will be called in advance and will transport the tissue to our Tumor Tissue Bank where the sample will be flash frozen and stored.

Additional samples of fresh primary tumor tissue and adjacent normal tissue as well as sample of tumor involved lymph node tissue (whenever the case) will be collected for the same patient from the surgical

specimen obtained at the time of surgery, after conclusion of the treatment with Durvalumab. Libby McWilliams will be informed in advance about the time of surgery and she will attend the surgical specimen in the Department of Pathology, collect the specimens with the help of the Pathologist on call and transport the specimen to the Tumor Tissue Bank where it will be fresh frozen and stored.

Tissue collection will be monitored by the IRB under the current protocol, including maintenance of patient confidentiality and the HIPAA-compliant sample database. The tissue as well as blood samples are kept in the Tumor Tissue Core Laboratory of the 4th floor of the Hanes Building, which is either manned by a member of the Tumor Tissue Core Laboratory or is locked at all times. The Core Lab's database resides on the Comprehensive Cancer Center of Wake Forest University's (CCCWFU) secure server behind the WFUHS firewall with HIPAA-compliant security. The database is only accessible by the Tumor Tissue Core personnel.

Fresh frozen tissue collected before and after treatment will be used for the following assays for the following immune assessments:

Tumor (primary tumor and involved lymph node) will be assayed using standing immunofluorescence techniques for PD-1+CD4+, PD 1+CD8+, PD-1L+, and Foxp3+CD4+ tumor-infiltrating cells. The results will be quantified (0 to 3+).

Immunohistochemical staining will be carried out on 4μm-thick sections utilizing an Autostainer Plus (Dako - Agilent Technologies) with appropriate positive and negative controls. Sections are baked for 60 minutes at 60 °C in a dehydration oven and heat-induced epitope retrieved in the PT link (Dako – Agilent technologies) using EnVision FLEX target retrieval solution for 20 minutes at 97 °C then cooled to room temperature in TBST Wash buffer for 5 minutes. Slides are incubated with the diluted antibodies. Antibody detection will utilize the Envision FLEX kit (K8023) with a DAB chromagen for visualization according to the manufacturer's instructions (Dako – Agilent technologies). Slides are then counterstained with hematoxylin. The percentage of tumor which have an infiltrate of lymphocytes or macrophages will be estimated and the average number of positive immune cells per high power field (HPF) in a minimum of 4 representative HPF areas will be determined utilizing a semi-quantitative four tiered scale used for scoring lymphocytes (0= no lymphocytes, 1= 1-10/HPF, 2= 11-50/HPF and 3= >50/HPF) and macrophages (0= no macrophages, 1= 1-50/HPF, 2= 50-100/HPF and 3=>100/HPF). Lymphocyte and macrophage infiltrate scores are obtained by multiplying these scores to attain a score from 0-300.

miRNA will be quantified in tumor tissue and involved lymph node using PCR-based techniques (as described in 8.3.1).

Remaining tissue samples will be retained for future research after the study report has been finalized if agreed by patients in the ICF. Otherwise it will be disposed.

8.3.5 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. Patient will be replaced in the study.

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.

Ensures that the subject is informed about the sample disposal.

9. DISEASE EVALUATION AND METHODS

9.1 Imaging response.

9.1.1. CT Scan or MRI

CT scan or MRI will be obtained before (within 14 days) treatment with Durvalumab and before surgery. Results of the CT scan or MRI performed after treatment with durvalumab will be compared and reported to the results of the same imaging study performed initially, before treatment. Both imaging evaluations (before and after treatment) should be performed using the same techniques and results will be interpreted by the same radiologist.

In interpretation of the results, the following will be considered:

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.

RECIST 1.1 criteria will be used to measure tumor size. However, based on the above considerations, the standard RECIST criteria will not be used to measure response. We will report percentage change in tumor measurements before and after treatment in each patient.

Only patients with measurable disease at baseline should be included in the study. Measurable disease is defined by the presence of at least 1 measurable (by RECIST 1.1) lesion.

Measurable: A lesion, not previously irradiated per the protocol prior to enrollment, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes which must have short axis ≥15 mm) with CT or MRI and that is suitable for accurate repeated measurements.

Non-measurable:

- All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 mm to <15 mm short axis at baseline).

- Truly non-measurable lesions include the following: bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusion, inflammatory breast disease, lymphangitic involvement of skin or lung, or abdominal masses/abdominal organomegaly identified by physical examination that is not measurable by CT or MRI.

- Lesions <2 cm biopsied within the screening period (newly acquired tumor biopsy).

Target lesions: A maximum of 5 measurable lesions (with a maximum of 2 lesions per organ), representative of all lesions involved suitable for accurate repeated measurement, should be identified as targeted lesions at baseline.

Non-target lesions: All other lesions (or sites of disease) not recorded as targeted lesions should be identified as non-target lesions at baseline.

A maximum of 5 measurable lesions, with a maximum of 2 lesions per organ (including lymph nodes), representative of all lesions involved should be identified as target lesions at baseline. Target lesions should be selected on the basis of their size (longest diameter for non-nodal lesions or short axis for nodal lesions), but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion, which can be measured reproducibly, should be selected. The site and location of each targeted lesion should be documented as well as the longest diameter for non-nodal lesions (or short axis for lymph nodes). All measurements should be recorded in millimeters. At baseline the sum of the diameters for all targeted lesions will be calculated and reported as the baseline sum of diameters. At follow-up visits the sum of diameters for all targeted lesions will be calculated and reported as the follow-up sum of diameters.

Special cases:

For target lesion measurable in 2 or 3 dimensions, always report the longest diameter. For pathological lymph nodes measurable in 2 or 3 dimensions, always report the short axis.

If the CT/MRI slice thickness used is >5 mm, the minimum size of measurable disease at baseline should be twice the slice thickness of the baseline scan.

If a lesion has completely disappeared, the longest diameter should be recorded as 0 mm.

If a target lesion splits into two or more parts, then record the sum of the diameters of those parts.

If two or more target lesions merge then the sum of the diameters of the combined lesion should be recorded for one of the lesions and 0 mm recorded for the other lesion(s).

If a target lesion is believed to be present and is faintly seen but too small to measure, a default value of 5 mm should be assigned. If an accurate measure can be given, this should be recorded, even if it is below 5 mm.

If a target lesion cannot be measured accurately due to it being too large, provide an estimate of the size of the lesion. Although a visit response of PD will be assigned in the vast majority of these cases, a case should be flagged and reviewed by the Study Physician in a blinded fashion if use of the estimated size in the calculation of TL would not give an overall visit response of PD

9.1.2. FDG-PET Scan

PET scan will be obtained before and after treatment whenever approved by Medical Insurance or funded. The initial PET scan should be obtained as close to the treatment start date as possible, with a maximum window period of 28 days. Similar technique and dosing of the 18-Fluoro-deoxyglucose should be targeted. Percentage change in SUV activity between the initial scan (obtained before treatment with Durvalumab) and follow up scan (obtained after treatment with Durvalumab and before surgery) will be reported for each targeted lesions identified on CT scan based on RECIST 1.1.
Little is known about the effect of short course of treatment with Durvalumab on metabolic activity in the tumor. While this can decrease due to inhibition of tumor growth, it is also possible that the metabolic activity measured at primary tumor site and lymph nodes to be increased initially due to increase in number and activity of inflammatory and immune effective cells.
Changes in SUV will be reported to changes in measurements by CT scan or MRI for each lesion.

9.2 Immunologic response

1. Effect of Durvalumab on systemic immune response to HPV and tumor associated antigens

Blood will be collected before and after treatment (before surgery) with Durvalumab. Peripheral blood mononuclear cell interferon-γ production in vitro (ELISA) in response to commercially available peptide pools corresponding to HPV, p53, Mage-A3, Her2/neu, and survivin will be measured by commercially available ELISA kits . Responses of patients whose tumor are HPV+ will be compared to those that are HPV−.

2. Examine the effects of Durvalumab on immune regulatory mechanisms:

- Blood samples will be collected before and after treatment with Durvalumab. The following immune effector and regulatory responses will be assessed in blood using standard flow cytometric techniques:

CD4+, CD8+, CD4+FoxP3+ Treg, and CD45RO+CD4+ memory T cells; CD3−CD56+ NK cells, and CD14−HLA-DR−CD15+ MDSC. Average change in pre- and post-treatment measurements will be compared between HPV+ and HPV- patients.

- Tumor (primary tumor and regional involved lymph nodes) will be collected before treatment (tissue biopsy) and at the time of surgery, after treatment. PD-1+CD4+, PD 1+CD8+, PD-1L+, and Foxp3+CD4+ tumor-infiltrating cells will be quantified (0 to 3+) using standing immunofluorescence techniques. The results of patients whose tumor are HPV+ will be compared to those that are HPV−.

3. Explore the association between levels of immune-regulatory miR in plasma and saliva and immune response. Blood and saliva samples will be collected before and after treatment with Durvalumab. Tumor (primary tumor and regional involved lymph nodes) will be collected before treatment (mandatory biopsy) and at the time of surgery. Levels of immune-regulatory miRs will be quantified using PCR-based techniques. Levels and change in levels before and after treatment will be compared among saliva, blood and tumor tissue.

The relationship between levels of the miRs and the immune response to HPV, immune response to tumor associated antigens, and immune regulatory molecules/cells will be assessed.

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 nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

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

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 F

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:

- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)

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

10.1.4 Pneumonitis

Adverse events of pneumonitis are of interest for AstraZeneca/Medimmune, as pneumonitis has been reported with anti-PD-1 MAbs (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 × ULN and concurrent increase in total bilirubin to be greater than 2 × 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 ≥3xULN **or** total bilirubin ≥ 2xULN 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.

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 nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

10.2.2 Assessment of relationship

The Investigator will assess the causal relationship between the IP and each AE and answer "yes" or "no" to the question "Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?"

For SAEs, causal relationship will also be assessed for other medications and study procedures. Note that, for SAEs that could be associated with any study procedure, the causal relationship is implied as "yes."

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

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

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

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

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

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

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship in difficult cases, other factors could be considered such as:
  - –Is this a recognized feature of overdose of the drug?
  - –Is there a known mechanism?

Causality of "related" is made if, following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship. The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as "not related." Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

10.3 Recording of adverse events and serious adverse events

Adverse events will be recorded in WISER 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.

The following variables will be collected for each AE:

AE (verbatim)

The date and time when the AE started and stopped

The maximum CTCAE grade reported

Changes in NCI CTCAE grade

Whether the AE is serious or not

Investigator causality rating against durvalumab (yes or no)

Action taken with regard to durvalumab.

Administration of treatment for the AE

Weather the AE caused the patient's withdrawal from the study

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

Seriousness of AE assessed per criteria in 10.1.2

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)

Causality assessment in relation to Additional Study Drug

The grading scales found in the revised NCI CTCAE version 4.03 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 4.03 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

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. This applies also in the situation when Durvaluamb was discontinued and patient was removed from the clinical study.

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.

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. After 90 days, only subjects with ongoing investigational product-related SAEs will continue to be followed for safety. AEs are documented in Appendix 7.

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 AstraZeneca/MedImmune Drug Safety.

10.3.2 Reporting of serious adverse events

DSMC SAE Reporting Requirements

The Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for CCCWFU Institutional studies as outlined in Appendix 6. DSMC currently requires that all unexpected 4 and all grade 5 SAEs on these trials be reported to them for review. All CCCWFU Clinical Research Management (CRM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source,

study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

Sponsor Reporting Requirements

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

The investigator and/or sponsor must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be faxed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.

***** A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:

"Notification from an Investigator Sponsored Study"

The investigator IND number assigned by the FDA

The investigator's name and address

The trial name/title and AstraZeneca ISS reference number (ESR-15-11576).

***** 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 FDA.

Serious adverse events that do not require expedited reporting to the FDA 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, 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 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 and AstraZeneca/MedImmune.

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 designated AstraZeneca representative will work with the Investigator to ensure that all relevant information is provided to the AstraZeneca Patient Safety data entry site within 1 to 5 calendar days for SAEs and within 30 days for all other pregnancies.

The same timelines apply when outcome information is available.

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 relevant Ethics Committees (ECs)/Institutional Review Boards (IRBs) prior to use.

11. STATISTICAL METHODS AND SAMPLE SIZE DETERMINATION

11.1 Description of analysis sets

Primary Objectives

The primary objectives of this pilot study are to investigate the effect of Durvalumab on local and systemic immune activation and compare the results in HPV positive and HPV negative patients with oral cavity and oropharynx HNSCC. Tumor tissue, blood and saliva will be collected before and after treatment with Durvalumab and will be analyzed for systemic immune response to HPV and tumor associated antigens and impact on immune regulatory mechanisms in tumor and blood. Levels of immune-regulatory miR in plasma and saliva will be correlated with other parameters of the local and systemic immune response in order to identify possible predictors of response. Results will be compared between HPV positive and negative patients to identify a possible differential effect of treatment with Durvalumab. Level of local immune response in the primary tumor and in the regional lymph nodes will be compared whenever possible.

Secondary Objectives

A. Investigate the effect of the treatment with Durvalumab on measures of tumor volume (from the CT scan) and tumor activity (from the PET scan).

B. Evaluate the safety of a short induction treatment with Durvalumab.

Primary Endpoints:

Since this is a pilot study and does not have a specific primary efficacy analysis, there are several primary endpoints (rather than a single primary efficacy endpoint) that will be collected. These can be described in three broad categories within the area of local and systemic immune activation. The categories are effects of Durvalumab on 1) systemic immune response to HPV and tumor associated antigens; 2) immune regulatory mechanisms; and 3) immune-regulatory miR responses as measured in plasma, saliva or tumor. Each of these categories has several endpoints that will now be described.

1. Systemic immune response to HPV and tumor associated antigens:
    a. Peripheral blood mononuclear cell interferon-γ production in vitro (ELISA) in response to commercially available peptide pools corresponding to HPV, p53, Mage-A3, Her2/neu, and survivin will be determined.

2. Immune regulatory mechanisms.
    a. The following immune effector and regulatory responses will be assessed in blood using standard flow cytometric techniques: CD4+, CD8+, CD4+FoxP3+ Treg, and CD45RO+CD4+ memory T cells; CD3−CD56+ NK cells, and CD14−HLA-DR−CD15+ MDSC.
    b. Tumor (primary tumor and regional involved lymph nodes) will be collected before treatment and at the time of surgery, after treatment. PD-1+CD4+, PD 1+CD8+, PD-1L+, and Foxp3+CD4+ tumor-infiltrating cells will be quantified (0 to 3+) using standing immunofluorescence techniques.
3. Immune-regulatory miR response.
    a. Levels of immune-regulatory miRs in blood, saliva and tumor (primary and regional involved lymph nodes) will be quantified using PCR-based techniques.

Secondary Endpoints

There are two types of secondary endpoints.

The first consist of measures of tumor volume (via CT scan) or metabolic activity (via PET scan).

The second are measures of clinical toxicities that may occur during the trial.

11.1.1 Safety analysis set

The Safety Analysis Set will consist of all patients who received at least one dose of Durvalumab. Analyses of safety data will be performed on this analysis set.

11.1.2 Efficacy analysis set

Since this trial is a pilot study and patients are not being randomized, the "efficacy" analysis set used for this study will be equivalent to a "per protocol" analysis set rather than a traditional intent-to-treat analysis set. With this in mind, the efficacy analysis set will include all patients who received at least two doses of Durvalumab and had CT scans or MRIs and blood, saliva and tissue collected before and after treatment. All analyses of primary and secondary outcomes (except for safety) will be performed using this analysis set.

11.2 Methods of statistical analyses

11.2.1 Safety Analyses

Analysis of safety endpoint(s)

All safety endpoints (adverse events (AEs)) described above will be documented. AEs will be coded using the MedDRA dictionary to their organ class by preferred term. Coded AEs will be displayed by frequency, severity, and relationship to treatment (Durvalumab) in the safety population. In addition, summary tables will be generated for the following situations: 1. fatigue, diarrhea, nausea and skin rash; 2. Immune-mediated reactions of any grade; 3. other adverse events graded as 3 or more by CTCAE Version 4.03; 4) Durvalumab dose reductions; 5) discontinuations of treatment with Durvalumab, with specification of reason for discontinuation; and 6) changes in the surgical treatment schedule with specification of reason will be provided using descriptive statistics.

Descriptive statistics will be gathered on additional measurements that will be collected. These include displays of mean, median, standard deviations and ranges for continuous measures and counts and percentages for categorical measures.

11.2.2 Efficacy Analyses

As stated above, there are several primary efficacy measures for this protocol. In addition, this is not a randomized clinical trial, thus there is not one primary efficacy analysis, rather there are a series of primary analyses proposed to be performed examining each of the primary efficacy measures described above.

Analysis of immunogenicity

1) Peripheral blood mononuclear cell interferon-γ production in vitro (ELISA) in response to commercially available peptide pools corresponding to HPV, p53, Mage-A3, Her2/neu, and survivin will be compared between patients who are HPV+ and HPV- using 2 sample t-tests. These measures will be compared in several ways. First, baseline, pre-treatment levels will be examined using descriptive statistics (n, mean, standard deviations, range). These measures will be examined overall and by HPV (+/-) groups. For each measure, and time point, 95% confidence intervals will be estimated. Next, two sample t-tests will be performed to compare levels of the measures at baseline. Next, measures taken post-treatment will be examined in a similar manner (descriptive statistics and 2-sample t-tests). Finally, comparisons between HPV+ and HPV- groups will be made by comparing the changes (pre-treatment to post-treatment) between groups using 2-sample t-tests.

2) Concentration of certain immune effector and regulatory cells will be assessed in blood (CD4+, CD8+, CD4+FoxP3+ Treg, and CD45RO+CD4+ memory T cells; CD3−CD56+ NK cells, and CD14−HLA-DR−CD15+ MDSC) pre- and post- treatment. Descriptive statistics, confidence intervals will be calculated and 2-sample t-tests will be performed as described above for the interferon- γ analyses.

3) Tumor-infiltrating immune-regulator and effector cells will be quantified (0 to 3+) using standing immunofluorescence techniques. Counts and percents will be calculated for these measures overall and by HPV (+/-) groups pre- and post-treatment. Fisher exact tests will be used to compare groups at pre- and post- treatment. Stuart-Maxwell tests (generalizations of the McNemar's Test) will be used to examine changes between groups (HPV +/-) from pre- to post- treatment.

4) Levels of immune-regulatory miRs assessed in blood, saliva and tumor tissue will be assessed pre- and post- treatments. Descriptive statistics, confidence intervals will be calculated and 2-sample t-tests will be performed as described above for the interferon- γ analyses. In addition, correlations between the different methods will be examined (i.e., correlation between saliva and blood measures, saliva and tumor measures, and blood and tumor measures).

Secondary endpoint analyses

Measures of tumor volume will be assessed using RECIST 1.1 criteria. These tumor volumes will be compared between groups (HPV +/-) pre- and post- treatment. Descriptive statistics, confidence intervals will be calculated and 2-sample t-tests will be performed as described above for the interferon- γ analyses.

SUV activity as measured by PET scans will also be compared between groups at each time point and descriptive statistics, confidence intervals will be calculated and 2-sample t-tests will be performed as described above for the interferon- γ analyses.

11.2.3 Interim analyses

There will not be any interim analysis.

11.3 Determination of sample size

The goal for this pilot study is to get preliminary descriptive data for a series of measures taken using blood, saliva and tumor tissue pre- and post- immunotherapy. With a sample size of 10 patients in each group (i.e. 10 with HPV+ and 10 HPV-) a 95% confidence interval for each group will have confidence limits +/- 0.72 standard deviations. In addition, the change in each measure (pre- versus post- therapy) can be used to estimate 95% confidence intervals to determine whether there are any significant changes from baseline (i.e., the measure increased (or decreased) by more than 0.72 standard deviations).

Furthermore, to compare groups (HPV+ versus HPV-), there is 80% power to detect a difference in measures equal to 1.3 standard deviations of the measure of interest using a 2-sample t-test with alpha=0.05.

The patients who are discontinued from the study treatment and/or from the study will be replaced.

It is anticipated that an accrual rate of 12 patients per year is reasonable and thus the goal of 20 evaluable patients should be achieved within approximately 18 months. Additional 6 mo might be needed for accruing replacement patients for the patients unable to complete study treatment or required investigations.

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

Institutional Review Board (IRB) will approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the IRB and to the study site staff.

The opinion of IRB should be given in writing. The Investigator should submit the written approval to AstraZeneca before enrolment of any patient into the study. AstraZeneca should approve any modifications to the ICF that are needed to meet local requirements.

The protocol should be re-approved by the IRB annually. Before enrolment of any patient into the study, the final study protocol, including the final version of the ICF, should be approved by the national regulatory authority or a notification to the national regulatory authority should be approved, according to local regulations. AstraZeneca will handle the distribution of these documents to the national regulatory authorities.

AstraZeneca will provide regulatory authorities, IRB, and Principal Investigator safety updates or reports according to local requirements.

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

12.3 Informed consent

The Principal Investigator will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure that each patient is notified that he or she is free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure that each patient provides a signed and dated informed consent before conducting any procedure specifically for the study
- Ensure that the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure that a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB.

12.4 Changes to the protocol and informed consent form

If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (revised clinical study protocol). The amendment is to be approved by the relevant IRB and, if applicable, the national

regulatory authority, before implementation. Local requirements will be followed for revised protocols.

12.5 Audits and inspections

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

13. STUDY MANAGEMEN

13.1 Training of study site personnel

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

13.2 Study timetable and end of study

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

We project recruiting one patient a month with a total recruiting period of about 18 month. In case patients will be withdrawn from the study for reasons such as toxicity, non-compliance, inability to complete study procedures, an additional 6 mo period should be allowed to complete recruitment of 20 patients, 10 patients HPV + and 10 patients HPV-.

14. DATA MANAGEMENT

Informed consent document	WISER
Protocol registration form	WISER
Adverse event log	WISER
Data collection form	REDCap

14.1 Study governance and oversight

The safety of all AstraZeneca clinical studies 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.

15. INVESTIGATIONAL PRODUCT AND OTHER TREATMENTS

15.1 Identity of investigational product(s)

Table 7. List of investigational products for this study

Investigational product	Dosage form and strength	Manufacturer
Durvalumab	1500 mg, solution, IV	MedImmune

16. LIST OF REFERENCES

Andorsky DJ, Yamada RE, Said J, Pinkus GS, Betting DJ, and Timmerman JM. Programmed death ligand 1 is expressed by non-hodgkin lymphomas and inhibits the activity of tumor-associated T cells. Clin Cancer Res. 2011. 17(13):4232-4244.

Bellati F, Napoletano C, Ruscito I, et al: Past, present and future strategies of immunotherapy in gynecological malignancies. Curr Mol Med 2013; 13:648-69.

Bookman MA, Brady MF, McGuire WP, et al: Evaluation of new platinum-based treatment regimens in advanced-stage ovarian cancer: a Phase III Trial of the Gynecologic Cancer Intergroup. J Clin Oncol 2009; 27:1419-25.

Brahmer JR, Tykodi SS, Chow LQM, Hwu WJ, Topalian SL, Hwu P, et al. Safety and activity of anti-PD-L1 antibody in patients with advanced cancer. N Engl J Med. 2012 Jun 28;366(26):2455-65.

Brusa D, Serra S, Coscia M, Rossi D, D'Arena G, Laurenti L, et al. The PD-1/PD-L1 axis contributes to T-cell dysfunction in chronic lymphocytic leukemia. Haematologica. 2013 Jun; 98(6):953-963.

Burger RA, Brady MF, Bookman MA, et al: Incorporation of bevacizumab in the primary treatment of ovarian cancer. The New England journal of medicine 2011; 365:2473-83.

Callahan MK and Wolchok JD. CTLA-4 and PD-1 blocking antibodies in cancer immunotherapy. J Leukoc Biol. 2013; 94(1):41-53.

Chow et al. Exploring novel immune-related toxicities and endpoints with immune-checkpoint inhibitors in non-small cell lung cancer. Am Soc Clin Oncol Educ Book. 2013

Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Coleman RL, Monk BJ, Sood AK, et al: Latest research and treatment of advanced-stage epithelial ovarian cancer. Nature Reviews Clinical Oncology 2013; 10:211-224.

Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. New response evaluation criteria in solid tumors: Revised RECIST guideline (version 1.1). Eur J Cancer. 2009;45:228-47.

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

Fagotti A, Ferrandina G, Fanfani F, et al: A laparoscopy-based score to predict surgical outcome in patients with advanced ovarian carcinoma: a pilot study. Ann Surg Oncol 2006; 13:1156-61.

Fellman, B. M. Stata command for calculating adverse event and efficacy stopping boundaries for phase II single-arm trials. *Stata Journal.* 2014; 14(2):407-417.

Food and Drug Administration Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation'. Available from URL: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf . Accessed 10 December 2013.

Hamanishi J, Mandai M, Iwasaki M, Okazaki T, Tanaka Y, Yamaguchi K, et al. Programmed cell death 1 ligand 1 and tumor-infiltrating CD8+ T lymphocytes are prognostic factors of human ovarian cancer. Proc Nat Acad Sci U S A. 2007;104(9):3360-5.

Hamid et al Safety and tumor responses with lambrolizumab (anti-PD-1) in melanoma. N Engl J Med. 2013 Jul 11;369(2):134-44

Kaehler et al. Update on immunologic therapy with anti-CTLA-4 antibodies in melanoma: identification of clinical and biological response patterns, immune-related adverse events, and their management. Semin Oncol. 2010 Oct;37(5):485-98

Kandalaft LE, Motz GT, Duraiswamy J, et al: Tumor immune surveillance and ovarian cancer: lessons on immune mediated tumor rejection or tolerance. Cancer Metastasis Rev 2011; 30:141-51.

Katsumata N, Yasuda M, Takahashi F, et al: Dose-dense paclitaxel once a week in combination with carboplatin every 3 weeks for advanced ovarian cancer: a phase 3, open-label, randomised controlled trial. Lancet 2009; 374:1331-8.

Keir ME, Butte MJ, Freeman GJ, Sharpe AH. PD-1 and its ligands in tolerance and immunity. Annu Rev Immunol. 2008;26:677-704.

Kim KW, Ramaiya NH, Krajewski KM, et al. Ipilimumab associated hepatitis: imaging and clinicopathologic findings. Invest New Drugs. 2013;31:1071.

Krambeck AE, Dong H, Thompson RH, Kuntz SM, Lohse CM, Leibovich BC, et al. Survivin and B7-H1 are collaborative predictors of survival and represent potential therapeutic targets for patients with renal cell carcinoma. Clin Cancer Res. 2007;13(6):1749-56.

Kryczek I, Wei S, Zhu G, et al: Relationship between B7-H4, regulatory T cells, and patient outcome in human ovarian carcinoma. Cancer Res 2007; 67:8900-5.

Lenz. Management and preparedness for infusion and hypersensitivity reactions. Oncologist. 2007 May;12(5):601-9.

Loos M, Giese NA, Kleeff J, Giese T, Gaida MM, Bergmann F, et al. Clinical significance and regulation of the costimulatory molecule B7-H1 in pancreatic adenocarcinoma. Cancer Lett. 2008;268(1):98-109.

Mu CY, Huang JA, Chen Y, Chen C, Zhang XG. High expression of PD-L1 in lung cancer may contribute to poor prognosis and tumor cells immune escape through suppressing tumor infiltrating dendritic cells maturation. Med Oncol. 2011 Sep;28(3):682-8.

Nishino M, Giobbie-Hurder A, Gargano M, Suda M, Ramaiya NH and Hodi FS. Developing a common language for tumor response to immunotherapy: immune-related response criteria using unidimensional measurements. Clin Cancer Res. 2013 Jul; 19(14):3936-3943.

Nomi T, Sho M, Akahori T, Hamada K, Kubo A, Kanehiro H, et al. Clinical significance and therapeutic potential of the programmed death-1 ligand/programmed death-1 pathway in human pancreatic adenocarcinoma. Clin Cancer Res. 2007 Apr 1;13(7):2151-7.

Park J, Omiya R, Matsumura Y, Sakoda Y, Kuramasu A, Augustine MM, et al. B7-H1/CD80 interaction is required for the induction and maintenance of peripheral T-cell tolerance. Blood. 2010;116(8):1291-8.

Perren TJ, Swart AM, Pfisterer J, et al: A phase 3 trial of bevacizumab in ovarian cancer. The New England journal of medicine 2011; 365:2484-96.

Raja FA, Chopra N, Ledermann JA. Optimal first-line treatment in ovarian cancer. Ann Oncol 2012 Sep; 23 Suppl 10:x118-27.

Segal NH, Ou S-HI, Balmanoukian AS, et al. Safety and efficacy of MEDI4736, an anti-PD-L1 antibody, in patients from a squamous cell carcinoma of the head and neck (SCCHN) expansion cohort. J Clin Oncol. 2015;33 (suppl; abstr 3011).

Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2015. CA Cancer J Clin 2015 Jan-Feb; 65(1): 5-29.

Sznol M and Chen L. Antagonist antibodies to PD-1 and B7-H1 (PD-L1) in the treatment of advanced human cancer. 2013; 19(5):1021-1034.

Tarhini A. Immune-mediated adverse events associated with ipilimumab ctla-4 blockade therapy: the underlying mechanisms and clinical management. Scientifica (Cairo). 2013;2013:857519

TCGA. Integrated genomic analyses of ovarian carcinoma. Nature 2011; 474:609-15.
Thall PF, Simon R. Practical Bayesian guideline for phase IIB clinical trials. Biometrics 1994 Jun;50(2):337-49.

Thall PF, Wooten LH, and Tannir NM. Monitoring Event Times in Early Phase Clinical Trials: Some Practical Issues, Clinical Trials 2005; 2, 467-478 (2005).

Thompson RH, Gillett MD, Chevillem JC, Lohsem CM, Dong H, Webster WS, et al.
Costimulatory molecule B7-H1 in primary and metastatic clear cell renal cell carcinoma. Cancer. 2005;104(10):2084-91.

Thompson RH, Kuntz SM, Leibovich BC, Dong H, Lohse CM, Webster WS, et al. Tumor B7-H1 is associated with poor prognosis in renal cell carcinoma patients with long-term follow-up. Cancer Res. 2006;66(7):3381-5.

Topalian SL, Hodi FS, Brahmer JR, Gettinger SN, Smith DC, McDermott DF, et al. Safety, activity, and immune correlates of anti-PD-1 antibody in cancer. N Engl J Med. 2012 Jun 28;366(26):2443-54.

US Department of Health and Human Services, National Institutes of Health, National Cancer Institute. Common Terminology Criteria for Adverse Events Version 4.03.
http://evs.nci.nih.gov/ftp1/CTCAE/About.html

Vergote I, Trope CG, Amant F, Kristensen GB, Ehlen T, Johnson N, Verheijen RHM, van der Burg MEL, Lacave AJ, Bendetti Panici P, Kenter GG, Casado A, Mendiola C, Coens C, Verleye L, Stuart GCE, Pecorelli S, Reed NS. Neoadjuvant Chemotherapy or Primary Surgery in Stage IIIc or IV Ovarian Cancer. NEJM 2010; 363; 10: 943-53.

Wang L, Ma Q, Chen X, Guo K, Li J, Zhang M. Clinical significance of B7-H1 and B7-1 expressions in pancreatic carcinoma. World J Surg. 2010;34(5):1059-65.

Weber et al. Management of immune-related adverse events and kinetics of response with ipilimumab. J Clin Oncol. 2012 Jul 20;30(21):2691-7

Wolchok JD, Hoos A, O'Day S, Weber JS, Hamid O, Lebbé, et al. Guidelines for the

evaluation of immune therapy activity in solid tumors: immune-related response criteria. Clin Cancer Res. 2009;15:7412-20.

Zou W, Chen L. Inhibitory B7-family molecules in the tumour microenvironment. Nat Rev Immunol. 2008;8(6):467-77.

Appendix 1. Dosing Modification and Toxicity Management Guidelines for Immune-mediated, Infusion Related, and Non Immune-mediated Reactions for Durvalumab Monotherapy

Table 1- Immune-Mediated Reactions

	Dose Modifications	**Toxicity Management**
Immune-related Adverse Events (Overall Management For toxicities not	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. In addition to the criteria for permanent discontinuation of study drug/regimen based on CTC grade/severity (table below) , permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** after last dose of study drug/regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing.	It is recommended that management of irAEs follow the guidelines presented in this table – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, infections, etc.) – In the absence of a clear alternative etiology, all events should be considered potentially immune related. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events – For persistent (greater than 3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events promptly start prednisone PO 1-2mg/kg/day or IV equivalent – If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume
	Grade 1 No dose modification	

<table>
<tr>
<td>noted below)</td>
<td>
<table>
<tr><td>Grade 2</td><td>Hold study drug/study regimen dose until grade 2 resolution to ≤ Grade 1
• If toxicity worsens then treat as Grade 3 or Grade 4
• If toxicity improves to baseline then treat at next scheduled treatment date
Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper
Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled , 2) the patient is clinically stable as per Investigator or treating physician’s clinical judgement, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.</td></tr>
<tr><td>Grade 3</td><td>Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below</td></tr>
<tr><td>Grade 4</td><td>Permanently discontinue study drug/study regimen</td></tr>
<tr><td colspan="2">Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work up shows no evidence of pancreatitis, may continue or resume study drug/regimen</td></tr>
</table>
</td>
<td>corticosteroid tapering at a slower rate (≥ 28 days of taper)
– More potent immunosuppressives such as TNF inhibitors (e.g. infliximab) – (also refer to the individual sections of the immune related adverse event for specific type of immunosuppressive) should be considered for events not responding to systemic steroids.
– Discontinuation of study drug is not mandated for Grade 3 / Grade 4 inflammatory reactions attributed to local tumour response (e.g. inflammatory reaction at sites of metastatic disease, lymph nodes etc.). Continuation of study drug in this situation should be based upon a benefit/risk analysis for that patient</td>
</tr>
</table>

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Pneumonitis/ILD	Grade of Pneumonitis (CTCAE version 4.03)	Any Grade	– Monitor 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 modification required. However, consider holding study drug/study regimen dosing as clinically appropriate and during diagnostic work-up for other etiologies	For Grade 1 (Radiographic Changes Only) - Monitor and closely follow up in 2-4 days for clinical symptoms, pulse oximetry (resting and exertion) and laboratory work-up and then as clinically indicated - Consider pulmonary and infectious disease consult
	Grade 2 (Symptomatic, medical intervention indicated, limiting instrumental ADL)	Hold study drug/study regimen dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then the decision to reinitiate study drug/regimen at next scheduled treatment date will be based upon treating physician's clinical judgment. Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper	For Grade 2 (Mild to Moderate New Symptoms) – Monitor symptoms daily and consider hospitalization – Promptly start systemic steroids (e.g., prednisone 1-2mg/kg/day or IV equivalent) – Reimaging as clinically indicated – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2-4mg/kg/day started – If still no improvement within 3-5 days despite IV methylprednisone at 2-4/g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥4 weeks and consider prophylactic antibiotics, antifungal or anti PCP treatment (refer to current

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii][1] – Consider pulmonary and infectious disease consult – Consider as necessary discussing with study physician
	Grade 3 or 4 (Grade 3: Severe symptoms; limiting self-care ADL; oxygen indicated; Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g. tracheostomy or intubation])	Permanently discontinue study drug/study regimen	For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Obtain pulmonary and infectious disease consult – Hospitalize the patient – Supportive Care (oxygen, etc.) – If no improvement within 3-5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g. infliximab at 5mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[iii]
Diarrhea/ Enterocolitis	Grade of Diarrhea (CTCAE version 4.03)	Any Grade	– Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus) – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for clostridium difficile toxin, etc.) – Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher

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

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			grade event – Use analgesics carefully; they can mask symptoms of perforation and peritonitis
	Grade 1 diarrhea (stool frequency of <4 over baseline per day)	No dose modification	For Grade 1 diarrhea : - Close monitoring for worsening symptoms - Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use of probiotics as per treating physician's clinical judgment.
	Grade 2 diarrhea (stool frequency of 4-6 over baseline per day)	Hold study drug/study regimen until resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If toxicity improves to baseline then treat at next scheduled treatment date Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper	For Grade 2 diarrhea: – 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 or IV equivalent – If event is not responsive within 3-5 days or worsens despite prednisone at 1-2 mg/kg/day or IV equivalent, GI consult should be obtained for consideration of further workup such as imaging and/or colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5mg/kg once every 2 weeks[2]). . **Caution**: Important to rule out

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

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			bowel perforation and refer to infliximab label for general guidance before using infliximab – Consult study physician if no resolution to ≤ Grade 1 in 3-4 days – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥7 over baseline per day; Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen	For Grade 3 or 4 diarrhea: – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent – Monitor stool frequency and volume and maintain hydration – Urgent GI consult and imaging and/or colonoscopy as appropriate – If still no improvement within 3-5 days of IV methylprednisolone 2 to 4mg/kg/day or equivalent, promptly start further immunosuppressives (e.g. infliximab at 5mg/kg once every 2 weeks). – Caution: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
Hepatitis (Elevated LFTs) **Infliximab should not be used for management of Immune Related Hepatitis**	Grade of Liver Function Test Elevation (CTCAE version 4.03) Any Grade Grade 1 (AST or ALT > ULN to 3 times ULN	No dose modification If it worsens, treat as Grade 2 event	– Monitor and evaluate liver function test: AST, ALT, ALP and total bilirubin – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications) For Grade 1 AST or ALT and/or TB elevation - Continue LFT monitoring per protocol

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	and/or TB > ULN to 1.5 times ULN)		
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or TB >1.5-3.0 times ULN)	Hold Study drug/study regimen dose until grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 • If improves to baseline then treat at next scheduled treatment date Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper	For Grade 2 AST or ALT and or TB elevation : – Regular and frequent checking of LFTs (e.g. every 1-2 days) until elevations of these are improving or resolved. – If no resolution to ≤ Grade 1 in 1-2 days, discuss with study physician. – If event is persistent (> 3-5 days) or worsens, promptly start prednisone 1-2mg/kg/day or IV equivalent. – If still no improvement within 3-5 days despite 1-2mg/kg/day of prednisone or IV equivalent, consider additional workup and prompt treatment with IV methylprednisolone 2-4mg/kg/day started. – If still no improvement within 3-5 days despite 2-4mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[3] . Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 3 (AST or ALT >5-20 times ULN and/or TB > 3.0-10 times ULN	For elevations in transaminases ≤ 8 × ULN, or elevations in bilirubin ≤ 5 × ULN -Hold study drug/study regimen dose until resolution to ≤ Grade 1 or baseline -Resume study drug/study regimen	For Grade 3 or 4 AST or ALT and/or TB elevation: – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent – If still no improvement within 3-5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent , promptly start treatment with immunosuppressive therapy (mycophenolate mofetil) Discuss with study

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

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline within 14 days Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 or baseline within 14 days For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue study drug/study regimen Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (ALT > 3x ULN + bilirubin > 2x ULN without initial findings of cholestasis (i.e. elevated alkaline P04) and in the absence of any alternative cause[iv]	physician if mycophenolate is not available. **Infliximab should NOT be used.** – Hepatology consult, abdominal workup, and imaging as appropriate. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation])
	Grade 4 (AST or ALT > 20 times ULN and/or TB > 10 times ULN)	Permanently discontinue study drug/study regimen	

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Nephritis or Renal Dysfunction (Elevated Serum Creatinine)	Grade of Elevated Serum Creatinine (CTCAE version 4.03) Any Grade		– Consult with Nephrologist – Monitor for signs and symptoms that may be related to changes in renal function (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
	Grade 1 [Serum Creatinine > 1-1.5X baseline; > ULN to 1.5X ULN]	No dose modification	For Grade 1 elevated creatinine: - Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If it worsens, depending on the severity , treat as Grade 2 or Grade 3 or 4 - Consider symptomatic treatment including hydration, electrolyte replacement, diuretics, etc.

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

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
Bullous skin formations)	(Please refer to NCICTCAE version 4.03 for definition of severity/grade depending on type of skin rash)		**IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****
	Grade 1	No dose modification	For Grade 1: – Consider symptomatic treatment including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream)
	Grade 2	For persistent (> 1- 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to ≤ Grade 1 or baseline • If toxicity worsens then treat as Grade 3 • If toxicity improves then resume administration at next scheduled dose • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper	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 3-5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, discuss with study physician and promptly start systemic steroids prednisone 1-2 mg/kg/day or IV equivalent – Consider skin biopsy if persistent for >1-2 weeks or recurs
	Grade 3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to ≤ Grade 1 or baseline	For Grade 3 or 4: – Consult dermatology – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent – Consider hospitalization

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		within 30 days, then permanently discontinue Study drug/study regimen	– Monitor extent of rash [Rule of Nines] – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – Discuss with Study Physician
	Grade 4	Permanently discontinue study drug/study regimen	
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any Grade (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity)		– Consult Endocrinologist – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc.) – Monitor and evaluate thyroid function tests: TSH, free T_3 and free T_4 and other relevant endocrine labs depending on suspected endocrinopathy. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing
	Grade 1 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade 1)	No dose modification	For Grade 1: (including those with asymptomatic TSH elevation) – Monitor patient with appropriate endocrine function tests – If TSH < 0.5X LLN, or TSH >2X ULN or consistently out of range in 2 subsequent measurements, include FT4 at subsequent cycles as clinically indicated and consider endocrinology consult.

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

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
	Grade 3 or 4 (Depending on the type of endocrinopathy, refer to NCI CTCAE version 4.03 for defining the CTC grade/severity 3 or 4)	For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled Resume study drug/study regimen administration if controlled at the next scheduled dose Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper	For Grade 3 or 4: – Consult endocrinologist – Isolated hypothyroidism may be treated with replacement therapy without treatment interruption and without corticosteroids – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent – Administer hormone replacement therapy as necessary. – For adrenal crisis, severe dehydration, hypotension, or shock: immediately initiate intravenous corticosteroids with mineralocorticoid activity – Once improving, gradually taper immunosuppressive steroids over ≥4 weeks and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]) – Discuss with study physician
Immune mediated Neurotoxicity (to include but not limited to limbic encephalitis . autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	Grade of Neurotoxicity Depending on the type of neurotoxicity , refer to NCI CTCAE version 4.03 for defining the CTC grade/severity		
	Any Grade		– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.) – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness) – Consider appropriate diagnostic testing (e.g. electromyogram and nerve conduction investigations)

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			– Symptomatic treatment with neurological consult as appropriate
	Grade 1	No dose modifications	See "Any Grade" recommendations above.
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to ≤ Grade 1 • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1. o If toxicity worsens then treat as Grade 3 or Grade 4 o If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to grade ≤1 and 5-7 days have passed after completion of steroid taper	– Discuss with the study physician – Obtain Neurology Consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin, duloxetine, etc.) – Promptly start systemic steroids prednisone 1-2mg/kg/day or IV equivalent – If no improvement within 3-5 days despite 1-2mg/kg/day prednisone or IV equivalent consider additional workup and promptly treat with additional immunosuppressive therapy (e.g. IVIG)
	Grade 3	• Hold Study drug/study regimen dose until resolution to ≤ Grade 1 • Permanently discontinue Study drug/study regimen if Grade 3 irAE does not resolve	For Grade 3 or 4: – Discuss with study physician – Obtain Neurology Consult – Consider hospitalization – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		to ≤ Grade 1 within 30 days.	equivalent
	Grade 4	• Permanently discontinue study drug/study regimen	– If no improvement within 3-5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g. IVIG) – Once stable, gradually taper steroids over ≥4 weeks
Immune-mediated peripheral neuromotor syndromes, such as Guillain-Barre and Myasthenia Gravis		Any Grade	– The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may unpredictably experience acute decompensations which can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms which may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes and medications, etc.). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in 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 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 IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 1	No dose modification	– Discuss with the study physician – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
			– Obtain a neurology consult unless the symptoms are very minor and stable
	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	Grade 2 – Discuss 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, duloxetine, etc.) *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. Important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 3	Hold study drug/study regimen dose until resolution to ≤ Grade 1 Permanently discontinue Study	For severe or life threatening (Grade 3 or 4) events: – Discuss with study physician

	Grade of the Event (NCI CTCAE version 4.03)	**Dose Modifications**	**Toxicity Management**
		drug/study regimen if Grade 3 irAE does not resolve to ≤ Grade 1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability	– Recommend hospitalization – Monitor symptoms and obtain neurological consult *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholine esterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE*: Important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG
	Grade 4	Permanently discontinue study drug/study regimen	

Table 2- Infusion-Related Reactions		
Severity Grade	**Dose Modifications**	**Toxicity Management**
Any Grade		– Management 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, skin rashes etc.) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, tachycardia, etc.)
Grade 1	The infusion rate of study drug/study regimen may be decreased by 50% or temporarily interrupted until resolution of the event	For Grade 1 or Grade 2: – Acetaminophen and/or antihistamines may be administered per institutional standard at the discretion of the investigator – Consider premedication per institutional standard prior to subsequent doses
Grade 2	The infusion rate of study drug/study regimen may be decreased 50% or temporarily interrupted until resolution of the event Subsequent infusions may be given at 50% of the initial infusion rate	
Grade 3/4	Permanently discontinue study drug/study regimen	For Grade 3 or 4: Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid)

Table 3- Non-immune Mediated Reactions

(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"

CTC Grade/Severity	Dose Modification	Toxicity Management
Any Grade	Note: dose modifications are not required for adverse events not deemed to be related to study treatment (i.e. events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly as per institutional standard
1	No dose adjustment	Treat accordingly as per institutional standard
2	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline	Treat accordingly as per institutional standard
3	Hold study drug/study regimen until resolution to ≤ Grade 1 or baseline For AEs that downgrade to ≤ Grade 2 within 7 days or resolve to ≤ Grade 1 or baseline within 14 days, resume study drug/study regimen administration at next scheduled dose. Otherwise, discontinue study drug/study regimen	Treat accordingly as per institutional standard
4	Discontinue Study drug/study regimen (Note for Grade 4 labs, decision to discontinue would be based on accompanying clinical signs/symptoms and as per Investigator's clinical judgment and in consultation with the sponsor)	Treat accordingly as per institutional standard

Abbreviations:

AChE = acetylcholine esterase; ADA = American Dietetic Association; AE = adverse event; ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CT = computed tomography; GI = gastrointestinal; IDS=Infectious Disease Service; ILD = interstitial lung disease; IM = intramuscular; irAE = immune-related adverse event; IV = intravenous; NCI CTCAE = National Cancer Institute Common Terminology Criteria for Adverse Events; PO = by mouth; TNF = tumor necrosis factor; TSH = thyroid stimulating hormone; ULN = upper limit of normal.

[1] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
[1] NCI CTCAE version 4.03
[1] ASCO Educational Book 2015 "Managing Immune Checkpoint Blocking Antibody Side Effects" by Michael Postow MD
[1] FDA Liver Guidance Document 2009 Guidance for Industry: Drug Induced Liver Injury – Premarketing Clinical Evaluation

Appendix 2: Schedule of study procedures: follow-up for subjects who have completed treatment or have discontinued treatment due to toxicity

Evaluation[a]	**Month 1**	**Month 2**	**Month 3**
Physical examination	X	X	X
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X	X	X
Weight	X	X	X
Urine hCG or serum βhCG	X		
AE/SAE assessment	X	X	X
Concomitant medications	X	X	X
ECOG performance status	X	X	X
Subsequent anti-cancer therapy			X
Hematology	X	X	X
Serum chemistry	X	X	X
Thyroid function tests (TSH, and fT3 and fT4)[b]	X		
sPD-L1 concentration (to assess target engagement), if applicable		X	

[a] A follow up visit for evaluation is preferred and will be scheduled monthly for 3 mo after the last administration of Durvalumab whenever possible. Alternatively, available data will be collected from medical records and phone evaluation will be attempted as well.

[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.

Appendix 3 – Subject Eligibility Checklist

IRB Protocol No.	**CCCWFU Protocol No.**
Study Title:	
Principal Investigator: Mercedes Porosnicu, MD	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
Histologically or cytologically confirmed HNSCC of the oral cavity (OC; more than 90% patients have HPV negative cancer) or oropharynx (about 60-80% of patient have HPV positive cancer).	☐	☐	
Presence of radiologically or clinically documented disease. All radiology studies must be performed within 28 days prior to registration.	☐	☐	
Any stage, considered candidates for surgery and planned for surgery either by robotic or by standard surgical technique.	☐	☐	
Documentation of HPV tested by PCR (resulted or pending)	☐	☐	
Willing to provide consent for an additional tissue biopsy for research purposes, to allow a part of their surgical tumor tissue to be utilized for research, (in case tumor tissue has not already been saved in the Tumor Tissue Bank), and to donate samples of blood and saliva collected before and after treatment	☐	☐	
All patients must have provided informed consent for correlative studies	☐	☐	
ECOG performance status of 0, 1, or 2	☐	☐	
Patients must have no prior exposure to immune-mediated therapy, including anti-CTLA-4, anti-PD-1, anti–PD-L1, or anti–programmed cell death ligand 2 antibodies, excluding therapeutic anticancer vaccines.	☐	☐	
At least 1 lesion, not previously irradiated, that can be accurately measured at baseline as ≥10 mm in the longest diameter (except lymph nodes, which must have a short axis ≥15 mm) with CT or MRI or clinical measurement and that is suitable for accurate repeated measurements as per RECIST 1.1 guidelines.	☐	☐	
Previous surgery is permitted provided that a minimum of 28 days (4 weeks) have elapsed between any major surgery and date of registration, and that wound healing has occurred	☐	☐	
Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L	☐	☐	
Platelet count ≥ 100 x 10^9/L	☐	☐	
Hemoglobin ≥ 9.0 g/dL	☐	☐	

Serum bilirubin ≤ 1.5 x ULN (institutional upper limit of normal) Total Bilirubin is less than or equal to ULN, except the case in which the elevated total bilirubin is not a sign of liver disease, such as the Gilbert Syndrome, in which case a Total Bilirubin less than or equal to 2X ULN is acceptable.	☐	☐	
AST and ALT ≤ 2.5 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: Creatinine CL (mL/min) = $\frac{\text{Weight (kg) x (140 – Age)}}{\text{72 x serum creatinine (mg/dL)}}$ Females: Creatinine CL (mL/min) = $\frac{\text{Weight (kg) x (140 – Age)}}{\text{72 x serum creatinine (mg/dL)}}$ x 0.85	☐	☐	
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	☐	☐	
In accordance with NCIC CTG policy, protocol treatment is to begin within 2 working days of patient registration	☐	☐	
Written informed consent and any locally-required authorization (e.g., HIPAA in the USA, EU Data Privacy Directive in the EU) obtained from the subject prior to performing any protocol-related procedures, including screening evaluations	☐	☐	
Age ≥ 18 years at time of study entry	☐	☐	
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	☐	☐	

Exclusion Criteria (as outlined in study protocol)	Criteria NOT present	Criteria is present	Source Used to Confirm * (Please document dates and lab results)
Involvement in the planning and/or conduct of the study (applies to both AstraZeneca staff and/or staff at the study site). Previous enrolment in the present study	☐	☐	
Participation in another clinical study with an investigational product during the last 6 mo	☐	☐	
Any previous treatment with a PD1 or PD-L1 inhibitor, including Durvalumab	☐	☐	
Receipt of any anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) within the last 6 months before the first dose of Durvalumab	☐	☐	
Mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction	☐	☐	
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	☐	☐	
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)	☐	☐	
Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1	☐	☐	
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	☐	☐	
Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis)	☐	☐	
History of primary immunodeficiency	☐	☐	
History of allogeneic organ transplant	☐	☐	
History of hypersensitivity to Durvalumab or any excipient	☐	☐	
History of pneumonitis or interstitial lung disease	☐	☐	
Subjects with uncontrolled seizures	☐	☐	
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, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent	☐	☐	
Known history of previous clinical diagnosis of tuberculosis	☐	☐	

Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving Durvalumab	☐	☐	
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	☐	☐	
Patients with body weight <30 kg	☐	☐	
Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

WISER Assigned PID: _____

Signature of research professional confirming eligibility:_____ Date: _____

Signature of Treating Physician**: _____ Date: _____

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix 4 – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: First Name:

_____ _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy) __ __ / __ __ /___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic
☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN
☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis:

_____

Date of Diagnosis: ___ ___ /___ ___/___

___

Performance Status: ___ ___ ___ ☐ ECOG ☐ Karnofsky

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO
(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by WISER): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling 336-713-6767 between 8:30 AM and 4:00 PM, Monday – Friday.

Completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at 336-7136772 or registra@wakehealth.edu.

Appendix 5 – Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:
   - ☐ Hispanic or Latino/a
   - ☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.
   - ☐ White or Caucasian
   - ☐ Black or African American
   - ☐ American Indian or Alaskan Native
   - ☐ Asian
   - ☐ Native Hawaiian or Other Pacific Islander
   - ☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?

☐ **Yes** ☐ **No**

Was a discrepancy found? ☐ **Yes** ☐ **No**

If yes, please provide what is currently indicated in the EMR:

Ethnicity: _____ Race: _____

Additional comments: _____

_____

_____

Appendix 6 – Mandatory DSMC SAE Reporting Guidelines

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	Date: 02/11/2021

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.
   There are three types of trials that are included in this category:

   a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these

AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization > 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC to the using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).

2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console inWISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.
3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either “Unrelated”, “Unlikely”, “Possibly”, “Probably”, or “Definitely”. Always include the following here:
    i. DSMC clinician name, date/time contacted and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail

d. Comments
e. Grade/Severity
f. Unexpected Y/N
g. DLT Y/N
h. Attributions
i. Action
j. Therapy
k. Click ADD to attach the AE Detail to the SAE.

14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the DSMC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars

Glenn Lesser, MD – Hematology Oncology
Mercedes Porosnicu, MD-- Hematology Oncology
Ryan Hughes, MD – Radiation Oncology
Michael Goodman, MD -- Hematology Oncology
Daniel Reed, MD -- Hematology Oncology
Mary Beth Seegars, MD -- Hematology Oncology

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate suspension of enrollment should be considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

Acronyms

AE – Adverse Event

DSMC-Data and Safety Monitoring Committee

SAE-Serious Adverse Event

WFBCCC – Wake Forest Baptist Comprehensive Cancer Center

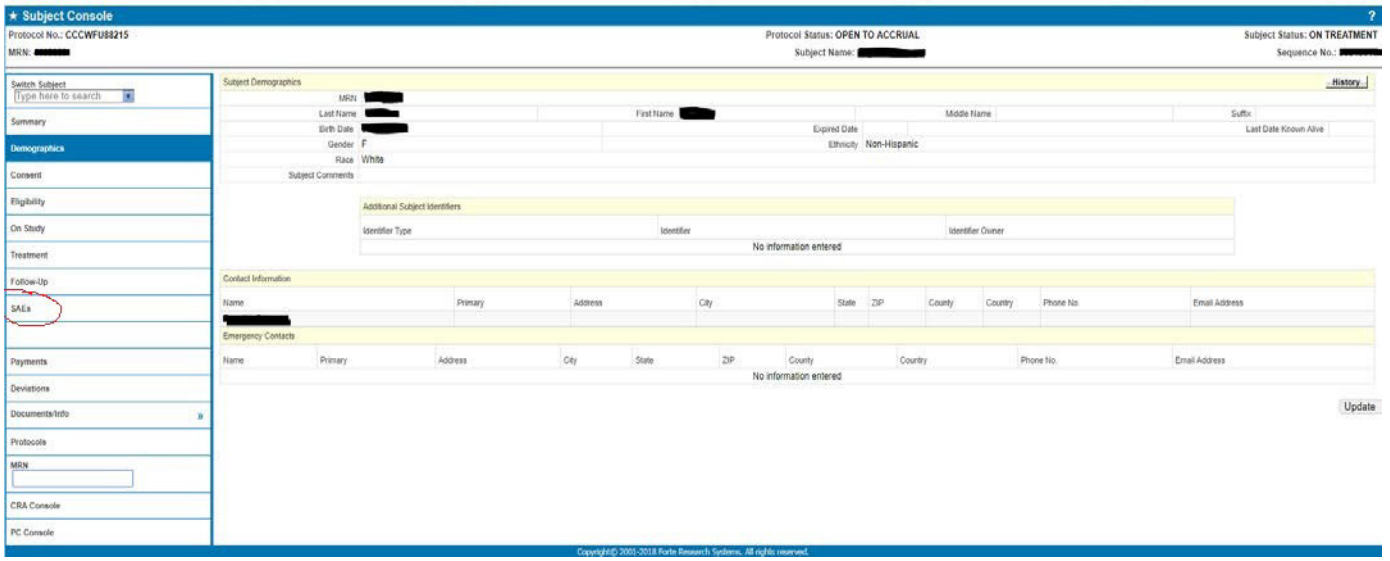
NCI-National Cancer Institute

WISER –Wake Integrated Solution for Enterprise Research

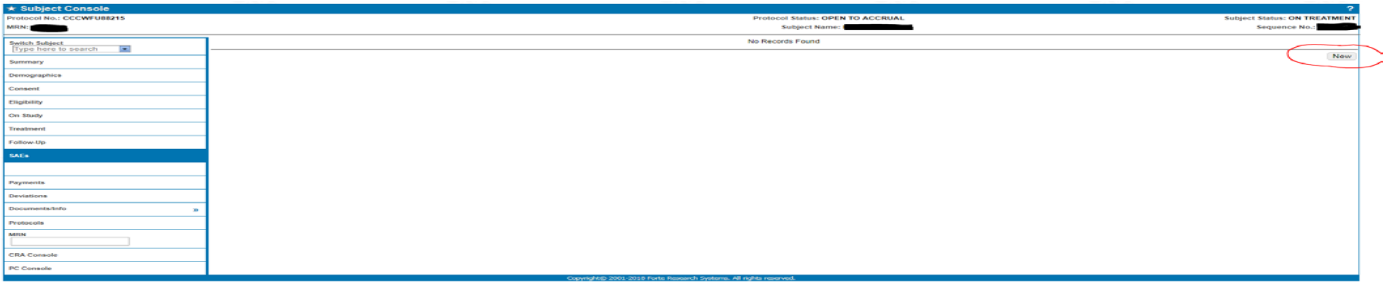
Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

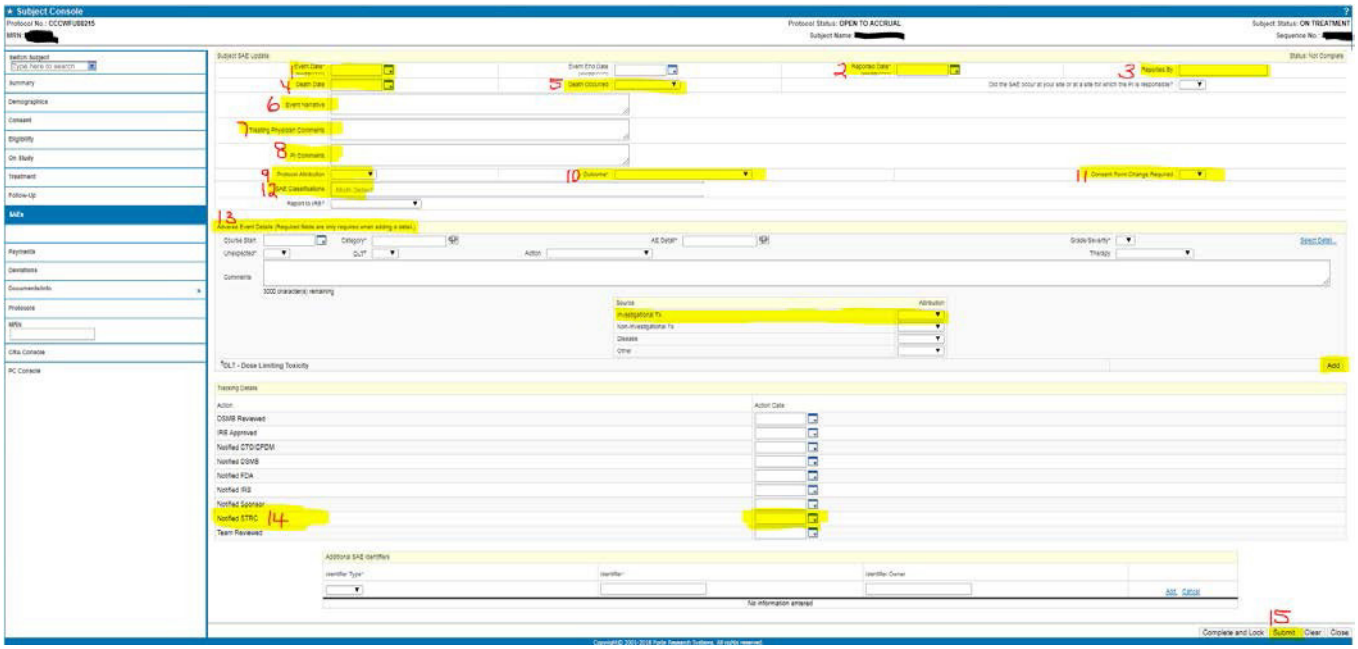
Screen Shot 1:



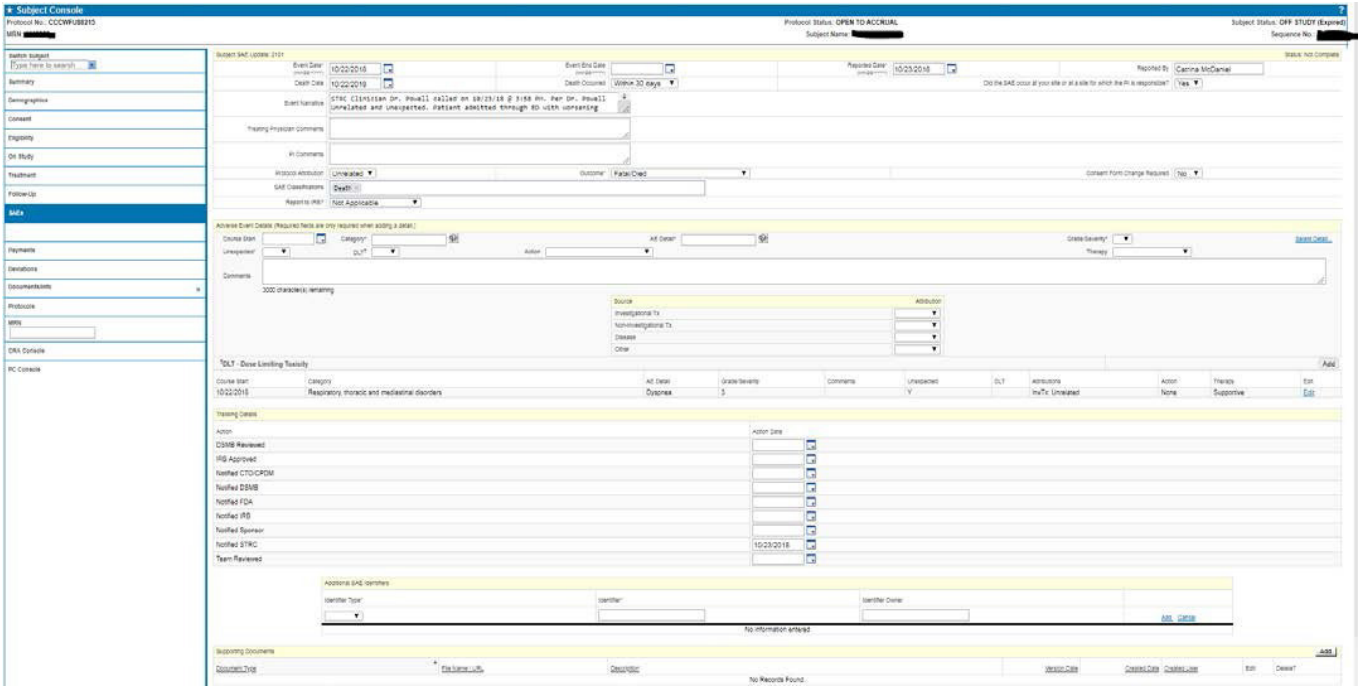
Screen Shot 2:



Screen Shot 3:



Screen Shot 4:



APPENDIX 7 – ADVERSE EVENT LOG

CCCWFU60116 ADVERSE EVENT (AE) LOG

PI: _____ **PID: _____** **MRN: _____**

Cycle Start Date: _____ **Cycle End Date: _____** **Cycle #:_____**

Adverse Event CTC Term	**Value** (-5 if nonnumeric)	**Grade** (0-5) per CTC	**Start Date**	**Attribution** 1=Related 2=Probably 3=Possible 4=Unlikely 5=Unrelated	**Treating MD Initials/Date**	**End Date**	**Expected** 1=Yes 0=No	**Serious Adverse Event (SAE)** 1=Yes 0=No	**Dose Limiting Toxitity (DLT)** 1=Yes 0=No	**Action Taken** 1=None 2=Tx withheld 3=Tx D/C 4=Tx adj. 5=Other	**Reportable** (1-IRB 2-DSMC, 3-FDA 4-Sponsor)
Nausea											
Vomiting											
Diarrhea											
Skin erythema											
alopecia											
esophagitis											
myelosuppression											
Urinary urgency											
Urinary frequency											
pneumonitis											

Serious Adverse Event: Hospitalization; Disability; Birth Defect; Life-threatening; Death.

CTCAE Version 4 - http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf