A Phase 2, Open-Label Study to Evaluate Efficacy of Combination Treatment with MEDI0457 (INO-3112) and Durvalumab (MEDI4736) in Patients with Recurrent/Metastatic Human Papilloma Virus Associated Cancers

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LIST OF ABBREVIATIONS

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

Abbreviation or special term	Explanation
AChE	Acetylcholinesterase
ADA	Anti-Drug Antibody
ADL	Activities of Daily Living
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
Anti PCP	Anti-Pneumocystis Pneumonia
Anti-PD-1	Anti-Programmed Cell Death Protein 1
Anti-PD-L1	Anti-Programmed Death Ligand 1
APTT	Activated Partial Thromboplastin Time
AST	Aspartate Aminotransferase
β-HCG	Beta-Human Chorionic Gonadotropin
CPK	Creatine Phosphokinase
CR	Complete Response
CRF	Case Report Form (electronic)

Abbreviation or special term	Explanation
CT	Computed Tomography
CTC	Common Terminology Criteria
CTCAE	Common Terminology Criteria for Adverse Event
CV	Cardiovascular
DCR	Disease Control Rate
DCR-16w	Disease Control Rate at 16 weeks
DCR-24w	Disease Control Rate at 24 weeks
DILI	Drug Induced Liver Injury
DLT	Dose-Limiting Toxicity
EC	Ethics Committee, synonymous to Institutional Review Board (IRB) and Independent Ethics Committee (IEC)
ECG	Electrocardiogram
ECOG	Eastern Cooperative Oncology Group
ELISPOT	Enzyme-Linked Immunosorbent Spot
EOS	End of Study
EOT	End of Treatment
EP	Electroporation
FACS	Fluorescence Activated Cell Sorting
FDA	Food and Drug Administration
FDG	Fludeoxyglucose
GCP	Good Clinical Practice
GI	Gastrointestinal
GLP	Good Laboratory Practice
HBcAb	Hepatitis Virus B Core Antibody
HBsAg	Hepatitis Virus B Surface Antigen
HIV	Human Immunodeficiency Virus
HL	Hy's Law
HPV	Human Papilloma Virus
HPV-16	Human Papilloma Virus Type 16
HPV-18	Human Papilloma Virus Type 18
HR	Heart Rate
IATA	Airline Transportation Association
IB	Investigator's Brochure

Abbreviation or special term	Explanation
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IFN-γ	Interferon-Gamma
IHC	Immunohistochemistry
IgG	Immunoglobulin G
IgG1	Immunoglobulin G1
ILD	Interstitial Lung Disease
IM	Intramuscular
IND	Investigational New Drug
INR	International Normalized Ratio
IP	Investigational Product
irAE	Immune-Related Adverse Event
irRECIST	Immune-Related Response Evaluation Criteria in Solid Tumors
IV	Intravenous(ly)
IVIG	Intravenous Immunoglobulin
LD	Longest Diameter
LFT	Liver Function Test
LIMS	Laboratory Information Management System
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cell
PCR	Polymerase Chain Reaction
PD	Progressive Disease
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death Ligand 1
PET	Positron Emission Tomography
PFS	Progression Free Survival
PHL	Potential Hy's Law
PI	Principal Investigator

Abbreviation or special term	Explanation
PO	Oral(ly); by mouth
PR	Partial Response
PR interval	Interval on the electrocardiogram, from the start of the P wave to the start of the R wave
QRS interval	Interval on the electrocardiogram from the start of the Q wave to the end of the of the S wave
QT interval	Interval on the electrocardiogram, from the beginning of the QRS complex to the end of the T wave
QTcF interval	QT interval corrected for heart rate based on the Fridericia formula
RECIST	Response Evaluation Criteria in Solid Tumors
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SCCHN	Squamous Cell Carcinoma of the Head and Neck
SD	Stable Disease
T_3	Triiodothyronine
T_4	Thyroxine
TBL	Total Bilirubin
TIL	Tumor Infiltrating Lymphocytes
TNF	Tumor Necrosis Factor
TNF-α	Tumor Necrosis Factor-Alpha
TSH	Thyroid Stimulating Hormone
ULN	Upper Limit of Normal
WBDC	Web Based Data Capture
WHO	World Health Organization

1. INTRODUCTION

1.1. Background and Rationale for Conducting This Study

Virtually all cervical cancers, most oropharyngeal and anal cancers, and a major proportion of penile, vaginal, and vulvar cancers are attributable to oncogenic types of human papillomavirus (HPV). Collectively, these cancers account for approximately 50,000 new cases, > 10,000 deaths, and approximately $1 billion in treatment costs annually in the U.S. Cervical cancer is a leading cause of cancer death in women in most of the developing world (number 1 in most of Africa). Anal cancer incidence in the U.S. is significantly increasing in both men and women. Penile cancer, though rare in developed countries, accounts for up to 10% of cancers in men in parts of the developing world. Additionally, HIV-positive individuals, including those treated with highly active antiretroviral therapy (HAART), remain at heightened risk of HPV-associated malignancies. For all HPV-related cancers, standard therapy for local regional disease does not always work, and no effective or established therapy is available for metastatic disease or even most local-regional recurrences.

In these malignancies, the HPV viral oncoproteins, E6 and E7, are predominantly responsible for oncogenesis. E6 promotes degradation of p53, indirectly activates telomerase, and disrupts the function of the cellular phosphatase tumor suppressor PTPN13. E7 inactivates pRb and activates Mi2beta. Together, these oncogenic alterations result in the expression of p16, drive rapid cellular proliferation, suppress or down regulate key tumor suppressor proteins, and lead to cellular immortality. In addition, E6/E7 expression is required to maintain a malignant transformed phenotype (Scheffner et al 1990, Jabbar et al 2009).

While the currently available prophylactic HPV vaccines are highly effective in preventing infection by HPV types 16 and 18, these have no therapeutic effect, and therefore are of no value for patients already diagnosed with human papilloma virus type 16 (HPV-16) or human papilloma virus type 18 (HPV-18) positive malignancies. HPV-16 and/or HPV-18 is found in 70% of all cervical cancers (de Sanjose et al 2010), 65% of anal cancers (Bosch et al 1995), and 70% of penile cancers (Maden et al 1993).

1.2. Summary of Clinical Experience

1.2.1. MEDI0457 with electroporation

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

The clinical experience with VGX-3100 is obtained from two completed Phase 1 studies, HPV-001 and HPV-002, which enrolled 18 and 13 patients, respectively, and a completed Phase 2 study, HPV-003, which enrolled 167 patients. There have been no significant safety findings. There were very few treatment-related Grade 3 adverse events (AEs) and no related Grade 4 AEs or serious adverse events (SAEs) after 551 doses given to 185 patients in these trials.

Importantly, the safety profile of the DNA immunogen with electroporation (EP) remains consistently unremarkable in the 965 patients and more than 2500 doses in 23 different studies as

of January 15, 2016 (refer to the MEDI0457 Investigator's Brochure [IB] for additional information).

There is an ongoing clinical trial in more advanced cancer patients with HPV-16 and/or HPV-18 associated head and neck cancers. In this prospective Phase I/IIa trial (HPV-005 Study), adult patients with HPV-positive (assessed by p16) squamous cell carcinoma of the head and neck (SCCHN) were enrolled into two cohorts. In Cohort 1, patients received MEDI0457 pre- and post-surgery. In Cohort 2, patients received MEDI0457 after the completion of cisplatin based chemoradiation. MEDI0457 (6 mg of VGX-3100 plus 1 mg of INO-9012) was delivered intramuscularly followed by EP with the CELLECTRA®5P device, once every 3 weeks for a total of four doses. Patients were followed for 2 years. As of December 2015, 20 patients had been enrolled and all patients have received four doses of MEDI0457, i.e., six Cohort 1 patients, and 14 Cohort 2 patients. MEDI0457 was well tolerated with no treatment-related Grade 3 AE, and no Grade 4 or higher AEs reported. The most frequent AE was injection site pain (n=14), all of which were Grade 1. Two patients had Grade 3 lymphopenia at baseline and no worsening during the trial. Three unrelated SAEs have been reported in the trial; Grade 2 post-surgical procedure hemorrhage, a Grade 3 acute non-traumatic kidney injury, and Grade 3 dyspnea due to neck swelling. Among samples tested, as compared to baseline, 4 of 5 evaluable patients showed increased anti-HPV-16/HPV-18 E6/E7 antibody titers and 9 of 10 evaluable patients exhibited increased HPV-specific cellular responses by interferon-gamma (IFN-γ) enzyme-linked immunosorbent spot (ELISPOT) assay demonstrating a vaccine response. In addition, 7 of 8 evaluable patients had HPV-specific CD8+ T-cell activation concurrent with increased lytic proteins (granzymes and perforin) by flow cytometric analysis.

The application of EP via the CELLECTRA®5P device increases the expression of the E6 and E7 antigens and interleukin-12 encoded by MEDI0457. Electroporation utilizes a transmembrane electric field pulse to induce microscopic pathways (pores) in a bio-membrane. The electric field allows macromolecules, ions, and water to pass from one side of the membrane to the other.

In a small (10 healthy volunteers) pilot study, pain was evaluated immediately, 5, 15, 30 minutes and 1 hour after EP with the CELLECTRA®5P device (Diehl et al 2013). Patients used a Visual Analog Scale questionnaire, 10 cm in length, anchored by word descriptors at each end, "No Pain" and "Worst Pain", to mark their pain related to the treatment. Patients reported a mean (±standard error of measurement) score of 6.3 (±0.7) immediately after treatment and 2.8 (±0.5) approximately 5 minutes after the procedure. These data showed that the pain associated with EP was brief and diminished quickly (Diehl et al 2013).

1.2.2. Durvalumab

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

As of the data cut-off (DCO) date (12 July 2016), an estimated 5225 patients have been exposed to 1 or more doses of durvalumab in AstraZeneca or MedImmune sponsored studies, either as monotherapy or in combination, including 2878 patients in open label trials, and 2347 patients as an estimate based on the randomization scheme in studies where the treatment arm is blinded. Additionally, more than 1700 patients have been exposed to 1 or more doses of durvalumab in externally-sponsored/investigator-initiated clinical trials (ESR/IITs). Please refer to the durvalumab IB for detailed data.

Safety data have been pooled for 4 durvalumab monotherapy studies (CD-ON-MEDI4736- 1108, D4190C00002, ATLANTIC and D4193C00001 [HAWK]) for patients who received a durvalumab dose of 10 mg/kg Q2W; a total of 1645 patients are included in this pooled data set.

- Overall, AEs reported in ≥10% of patients were fatigue (31.1%), decreased appetite (22.5%), nausea (20.5%), dyspnea (17.9%), constipation (17.8%), cough (17.4%), diarrhea (16.0%), anemia (15.3%), pyrexia (15.0%), vomiting (13.4%), back pain (12.5%), pruritus (11.0%), arthralgia (10.6%) and abdominal pain (10.2%).
- AEs that were considered by the investigator as related to durvalumab in ≥5% of patients were fatigue (14.5%); nausea (7.3%); diarrhea (6.9%); hypothyroidism (6.6%); pruritus (6.4%); decreased appetite (6.0%) and rash (5.2%).
- A total of 820 patients (49.8%) reported AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher: of these, 487 patients (29.6%) had events of Grade 3, 63 patients (3.8%) had events of Grade 4 and 270 patients (16.4%) had Grade 5 (fatal) events. AEs of Grade 3 or higher considered related to durvalumab were reported in 164 patients (10.0%): of these, 144 patients (8.8%) had events of Grade 3, 12 patients (0.7%) had events of Grade 4 and 8 patients (0.5%) had Grade 5 (fatal) events.
- Grade 3 events occurring in ≥1% of patients were: anemia (5.5%); dyspnea (4.4%); hyponatremia (4.1%); fatigue (2.9%); gamma-glutamyltransferase (GGT) increased (2.7%); abdominal pain (2.0%); decreased appetite and back pain (1.9% each); pneumonia (1.8%); aspartate aminotransferase (AST) increased and dehydration (1.6% each); hypertension (1.3%); blood alkaline phosphatase (ALP) increased, hypokalemia, urinary tract infection and vomiting (1.2% each); alanine aminotransferase (ALT) increased and pleural effusion (1.1% each); bilirubin increased, asthenia, nausea and pulmonary embolism (1.0% each). Grade 3 events considered related to durvalumab occurring in ≥0.5% patients were fatigue (1.2%), GGT increased (0.8%) and AST increased (0.6%).
- The most commonly reported Grade 4 event was sepsis (15 patients [0.9%]). Other commonly reported Grade 4 events were: GGT increased (9 patients [0.5%]); dyspnea, hypercalcemia and respiratory failure (7 patients each [0.4%]) and pneumonia (5 patients [0.3%]). All other Grade 4 events were reported in less than 5 patients each. Grade 4 events considered related to durvalumab occurring in ≥2 patients were GGT increased and pneumonitis (0.1% each).
- Grade 5 events occurred in the system organ class (SOC) of ‘neoplasms benign, malignant and unspecified (including cysts and polyps)’ for 172 of the 270 patients with Grade 5 events (63.7%), with the highest number of events occurring for NSCLC (40 patients). Amongst the other SOCs, the most common Grade 5 events were general physical health deterioration (12 patients), respiratory failure (8 patients); Grade 5 events of pneumonia

and sepsis occurred in 5 patients each with the remainder of the Grade 5 events occurring in ≤4 patients for each event. The only Grade 5 event considered related to durvalumab occurring in ≥2 patients was pneumonitis (0.1%).

- A total of 134 patients (8.1%) discontinued from study treatment due to an AE. The most common events leading to treatment discontinuation were: general physical health deterioration (10 patients); pneumonitis (7 patients); pneumonia (6 patients); dyspnea and NSCLC (5 patients each); all other discontinuation events occurred in ≤4 patients.
- A total of 89 patients (5.4%) had serious treatment-emergent AEs (TEAEs) that were considered by the investigator as related to durvalumab. The most common were: pneumonitis (12 patients [0.7%]); fatigue (5 patients [0.3%]); colitis, infusion related reaction and ILD (4 patients each [0.2%]); dehydration, diarrhea, nausea and nervous system disorder (3 patients each [0.2%]); abdominal pain, acute kidney injury, adrenal insufficiency, AST increased, bilirubin increased, dyspnea, hepatic function abnormal, nephritis, transaminases increased, tumor hemorrhage and vomiting (2 patients each [0.1%]).

A total of 854 patients (51.9%) experienced an adverse event of special interest (AESI) during the study. The most common grouped term AESI was diarrhea (263 patients [16.0%]; of whom 12 patients [0.7%] had events of Grade ≥3). Other common AESIs (grouped term) were: selected hepatic events (248 patients [15.1%]; of whom 113 patients [6.9%] had events of Grade ≥3); dermatitis (237 patients [14.4%]; of whom 3 patients [0.2%] had events of Grade ≥3); rash (199 patients [12.1%]; of whom 7 patients [0.4%] had events of Grade ≥3); hypothyroidism (170 patients [10.3%]; of whom 2 patients [0.1%] had events of Grade ≥3); hyperthyroidism (93 patients [5.7%]; of whom 1 patient [<0.1%] had events of Grade ≥3); and select renal events (87 patients [5.3%]; of whom 16 patients [1.0%] had events of Grade ≥3). There were 6 patients who had AESIs of CTCAE Grade 5 (fatal events): three patients had hepatic events (autoimmune hepatitis; hepatic failure and hyperbilirubinemia); two patients had pneumonitis and 1 patient had immune thrombocytopenic purpura.

1.3. Rationale for Study Design, Doses and Control Groups

1.3.1. Rationale for the study

Although HPV associated cancers appear to have a better prognosis at diagnosis, recurrent/metastatic HPV-associated cervical, rectal, and penile cancers are largely incurable with very few therapeutic options. For women with cervical, anal, and penile cancers, recurrence rates can be as high as 40%. (Leijte et al 2008, Uronis et al 2007) For these cancers, current therapeutic options rarely achieve response rates >25% and 5-year survival after first recurrence is <5% for those patients not amenable to radical surgical resection or radiation salvage. There is a large unmet need for these patients with recurrent HPV-associated cancers.

As HPV-associated tumors by nature involve evasion of the immune system for malignant transformation from pre-invasive to invasive disease, immunotherapy combinations are an appealing strategy for these malignancies. Immune checkpoint inhibitors are currently under investigation in many HPV associated tumors. In anal cancer, results of a phase II study with nivolumab has recently been presented showing response rates of 24% including 2 complete responses (CRs) and an additional 46% of patients with stable disease (SD) for an overall clinical

benefit rate of 70%. (Morris et al 2016) The GOG/NRG recently completed a similar study of nivolumab in women with recurrent cervical cancer (GYN-002) although results are not yet known. Furthermore, as HPV-16 and/or HPV-18 subtypes are found in 70% of all cervical cancers, (deSanjose et al 2010) 65% of anal cancers, (Bosch et al 1995) and 70% of penile cancers, (Maden et al 1993) there is a strong rationale for combining an immune checkpoint inhibitor with a therapeutic HPV16/18 vaccine.

MEDI0457 (INO-3112) is a plasmid DNA vaccine consisting of three plasmids expressing HPV-16 and HPV-18 E6 and E7 proteins along with interleukin-12 as an adjuvant. pGX3001 plasmid (also called HPV-16 DNA) consists of 3782 DNA base pairs and the pGX3002 plasmid (also called HPV-18 DNA) consists of 3824 base pairs. pGX6001 (also called interleukin-12 DNA) plasmid is circular double-stranded DNA consisting of 6259 base pairs. The vaccine contains 3 mg of pGX3001, 3 mg of pGX3002, and 1 mg of pGX6001.

Interim data from the HPV-005 Phase I/IIa trial (HPV-005 Study) in patients with head and neck cancer showed that MEDI0457 was safe and associated with an immune response against the target antigens. There were increases in anti-HPV-16/HPV-18 E7 antibody titers and HPV-16/HPV-18 E6/E7-specific T-lymphocytes following the administration of MEDI0457 followed by EP (Aggarwal et al 2015).

The proposed study is designed to study MEDI0457 in combination with durvalumab (also known as MEDI4736) in patients with cancers associated with HPV-16 and/or HPV-18.

This combination is being studied for the first time in patients with HPV-16 and/or HPV-18 associated recurrent/metastatic cancers. Based on available scientific literature, including preliminary data and the non-redundant mechanism of action of each single agent, benefit is anticipated in this patient population. It is anticipated that MEDI0457 and durvalumab will additively or synergistically enhance T-lymphocyte activities against cancers associated with HPV-16 and/or HPV-18 and thereby enhance their respective clinical anti-tumor effects.

1.3.2. Rationale for endpoints

In this study of MEDI0457 and durvalumab in combination, efficacy (response rate) will be the primary endpoint. The secondary endpoints of immunogenicity, disease control rate (DCR), progression free survival (PFS) and overall survival (OS) will be used for deciding if further studies are warranted. Sample collection for pharmacokinetics analysis of durvalumab and for HPV-16/HPV-18 humoral and cellular immunogenicity testing will be done to inform further the safety and efficacy of combination treatment.

1.3.3. Rationale for doses selected

MEDI0457 (also known as INO-3112) at the proposed dose is being used in two ongoing studies (HPV-004 Study and HPV-005 Study) with >25 patients enrolled thus far. There is a larger clinical experience with VGX-3100, a key component of MEDI0457, with two completed Phase 1 studies that enrolled 18 and 13 patients respectively, and a completed Phase 2 study, which enrolled 169 patients in cervical intraepithelial neoplasm. There have been no significant safety findings. There were very few treatment-related Grade 3 AEs and no related Grade 4 AE's or SAEs after 551 doses given to 185 patients in these trials.

Importantly, the safety profile of the DNA immunogen with EP remains consistently unremarkable in >1000 patients and more than 2500 doses in 23 different studies as of April 06, 2016 (Refer to the MEDI0457 IB for additional information).

A total dose of 6 mg VGX-3100 DNA has been selected for this study based on the safety and immunogenicity data generated in the HPV-001 study, where 6 mg of DNA were delivered intramuscular (IM) followed by electroporation, which showed trends toward higher response rates and magnitudes of IFN-γ ELISpot responses in the high dose cohort compared to the low (0.6 mg) and mid- dose (2 mg) cohorts without significant safety issues (Bagarazzi et al., 2012).

This dose-trend was consistent with prior expectation, a feature of the finding that suggests it is a "real" effect rather than random variation. Adverse events from previous human studies with closely related DNA plasmid products have been limited to injection site pain from the injection and electroporation procedure. No unexpected or severe adverse events were observed in any of the three dose cohorts tested in Study HPV-001.

There were no significant safety findings in the 18 female subjects enrolled in HPV-001, the phase 1 study of VGX-3100, with only mild to moderate adverse events, injection site reactions and laboratory abnormalities which resolved without sequelae. All subjects returned home after at least 30 minutes observation in the study unit post injection/electroporation. CPK and ECGs were unremarkable post electroporation. Study participants judged the injection/ electroporation to be relatively painful (mean VAS score 6.2 immediately after and 2.8 approximately 5 minutes after EP) but transient, but did not preclude subsequent injection/ electroporation administration. There were no serious adverse events attributed to treatment in any of the subjects and there were no early discontinuations in the study. Thirteen women participated in HPV-002 in which a fourth dose (6 mg only) of VGX-3100 was evaluated and the safety findings were consistent with those observed in the parent study, HPV-001.

The IL-12 plasmid dose is based on previous experience in the HVTN-080 study, where 1 mg was co-administered with PENNVAX®-B followed by electroporation. HIV- specific CD4+ T cell responses were generated in ~81% of PENNVAX®-B + IL- 12 recipients after three vaccinations, compared to 44% with PENNVAX®-B alone. Delivery of PENNVAX®-B via electroporation also increased the frequency of CD8+ T cell responses. CD8+ responses were detected in 33% of PENNVAX®-B and 52% of PENNVAX®-B + IL-12 recipients after 3 vaccinations. Six months after the third vaccination 43% of individuals were still able to respond to HIV peptide pools. Overall, 89% of individuals vaccinated with PENNVAX®-B + IL-12 plasmid followed by electroporation developed either a CD4+ or CD8+ T-cell response after the third vaccination. No unexpected or severe adverse events were observed in HVTN-080 or earlier studies of IL-12 DNA delivered without electroporation.

In summary, a total of 7 mg VGX-3100 + INO-9012 DNA was selected for this study based on the safety and immunogenicity data generated in HPV-001, the follow-on study HPV-002, and HVTN-080.

Durvalumab (also known as MEDI4736) has an acceptable safety profile as detailed in Section 1.2.2 and the durvalumab IB. The 20 mg/kg (or its equivalent 1500 mg fixed dose) of durvalumab every 4 weeks has been tested in multiple studies and has been well tolerated.

1.3.3.1. Rationale for fixed dosing

A population PK model was developed for durvalumab using monotherapy data from a Phase I 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 the PK of durvalumab (coefficient of ≤ 0.5). The impact of body WT-based (10 mg/kg Q2W) and fixed dosing (750 mg Q2W) of durvalumab was evaluated by comparing predicted steady state PK concentrations (5th, median and 95th percentiles) using the population PK model. A fixed dose of 750 mg was selected to approximate 10 mg/kg (based on median body WT of ~75 kg). A total of 1000 subjects 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 (Wang et al 2009). In addition, they investigated 18 therapeutic proteins and peptides and showed that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters (Zhang et al 2012).

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar pharmacokinetic exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body WT of 75 kg, a fixed dose of 1500 mg Q4W durvalumab (equivalent to 20 mg/kg Q4W) is included in the current study.

1.3.4. Rationale for study population

Recurrent HPV-associated cancers not amenable to surgical resection or radiation salvage are largely incurable with short overall survivals after recurrence. There is a large unmet need for therapeutics for these patients. Anti-PD1/PDL1 checkpoint inhibitors have been shown to have good activity in HPV associated cancers (Morris et al 2016). Furthermore, HPV-16 and/or HPV-18 subtypes are found in 70% of all cervical cancers, (deSanjose et al 2010) 65% of anal cancers, (Bosch et al 1995) and 70% of penile cancers (Maden et al 1993). The combination of HPV vaccine with anti-PD-L1 antibody is expected to enhance HPV-specific T-lymphocyte responses, resulting in improved outcome for these patients.

1.4. Benefit/Risk and Ethical Assessment

1.4.1. Potential benefits - MEDI0457

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

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

1.4.2. Potential benefits - Durvalumab

The majority of the safety and efficacy data currently available for durvalumab are based on the first-time-in-human, single agent study (CD-ON-MEDI4736-1108) in patients with advanced solid tumors. Safety data are described in the current durvalumab IB. As of 12 July 2015, 456 of 694 patients with advanced solid tumors treated with durvalumab 10 mg/kg every two weeks 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 ORR, based on investigator assessment per Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1, ranged from 0% in uveal melanoma to 20.0% in bladder cancer, and DCR at 24 weeks (DCR-24w) ranged from 4.2% in triple negative breast cancer to 39.1% in advanced cutaneous melanoma. PD-L1 status was known for 383 of the 456 response evaluable patients. Across the PD-L1-positive tumors, ORR was highest (> 10%) for bladder cancer, advanced cutaneous melanoma, hepatocellular carcinoma (33.3% each), non-small cell lung cancer (26.7%), and SCCHN (18.2%). In the PD-L1-positive subset, DCR-24w was highest (> 10%) in advanced cutaneous melanoma (66.7%), non-small cell lung cancer (36.0%), hepatocellular carcinoma and bladder cancer (33.3% each), and SCCHN (18.2%). In the PD-L1-negative subset, ORR was 6.3% and DCR-24w was 25.3%. For further details, please refer to the durvalumab IB.

1.4.3. Potential benefits - DNA immunotherapy delivery with electroporation

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

1.4.4. Possible risks - MEDI0457 with electroporation

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

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

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

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

Interleukin-12 may cause autoimmune events. This is at least partially associated with its Th1-promoting activity, which could favor Th1-mediated immunopathology and, in particular, the induction of Th1-mediated autoimmune diseases (Adorini 1999). With our clinical experience in the HPV-005 Study, we have not observed any AEs that suggest autoimmune activity or autoimmune disorder in patients who have received a DNA vaccine treatment that contains INO-9012 (human interleukin-12 DNA plasmid). This may reflect the use of IL-12 as a local adjuvant in relatively low concentrations as opposed to the administration of systemic doses. The study team will continue to vigilantly monitor patients for any possible risk of autoimmune AEs during the trial.

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

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

1.4.5. Possible risks - Durvalumab

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

Immune-mediated reactions/immune-related AEs (irAEs) that are important risks include: dermatitis, hepatitis/hepatotoxicity, endocrinopathy (hypothyroidism, hyperthyroidism, hypophysitis, and adrenal insufficiency), neuropathy/neuromuscular toxicity, nephritis, pancreatitis (elevated lipase/amylase), pneumonitis, and colitis. Hypersensitivity and serious allergic reaction events include infusion-related reactions, anaphylaxis/serious allergic reactions, and immune complex disease. These events are managed based on established administration and

toxicity management guidelines for this entire class of therapeutics (see **Appendix D**, Postow 2015).

For further details, please refer to the durvalumab IB.

1.4.6. Possible risks and mitigations - MEDI0457 with electroporation + Durvalumab

Risks observed (administration site reactions) and anticipated (CPK elevations and autoimmune AEs [immunogenicity]) with the administration of MEDI0457 with EP are described in Section 1.4.4. Mitigations in place to reduce the adverse effects of MEDI0457 with EP administration include the following:

- rotation of injection sites,
- patients will be told to promptly report potential skin reactions and obtain visual assessment,
- protocol guidelines are in place for management and reporting of injection/administration site reactions,
- administration of MEDI0457 with EP will not occur in an extremity that contains a metal prosthesis or skin which is obscured with tattoos or having in the ipsilateral extremity of the chest an electronic defibrillator/pacemaker device
- monitoring of possible muscle damage by measurement of CPK testing,
- clinical manifestation and laboratory monitoring for immunogenicity, and
- persistent Common Terminology Criteria for Adverse Event (CTCAE) Grade 3 injection site reactions that exist for > 5 days.

Clinically significant risks associated with immune oncology drugs (immune-mediated reactions and their associated signs/symptoms, and risks due to immunogenicity) have been briefly discussed in Section 1.4.5. It is reasonable to assume there is a risk of additive or synergistic toxicities with this combination. Mitigations in place to detect and reduce the adverse effects of potential immune-mediated reactions include the following:

- eligibility criteria excluding certain auto-immune conditions present at baseline,
- baseline laboratory tests and monitoring per protocol,
- patients educated and instructed to notify the sites for any signs/symptoms that may represent an immune-mediated reaction,
- protocol guidelines for dose delay/withdrawal,
- physical examinations at each site visit, and
- enlisting investigators familiar with the latest immune oncology toxicities and management guidelines (**Appendix D**, Postow 2015).

Risks commonly associated with the administration of any foreign protein include immune complex disease, infusion reactions (durvalumab), and anaphylaxis and serious allergic reactions. Mitigations to monitor, detect, and treat these potential adverse effects are monitoring for the induction of anti-drug antibodies with signs/symptoms of immune complex disease and

monitoring of patients during and after administration of both investigational products (IPs) to detect and treat anaphylaxis/infusion reactions. Management criteria are in the protocol and in the appended immune oncology toxicity management guidelines (**Appendix D**, Postow 2015).

1.5. Research Hypotheses

- MEDI0457 treatment in combination with durvalumab will be safe in patients with recurrent/metastatic HPV-16 and/or HPV-18 associated cancers.
- MEDI0457 treatment in combination with durvalumab will have good anti-tumor activity as defined by response rate in patients with recurrent/metastatic HPV-16 and/or HPV-18 associated cancers.

1.6. Study Design

This study will be an open label, multi-cohort, phase II trial for the combination therapy of MEDI0457 (INO-3112) and Durvalumab (MEDI4736) in patients with HPV-16 and/or -18 related malignancies. This study will enroll 3 cohorts of patients with HPV-16/18 (+) tumors. The three cohorts are:

1. HPV-16/18 cervical cancer,
2. HPV-16/18 rare tumors (anal, penile, vulvar, vaginal), and
3. HIV (+) HPV-16/18 malignancies (any site).

Each cohort will have a two-stage design with predetermined stopping rules based on ORR after stage I and each cohort will function independently clinically. *After each cohort completes accrual to stage I, only the two cohorts with the most responses will move on to stage 2. Therefore, accrual to stage 2 will not start till all three cohorts have completed stage I. However, if a single cohort has a high response rate (≥4 responses out of 9 patients), the second stage of accrual may proceed prior to other cohorts completing stage I.*

At the onset of the study, only patients with cervical, vulvar, or vaginal cancers will be enrolled for the first 3 slots. Once all 3 of these patients have completed the first 6 weeks of treatment, enrollment will be opened to all included cancer histotypes.

Both MEDI0457 and durvalumab treatment will continue until confirmed disease progression or unacceptable toxicity. Either treatment may be stopped by the investigator if a SAE is deemed to be related to that treatment while the other treatment continues.

The target population consists of male or female patients 18 years of age or older with recurrent or metastatic HPV 16- or 18-associated cancers with persistent or progressive disease (PD) after initial standard-of-care treatment and lacking a curative treatment option.

Eligible patients must have at least one "measurable target lesion"—according to RECIST version 1.1—that has not been previously irradiated. In addition, if the primary lesion is not large enough for a biopsy without changing radiologic findings for following response, one additional lesion

that can be safely biopsied at screening and prior to the first dose of MEDI0457 at Week 1 will be required.

All patients will receive combination treatment with MEDI0457 and durvalumab as per the **Planned Dosing Schedule** (**Section 4.4.1**, **Figure 1**, and **Table 3**).

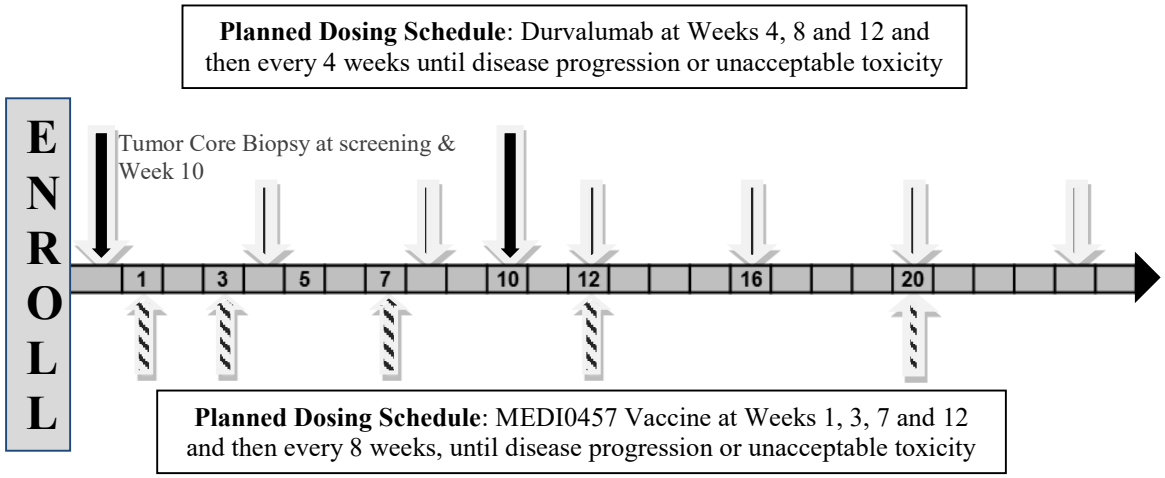


Figure 1. Overall Study Design Study Flow Chart

In the case that the first stopping boundary is crossed (**Section 8.1.3**), a **Revised Dosing Schedule** will be decided by the Principal Investigators, collaborators, supporters, and IND Office Medical Monitor and will be used for the remaining patients. Two options are to decrease the number of doses of vaccine given from a total of 3 to either 1 or 2 during the first 7 weeks and/or decrease dose of durvalumab to 750 mg Q4W. Other options may also be considered based on toxicity profile.

2. STUDY OBJECTIVES

2.1. Primary

To evaluate the anti-tumor activity of MEDI0457 in combination with durvalumab.

2.2. Secondary

The secondary objectives are as follows:

- To determine the safety profile of MEDI0457 in combination with durvalumab in patients with recurrent/metastatic HPV 16- or 18- associated cancer,
- To evaluate the PFS and OS of patients with recurrent/metastatic incurable HPV-16/18 positive solid malignancies receiving the combination of MEDI0457and durvalumab,

- To evaluate ORR by immune-related criteria of the combination of MEDI0457 and durvalumab in patients with recurrent/metastatic incurable HPV-16/18 positive solid malignancies, and
- To evaluate the disease control rate at 24 weeks.

2.3. Exploratory

The exploratory objectives are as follows:

- To determine the cellular and humoral immune response to immunotherapy with MEDI0457 in combination with durvalumab,
- To examine the correlation between anti-tumor activity and biomarkers including:
  - HPV-specific cellular and humoral responses
  - programmed death ligand 1 status
  - the number of tumor infiltrating lymphocytes
  - HPV 16/18 E6/E7 DNA levels and HPV 16/18 E6/E7 DNA sequence in biopsy tissue and plasma.
- To evaluate the pharmacokinetics and anti-drug antibodies (ADA) for durvalumab.

3. SUBJECT SELECTION AND PARTICIPATION

Each patient should meet all of the inclusion criteria and none of the exclusion criteria for this study.

Patients who fail to meet the eligibility criteria should not be enrolled or receive study medication. Patients who are enrolled but subsequently found not to meet all the eligibility criteria must not be initiated on treatment and must be withdrawn from the study.

Where a patient does not meet all the eligibility criteria but is incorrectly started on-treatment, the investigator should discuss with the supporting company and the IND sponsor (MDACC IND Office) to determine whether to continue or discontinue the patient from treatment.

3.1. Inclusion Criteria

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

1. Written informed consent in accordance with institutional guidelines.
2. Male and female patients age 18 years or older who are able and willing to comply with all study procedures.
3. For patients who are not HIV positive, cervical, anal, penile, vulvar, or vaginal cancer positive for HPV-16 and/or HPV-18 by the institutionally approved assay. For patients who are HIV positive, histologically or cytologically confirmed diagnosis of cancer at any site that is positive for HPV-16 and/or HPV-18 by the institutionally approved assay. Tumors may be positive for more than 1 HPV subtype as long as HPV-16 and/or HPV-18

is present. Note: For the first 3 patients, only cervical, vulvar, or vaginal cancers will be enrolled.

4. Patients with cancer that is refractory to standard therapy, that have either relapsed after standard therapy or has no standard therapy that increases survival by at least three months, and/or that are not curable by salvage approaches including resection and/or re-irradiation.
5. Has measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded) with a minimum size of 10 mm by computed tomography (CT) scan, except lymph nodes which must have minimum short axis size of 15 mm (CT scan slice thickness no greater than 5 mm in both cases). Indicator lesions must not have been previously treated with surgery, radiation therapy, or radiofrequency ablation unless there is documented RECIST v1.1 progression in the lesion after such therapy.
6. All patients must consent to pre-treatment biopsy of the tumor if it can be done safely (as judged by the investigator) during screening. Week 10 on-treatment biopsies will be required for a minimum 10 patients. After 10 paired biopsies have been obtained then Week 10 on-treatment biopsy will be made optional.
7. World Health Organization (WHO)/Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1.
8. Adequate organ and bone marrow function within 28 days of Day 0. Criteria "a" to "c" cannot be met with recent (within 28 days of screening test except as noted below) blood transfusions or require ongoing growth factor support:
    a. Hemoglobin ≥ 9 g/dL (**Note:** No Transfusion within 7 days of beginning study treatment. Ongoing growth factor support is acceptable if on a stable dose for the past 56 days.),
    b. Absolute neutrophil count ≥ 1,000/mm^3,
    c. Platelet count ≥ 100,000/mm^3 and no transfusion in prior 4 weeks,
    d. Total bilirubin (TBL) ≤ 1.5 × upper limit of normal (ULN) except patients with documented Gilbert's syndrome (> 3 × ULN),
    e. Alanine aminotransferase (ALT) and aspartate aminotransferase (AST) ≤ 3 × ULN,
    f. Serum creatinine ≤ 2.0 mg/dL or creatinine clearance ≥ 40 mL/min (measured or calculated according to the method of Cockcroft and Gault), and
    g. For HIV+ patients: Documented HIV-1 infection with CD4 count > 200 cells/mm3 and viral load < 75 copies/mL.

3.2. Exclusion Criteria

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

1. Any concurrent chemotherapy, IP, biologic, or hormonal therapy for cancer treatment; receipt of any investigational or approved anticancer therapy (chemotherapy, targeted

therapy, biologic therapy, monoclonal antibodies, etc.) within 21 days or 5 half-lives, whichever is shorter, prior to the first dose of MEDI0457; concurrent enrollment in another clinical study, unless it is an observational (non-interventional) clinical study or during the follow-up period of an interventional study.

2. Major surgical procedure or significant traumatic injury within 28 days before the first dose of study drug or anticipation of the need for major surgery during the course of study treatment.
3. Any unresolved toxicity (National Cancer Institute Common Terminology Criteria for Adverse Event [CTCAE] version 4.03 [v4.03]) Grade 2 or greater from previous anticancer therapy with the exception of alopecia, and the laboratory values defined in the inclusion criterion 8. Hearing loss of Grade 3 or lower and peripheral neuropathy of Grade 2 or lower is allowed. Subjects with Grade ≥ 2 neuropathy will be evaluated on a case-by-case basis after consultation with the Study Physician. Subjects with irreversible toxicity not reasonably expected to be exacerbated by treatment with durvalumab may be included only after consultation with the Study Physician.
4. Current or prior use of immunosuppressive medication within 14 days prior to first study dose, with the exception of intranasal and inhaled corticosteroids or systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or equivalent. Steroids as premedication for hypersensitivity reactions due to radiographic contrast agents are allowed.
5. Patients requiring therapeutic anticoagulation and irreversible platelet inhibitors (e.g. clopidogrel, prasugrel, or ticagrelor). Low dose aspirin for cardiac prophylaxis is allowed.
6. History of primary immunodeficiency.
7. Patients who have had prior exposure to immune-mediated therapy, including but not limited to prior exposure to T-cell and natural killer cell directed therapy, anti-PD-1, anti-PD-L1, anti-CD137, and anti-CTLA4.
8. History of allogeneic organ transplantation.
9. Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g. colitis, ulcerative colitis or Crohn's disease], diverticulitis [with the exception of diverticulosis], systemic lupus erythematosus, Sarcoidosis syndrome, or Wegener syndrome [granulomatosis with polyangiitis, Graves' disease, rheumatoid arthritis, hypophysitis, uveitis, etc.]). The following are exceptions to this criterion:

    - Patients with vitiligo or alopecia,
    - Patients with hypothyroidism (e.g. following Hashimoto syndrome) stable on hormone replacement,
    - Any chronic skin condition that does not require systemic therapy,
    - Patients without active disease in the last 5 years may be included but only after consultation with the study physician, and
    - Patients with celiac disease controlled by diet alone.

10. Uncontrolled intercurrent illness, including, but not limited to, ongoing or active infection, uncontrolled hypertension, interstitial lung disease, serious chronic gastrointestinal conditions associated with diarrhea, or psychiatric illness/social situations that would limit compliance with study requirement, substantially increase risk of incurring AEs, or compromise the ability of the patient to give written informed consent.
11. Patients with spinal cord compression or a history of leptomeningeal carcinomatosis. At the time of Day 1 of the study, patients with central nervous system metastases must have been treated and must be asymptomatic and meet the following criteria.
    - No concurrent treatment, inclusive of, but not limited to, surgery, radiation, and/or corticosteroids. **Note:** patients are allowed on systemic steroids as detailed in Exclusion Criterion 4 unless these are being administered to manage central nervous system metastases.
    - Neurologic stability (lack of signs or symptoms greater than baseline prior to radiotherapy) until the time of dosing of MEDI0457.
    - For radiation treatment, patients must be:
        i. At least 14 days between last day of stereotactic radiosurgery or gamma-knife treatment and Day 1 of protocol treatment,
        ii. At least 28 days between last day of whole brain radiation therapy and Day 1 of protocol treatment, and/or
        iii. At least 14 days since last dose of corticosteroids and Day 1 of protocol treatment.
12. Patients with cardiovascular (CV) disease conditions including New York Heart Association Class 3 or 4 congestive heart failure, unstable angina pectoris, or clinically important cardiac arrhythmias OR a recent (< 3 months) CV event, including myocardial infarction, unstable angina pectoris, or stroke.
13. Mean QT interval corrected for heart rate (QTc) ≥ 470 ms calculated from ECG using Fridericia's Correction by manual read.
14. Active tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and tuberculosis testing in line with local practice) infection.
15. Presence of acute or chronic hepatitis B (HBV) or active hepatitis C (HCV). Patients with a past or resolved HBV infection (defined as the presence of hepatitis B core antibody [anti-HBc] and absence of HBsAg) are eligible. Patients positive for HCV antibody are eligible only if polymerase chain reaction is negative for HCV RNA.
16. Receipt of live, attenuated vaccine within 30 days prior to the first dose of MEDI0457. **Note:** Patients, if enrolled, should not receive live vaccine during the study and up to 30 days after the last dose of IP.
17. Other untreated coexisting HIV related malignancies.
18. History of another primary malignancy except for:

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

19. Pregnant or breastfeeding female patients.
20. Known allergy or hypersensitivity to study treatment or any of the study drugs excipients.
21. Any medical condition that, in the opinion of the investigator, would interfere with evaluation of the study treatment or interpretation of patient safety or study results.
22. Patients with active or prior digestive tract bleeding.
23. Patients with uncontrolled seizures.
24. Fewer than two acceptable sites exist for IM injection and EP between the deltoid and lateral quadriceps muscles. **Note:** A site for injection/EP is not acceptable if there are tattoos or scars within 2 cm of the proposed injection/EP site or if there is implanted metal within the same limb. Any device implanted in the chest (e.g. cardiac pacemaker or defibrillator) excludes the use of the deltoid muscle on the same side of the body.
25. Patients who are unable to provide informed consent, are incarcerated, or are unable to follow protocol requirements.

3.3. Patient Instructions

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

Patients will be offered medications to manage anxiety and pain due to the EP procedure by the investigator (see Section 4.4.3).

3.3.1. Concomitant Medications

3.3.1.1. Allowed

Concomitant medications which are allowed while participating on this trial are listed in **Table 1**.

Table 1. Supportive Medications

Supportive medication/class of drug:	**Usage:**
Concomitant medications or treatments (e.g. acetaminophen or diphenhydramine) deemed necessary 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 [including palliative radiotherapy to non-target lesions, etc.])	Should be used, when necessary, for all subjects
Inactivated viruses, such as those in the influenza vaccine	Permitted
Highly active antiretroviral therapy (HAART)	Patient remains stable on current HAART (Highly active antiretroviral therapy) while on study. Viral load<75 copies/mL. CD4 counts ≥ 200 criteria at all times. Obtain routine outpatient ID consult for management of HIV prior to commencing study.

3.3.1.2. Prohibited

The following medications are considered exclusionary during the study, andexceptions to the exclusion are included. The MDACC IND Office must be notified if a patient receives any of these during the study.

1. Any concurrent chemotherapy, radiotherapy, immunotherapy, IP, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormones for non-cancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable. Local treatment of isolated lesions, excluding target lesions, for palliative intent is acceptable (e.g., by local surgery or radiotherapy).
2. Immunosuppressive medications including, but not limited to, systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-alpha (TNF-α) blockers. Use of immunosuppressive medications for the management of IP-related AEs, or in subjects with contrast allergies is acceptable). In addition, use of inhaled, topical, and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications after discussion with the medical monitor (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).
3. Use of anticoagulants and irreversible platelet inhibitors (e.g. clopidogrel, prasugrel, ticagrelor etc.) are not allowed. Low dose aspirin for cardiac prophylaxis is allowed.
4. Drugs with laxative properties and herbal or natural remedies for constipation should be used with caution through 90 days after the last dose of durvalumab during the study.
5. Sunitinib should not be given concomitantly or through 90 days after the last dose of durvalumab (acute renal failure has been reported with combination therapy of durvalumab and sunitinib).
6. Live attenuated vaccines should not be given through 30 days after the last dose of IP (including SoC)

3.3.2. Contraception

Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective methods of effective contraception (**Table 2**) from the time of screening and must agree to continue using such precautions for 90 days after the last dose of IP. Cessation of birth control after this point should be discussed with a responsible physician.

Females subjects of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal. Women will be considered post-menopausal if they have been amenorrheic for 12 months without an alternative medical cause. The following age-specific requirements apply:

- Women > 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of exogenous hormonal treatments and if they have luteinizing hormone and follicle-stimulating hormone levels in the post-menopausal range for the institution or underwent surgical sterilization (bilateral oophorectomy or hysterectomy).
- Women ≤ 50 years of age would be considered post-menopausal if they have been amenorrheic for 12 months or more following cessation of all exogenous hormonal treatments, had radiation-induced menopause with last menses >6 months ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

A highly effective method of contraception is defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly. Highly effective methods of contraception are presented in **Table 2.**

Table 2. Effective Methods of Contraception

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

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

Non-sterilized male patients who are sexually active with a female partner of childbearing potential must use a condom with spermicide from screening to 90 days after the final dose of IP.

3.3.3. Blood donation

Subjects should not donate blood while participating in this study until 90 days after the last dose of IP.

3.4. Discontinuation of Investigational Product

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

- Initiation of subsequent anticancer therapy including another investigational agent.
- Confirmed PD: the initial assessment of PD by RECIST v1.1 (baseline PD assessment) will be confirmed by a repeat evaluation at the next tumor assessment time point, but no sooner than 4 weeks later. If any tumor assessment time point (beyond the first PD assessment) shows ≥ 20% increase in the overall tumor burden (the sum of diameters of target lesions and new lesions), when compared to the baseline PD assessment (the sum of diameters of target lesions and new lesions), the patient would be deemed as having confirmed PD and must be discontinued.
- An AE that, in the opinion of the Investigator, supporting company, or the MDACC IND Office, contraindicates further dosing.
- Patient experienced a DLT as defined in Section 6.7.2.
- Withdrawal of consent from further treatment with IP or lost to follow-up.

- Patient is determined to have met one or more of the exclusion criteria or failed to meet all of the inclusion criteria for study participation and continuing to receive IP might constitute a safety risk.
- Pregnancy or intent to become pregnant.
- Non-compliance with the study protocol that, in the opinion of the Investigator, supporting company, or the MDACC IND Office, warrants withdrawal from treatment with IP (e.g., refusal to adhere to scheduled visits).
- The treating Physician determines it is not in the best interest of the patient to continue.

At any time, patients are free to discontinue IP or withdraw from the study (i.e., IP and assessments) without prejudice to further treatment. If a patient is withdrawn from study, see Section 3.5.2.

3.5. Criteria for Withdrawal

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

If a patient discontinues or is withdrawn at any time after initiation of study treatment, the investigator should make every effort to have the patient complete all assessments designated for the follow-up visit. The investigator will make every effort to have all scheduled assessment blood samples collected as indicated in **Table 3**. Any AEs present at the time of discontinuation/withdrawal should be followed in accordance with the safety requirements outlined in Section 7.

Patients who discontinue study treatment will be followed for: (1) up to 90 days after last study treatment with durvalumab and/or MEDI0457; (2) until AE/SAE resolution or an outcome is reached for all events (see Section 7.4.2); or (3) until patient initiates alternative anticancer therapy. Patients who leave the study because of a serious or significant safety issues should be followed closely until the AEs are fully and permanently resolved or stabilized (if complete resolution is not anticipated), with the follow-up data recorded in the database (see Section 7.4.2 for further details regarding the follow-up of unresolved AEs).

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

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

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

- Adverse Event: Clinical or laboratory events occurred that, in the medical judgment of the investigator for the best interest of the patient, are grounds for discontinuation. This includes serious and non-serious AEs regardless of relation to study treatment.

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

3.5.1. Screen failures

Screen failures are patients who do not fulfill the eligibility criteria for the study, and therefore must not be enrolled into the study. These patients should have the reason the patient does not meet the required inclusion/exclusion criteria for study withdrawal recorded. This reason for study withdrawal is only valid for screen failures.

3.5.2. Withdrawal of the informed consent

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

A patient who withdraws consent should always be asked about the reason(s) and the presence of any AE. The investigator should follow-up AEs outside of the clinical study. If possible, they will be seen and assessed by an investigator(s), and AEs will continue to be followed (see Section 7).

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

4. INVESTIGATIONAL PRODUCTS

4.1. Identity of Investigational Products

4.1.1. MEDI0457

MEDI0457 is a plasmid DNA vaccine consisting of three plasmids as a 3:3:1 (w/w) combination of pGX3001, pGX3002 and pGX6001.

MEDI0457 will be supplied in a single pre-filled 2 mL glass vial containing all three components. The minimum fill volume for MEDI0457 vials is 1 mL.

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

4.1.1.1. pGX3001

Chemical name: Circular double-stranded DNA plasmid consisting of 3782 base pairs.

Distinguishing name: Eukaryotic expression plasmid containing HPV-16 E6 and E7-encoding transcription unit controlled by a synthetic, cytomegalovirus promoter, and elements required for replication and selection in *E. coli*, namely a pUC origin of replication (pUC Ori) and a kanamycin resistance gene (Kan R).

4.1.1.2. pGX3002

Chemical name: Circular double-stranded plasmid DNA consisting of 3824 base pairs.

Distinguishing name: Eukaryotic expression plasmid containing HPV-18 E6 and E7-encoding transcription unit controlled by a synthetic, cytomegalovirus promoter, and elements required for replication and selection in E. coli, namely a pUC origin of replication (pUC Ori) and a kanamycin resistance gene (Kan R).

4.1.1.3. pGX6001

Chemical name: Circular double-stranded plasmid DNA consisting of 6259 base pairs.

Distinguishing name: Eukaryotic expression plasmid containing synthetic interleukin-12 p35 light chain and p40 heavy chain (pGX6001) controlled by a dual promoter vector, a bGH poly A tract, bacterial origin of replication to support production of the plasmid in *E. coli*, and a kanamycin resistance gene (Kan R).

4.1.2. Durvalumab

Durvalumab (also known as MEDI4736) is a human IgG1 kappa monoclonal antibody directed against human PD-L1. Durvalumab selectively binds human PD-L1 with high affinity and blocks its ability to bind to PD-1 and CD80. The fragment crystallizable domain of durvalumab contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to the complement component C1q and the Fcγ receptors responsible for mediating antibody dependent cell mediated cytotoxicity (Oganesyan et al 2008).

Durvalumab will be supplied by AstraZeneca/MedImmune or its designee as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% (w/v) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10.0 mL. IP 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.

4.1.3. CELLECTRA®5P device for in vivo electroporation

The use of EP via the CELLECTRA®5P device increases the immunogenicity of MEDI0457. Electroporation utilizes a transmembrane electric field pulse to induce microscopic pathways (pores) in a bio membrane. The electric field allows macromolecules, ions, and water to pass from one side of the membrane to the other. The presence of a constant field influences the kinetics of directional translocation of the macromolecular plasmid, such that the plasmid delivery in vivo has been sufficient to achieve physiological levels of secreted proteins. Intramuscular injection of plasmid followed by EP has been used very successfully to deliver therapeutic genes that encode for a variety of hormones, cytokines or enzymes in a variety of species (Prud'homme et al 2006, Prud'homme et al 2007). The design of software that enables constant current EP to deliver plasmids allows for the individual resistance of the treated muscle to be taken into consideration and yields highly efficient in vivo plasmid expression (Khan et al 2005).

The target organ for EP is skeletal muscle. The skeletal musculature is an excellent candidate for the target tissue of gene expression, because muscle fibers have a long lifespan and can be transduced by circular plasmids, allowing the gene to be expressed efficiently in immunocompetent hosts (Davis et al 1993, Tripathy et al 1996). Furthermore, muscle is well vascularized, allowing the newly produced transgene product to gain access to the circulation.

The CELLECTRA®5P) device and its components bear labels that identify the device name and place of business of the manufacturer. The CELLECTRA®5P User Manual describes all relevant contraindications, hazards, adverse effects, interfering substances or devices, warnings, and precautions. Each CELLECTRA®5P Pulse Generator has a unique serial number and each CELLECTRA®5P Applicator has a unique serial number. Each CELLECTRA®5P Array has a Lot Number, Manufacture Date and Expiration Date.

The CELLECTRA®5P device, and its components, will be shipped directly from the manufacturer to 1) the study site or 2) the study depot prior to shipping to the study site. The investigational labels in Section 4.2 below are presented as examples. Please note, information such as expiration date, lot and serial numbers (as applicable) is included at the time of manufacture and may vary from these examples. The information found on the actual device labels should always be used to manage, track and record IP accountability during study conduct.

4.2. Labeling

This study is open-labeled; therefore, the patient, the investigator's site personnel, supporting company representative, and the MDACC IND Office or its designee are not blinded to study treatment. Each vial of IP will be labeled with a single panel label.

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

Example labels for the CELLECTRA®5P Device (Pulse Generator, Applicator and Array) are shown in **Figure 2**.

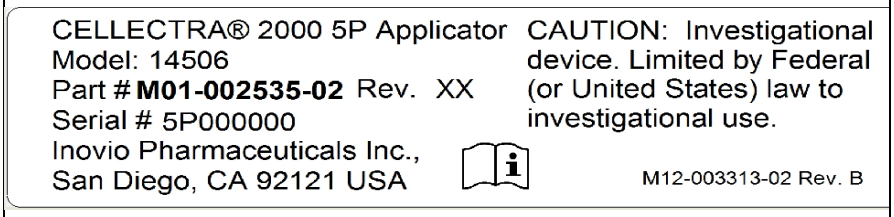
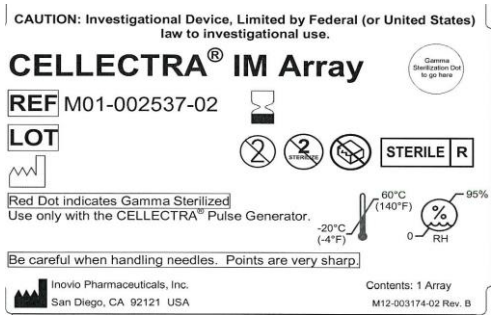
Device Component	Example Label
CELLECTRA® 5P Pulse Generator Model 14510 Part Number: M01-003188	
CELLECTRA® 5P Applicator Model 14506 Part Number: M01-002535	
CELLECTRA® IM Array REF: M01-002537	

Figure 2. Examples of labeling for the CELLECTRA®5P

4.3. Study Drug Preparation

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

4.3.1. MEDI0457

Vial contents must be thawed at ambient room temperature and must be administered within 4 hours of removal from freezer.

The study personnel will draw 1 mL of MEDI0457 from the pre-filled vials using a syringe. This syringe will be used to administer IP to the patients IM through the CELLECTRA®5P device.

The syringe must be labeled with the date and time it was removed from the freezer and a 4-hour expiration date and time from the time the vial is removed from the freezer. The label should also contain the words "administer as soon as possible".

4.3.2. Durvalumab

All doses will be prepared in infusion bags under aseptic conditions by trained personnel; it should not be prepared on the ward. No incompatibilities between Durvalumab and polyvinylchloride or polyolefin IV bags have been observed.

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

For patients ≥30 kg, remove 30.0 mL of IV solution from the IV bag prior to addition of Durvalumab. Next, 30.0 mL of Durvalumab (i.e., 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.

For patients < 30 kg, calculate the dose volume of Durvalumab and number of vials needed for the subject to achieve the accurate dose according to **Appendix F**.

4.4. Doses and Treatments

4.4.1. Planned Dosing Schedule

All patients will receive combination treatment with MEDI0457 and durvalumab as per the following **Planned Dosing Schedule** (treatment should be given at the beginning of the week, unless otherwise specified) as detailed in **Figure 1** and **Table 3.**

Durvalumab will be administered at a fixed dose of 1500 mg q4wk for patients that are ≥30 kg. For patients who weigh <30 kg, weight-based dosing will be used at a dose of 20 mg/kg q 4 weeks, and if their weight increases to ≥30 kg they can be switched to durvalumab at 1500 mg every 4 weeks.

Patients will receive 7 mg MEDI0457 delivered by IM followed by EP on Day 1 (Week 1), Week 3, Week 7, Week 12 and then every 8 weeks until disease progression or unacceptable toxicity. Durvalumab will be administered on Week 4, Week 8, Week 12 and then every 4 weeks until disease progression or unacceptable toxicity. On days when both MEDI0457 and durvalumab administrations will occur on the same day (Week 12 then every 8 weeks), MEDI0457 will be administered first, and durvalumab IV infusion will start approximately 1 hour after MEDI0457 is delivered intramuscularly followed by EP.

Minimum time between Week 3 MEDI0457 dose and the Week 4 first durvalumab dose, and the Week 7 MEDI0457 dose and the Week 8 durvalumab dose is 7 days.

4.4.2. Durvalumab

Durvalumab will be administered at a fixed dose of 1500 mg q4w in the combination and monotherapy arms for patients weighing ≥30 kg. For patients weighing <30 kg, the dose will be 20 mg/kg. The maximum number of doses of checkpoint inhibitor therapy will equal 13.

The duration will be approximately 1 hour (± 5 minutes) for each durvalumab infusion. A 1- hour observation period is required after the first infusion of durvalumab is administered. If no clinically significant infusion reactions are observed during or after the first dose, subsequent infusion observation periods can be at the investigator's discretion (suggested 30 minutes after each durvalumab infusion).

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

See Section 6.7.1 dose administration changes in the event of Grade 1 or 2 infusion-related reactions.

4.4.3. MEDI0457

The DNA vaccine is administered in two steps. In step 1 the vaccine is injected intramuscularly through the CELLECTRA®5P device. Step 2 follows immediately as the CELLECTRA®5P device delivers a sequence of electroporation pulses to the injection area.

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

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

Patients will be offered an analgesic (e.g., ibuprofen, ketorolac) after study treatment. The use of any narcotic (including Tylenol® [acetaminophen] with codeine) for pain meets the definition of severe pain (Grade 3) and therefore will not be offered to the patients unless clinically indicated.

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

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

The instructions for use of the CELLECTRA®5P device are located in the Operations Manual. Each clinical site will receive training for the use of the CELLECTRA®5P device. The following specifications will be used during the study:

- Number of pulses=3
- Current Strength=0.5 Amp
- Electroporation pulse duration=52 milliseconds/pulse
- Interval separating pulses=1 second

The injection/EP procedure must be performed by qualified personnel. Any individual designated to perform the procedure should be permitted by the relevant local authorities to administer parenteral medications to patients in addition to receiving device training from Inovio personnel. Individuals whose credentials do not meet the relevant local requirements may perform the injection/EP procedure under the conditions below:

- The procedure must be performed under the direct supervision of the Principal Investigator or an approved Sub-Investigator who has already been trained by the supporting company's designated personnel.
- The curriculum vitae and any relevant qualifications of the individual have been reviewed and approved by the Inovio or its designee to perform the procedure.

Any deviation from the above procedures must be approved by Inovio and MDACC IND Office or its designee.

4.4.4. Downloading of electroporation data from CELLECTRA®5P device

Within 48 hours following each treatment with MEDI0457, data should be downloaded from the EP device and the data file that is created should be sent to the Inovio or designee by e mail to CELLECTRAdata@inovio.com. Instructions on how to download the data are provided separately. Training will be provided.

4.5. Accountability and Disposition

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the agent using the NCI Drug Accountability Record Form (DARF). See the CTEP home page at http://ctep.cancer.gov for the Procedures for Drug Accountability and Storage or to obtain a copy of the DARF. Any deviation or error in use of CELLECTRA®5P device must be reported error reporting form (Appendix C)

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

5. STUDY PLAN

All study procedures will be performed according to **Table 3**.

Table 3. Schedule of Study Procedures

	Screening	Cycle 1			Cycle 2		Cycle 3		Cycle 4[a]	Cycle 5[a]	EOT[b]	Follow-up[c]
Week of Study	-	1	3	4	7	8	10	12	16	20	-	-
Procedures **Day of Week**	-28 to -1	1	±7 days (unless otherwise noted)									
Informed consent	X											
Demographics	X											
Medical histories[d]	X											
Inclusion/exclusion criteria	X	X										
Physical examination[e]	X	X[f]	X	X	X	X	X	X	X	X	X	
ECOG performance status	X	X[f]	X	X	X	X	X	X	X	X	X	
Adverse events assessment	X	X	X	X	X	X	X	X	X	X	X	
Concomitant medications/procedures	X	X	X	X	X	X	X	X	X	X	X	
Disease status[g]	X[h]							X[i]		X[i,j]	X	X[k]
Hepatitis/HIV screening[l]	X											
Vital signs[m]	X[g]	X[f]	X	X	X	X	X	X	X	X	X	
12-lead ECG	X	X[f]				X		X		X[n]	X	
HPV typing[o]	X											
Hematology[p]	X	X[f]	X	X	X	X	X	X	X	X[q]	X	
Serum chemistry[r]	X	X[f]	X	X	X	X	X	X	X	X[q]	X	
Coagulation testing[s]	X	As clinically indicated.										
Thyroid function testing[t]	X	X[f]		X		X		X	X	X[q]	X	
Urinalysis[u]	X	As clinically indicated.										
Pregnancy test[v]	X[w]	X[x]		X		X		X	X	X	X	
MEDI0457 administration[y]		X	X		X			X		X		
MEDI0457 post-treatment reaction[z]		X	X		X			X		X		
Download EP data		X	X		X			X		X		
Durvalumab administration[aa]				X		X		X	X	X		
Tumor biopsy[bb]	X						X[cc]				X[dd]	
Immune Profiling/HPV Serology Research Blood[ee]		X		X		X	X		X[ff]		X	
Pharmacokinetics/ADA Research Blood[gg]				X		X			X[hh]			
Viral load[ii]	X			X		X		X	X	X	X	
HBV DNA/Hep BsAg[ij]				X		X		X			X	

[a] Patients can continue on the study until progression or unacceptable toxicity as long as the physician feels the patient is receiving benefit. Cycles 4 and 5 should be repeated to continue this treatment. [b] End of treatment (EOT) is defined as the last visit where the decision is made to discontinue protocol directed treatment.

[c] A clinic visit is not required for follow-up. Patients who are taken off study due to disease progression or intolerable toxicities will be followed for vital status every 6 months via phone and/or review of medical record.

[d] Histories include medical history, history of prior cancer treatment, history of procedures

[e] Complete physical examination during Screening and at the Follow-up visit; targeted physical examination at all other visits.

[f] If performed within 3 days prior to Day 1, they do not need to be repeated.

[g] The preferred method of disease assessment is CT with contrast. The same method is preferred for all subsequent tumor assessments for the same patient. Patients discontinued from treatment for reasons other than PD will continue disease assessments until confirmed PD or start of subsequent anticancer therapy.

[h] Magnetic resonance imaging scan of the brain will be performed only at screening or at each assessment if the patient is neurologically symptomatic during treatment outside of the setting where the patient has known central nervous system metastases.

[i] If possible, disease status assessments will be performed on the day prior to scheduled drug administration.

[j] Disease status assessments will be performed every 8 weeks (± 3 days) (relative to the date of the first MEDI0457 administration) for 1 year, if CR/PR/SD are achieved then disease status assessments should be performed every 12 weeks (± 7 days) until the EOT.

[k] If no PD, disease assessment should be performed on Day 90 (± 7 days) after EOT, every 3 months (± 7 days) after Day 90 up to Month 12, and then every 6 months (± 14 days) after Month 12 until the end of study (EOS).

[l] Hepatitis screening tests include: HBV-DNA, HCV-Ab, HBsAg, HBcAB, and HBsAb.

[m] Temperature, respiratory rate, pulse oximetry, blood pressure, HR and weight. Height will be measured only during Screening. See **Section 6.5.7** for details.

[n] Every 12 weeks until end of treatment.

[o] Historical tissue samples may be used; there is no need for additional samples/test for the HPV 16/18 test to be collected just for this protocol.

[p] Hematology panel includes: basophils, eosinophils, hematocrit, hemoglobin, lymphocytes, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, monocytes, neutrophils, platelet count, red blood cell count, total white cell count. For patients in the HIV(+) cohort, CD4 and CD8 counts will be performed.

[q] Every 4 weeks for first 12 months and every 3 months thereafter until study discharge.

[r] Serum Chemistry panel includes: albumin, alkaline phosphatase, ALT, AST, bicarbonate, calcium, chloride, glucose, lactate dehydrogenase, magnesium, potassium, sodium, total bilirubin (if Total bilirubin is ≥2xULN [and no evidence of Gilbert's syndrome] then fractionate into direct and indirect bilirubin), total protein, creatinine, creatinine phosphokinase, blood urea nitrogen, uric acid, amylase and lipase. Please note: GGT to be collected at baseline and as clinically indicated.

[s] Prothrombin time, APTT and INR.

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

[u] Urinalysis panel includes: bilirubin, blood, glucose, ketones, pH, protein, specific gravity, and color/appearance.

[v] Only for women of childbearing potential.

[w] To include luteinizing hormone and follicle-stimulating hormone only for women of child bearing potential who may be post-menopausal.

[x] Patients with a negative serum pregnancy test within 3 days prior to Day 1 do not require a Week 1 Day 1 pregnancy test to be performed.

[y] A window of ±3 days for all time points except C1D1. For Cycles 1 and 2, an interval of 7 days must occur between MEDI0457 and durvalumab treatments.

[z] MEDI0457 post-treatment reactions will be assessed 30 to 60 min after study treatment.

[aa] A window of ±3 days applies to all time points.

[bb] Core tumor biopsies will be collected as per **Section 6.6.1**.

[cc] ± 3 days. Biopsies at this time point are required until 10 subjects have provided tissue and then are optional for all subsequent subjects.

[dd] At time of confirmed disease progression; Optional

[ee] See **Section 6.6.2.1** for HPV Serology Research Blood details.

[ff] Week 16 and then every 8 weeks until end of treatment.

[gg] See **Section 6.6.2.2** for Pharmacokinetics/ADA details.

[hh] Week 16 only.

[ii] For HIV(+) patients, viral load will be drawn at baseline, every month for the first 3 months, then every 3 months thereafter while on therapy.

[jj] For patients with inactive Hepatitis B (Hep B core Ab(+)/HepB sAg (-)),HBV DNA and Hep BsAg will be monitored every month for the first 3 months, then every 3 months thereafter while on therapy.

6. STUDY ASSESSMENTS

The Prometheus system will be used as the database for data collection and query handling. This database system was developed at MD Anderson for conduction of phase II and phase III clinical trials. The investigator will ensure that data are recorded in the database as specified in the study protocol and in accordance with the instructions provided.

The investigator ensures the accuracy, completeness, and timeliness of the data recorded and of the provision of answers to data queries according to the Clinical Study Agreement.

6.1. Demographics

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

6.2. Medical History

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

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

6.3. Efficacy Assessments

RECIST v1.1 will be used to assess patient response to treatment by determining ORR, Disease Control Rate at 24 weeks (DCR-24w), and PFS. Objective response rate will also be assessed using immune-related RECIST (irRECIST). OS will also be evaluated.

The methods of assessment of tumor burden used at baseline are CT and/or MRI scans, preferably with IV contrast imaging, of the chest, abdomen, and pelvis. Any other areas of disease involvement should be additionally imaged based on the signs and symptoms of individual patients.

Radiologists at the MD Anderson Cancer Center have developed a multimedia structured reporting system, called ViSion, which will be used to capture the key images and metrics recorded by a radiologist for tumor response assessment. The captured images are tagged by a radiologist with metadata referenced to the SNOMED-CT ontology to indicate the anatomical location and radiological observation/diagnosis of each finding. The ViSion system displays serial image findings linked in graphical disease timelines. Target and non-target lesions may be designated by a radiologist from which the calculation and display of disease response criteria (e.g., RECIST) is automated. The radiologist's actual image analysis is performed using the institution's FDA-cleared Philips iSite picture archiving and communications system (PACS) display that is enabled with electronic calipers – ViSion only captures the annotated key images and metrics for subsequent storage, analysis and display. The ViSion database is housed within the

institutional firewall on an MD Anderson server, and the system is HIPAA-compliant requiring institutional passwords for controlled access.

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

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

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

The response to immunotherapy may differ from the typical responses observed with cytotoxic chemotherapy including the following:

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

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

- RECIST will be modified so that PD must be confirmed with a second radiologic assessment, preferably, 5 weeks (+/- 7 days) after the initial assessment of PD in the absence of clinically significant deterioration. Treatment with study regimen should continue between the initial assessment of progression and confirmation for progression at outlined in Tables 4.
- In addition, subjects may continue to receive the study regimen beyond confirmed PD in the absence of clinically significant deterioration and if investigators consider that subjects may be deriving benefit from treatment and there are no more suitable alternative treatments available for the subject.

Modification of RECIST as described is meant to discourage the early discontinuation of the study regimen and provide a more complete evaluation of its anti-tumor activity than would be seen with conventional response criteria. Nonetheless, the efficacy analysis will be conducted by programmatically deriving each efficacy endpoint based on the first evidence of progression (by modified RECIST 1.1 criteria described below) when progression is confirmed by a second scan.

Of note, clinically significant deterioration is considered to be a rapid tumor progression that necessitates treatment with anti-cancer therapy other than the study regimen or other symptomatic progression that requires urgent medical intervention (e.g., central nervous system metastasis, respiratory failure due to increasing malignant pleural effusion, or development of mechanical bowel obstruction due to carcinomatosis or tumor compression)

6.4. HPV-16 or HPV-18 Testing

Patients will be enrolled into the study based on a fresh or historical sample that has been tested and is positive for HPV-16 or HPV-18 positive by the institutionally approved assay. Please refer to section 6.6.1 for details regarding tissue collection.

6.5. Safety Assessments

6.5.1. Laboratory safety assessments

Clinical laboratory tests (blood and urine) will be performed as detailed in the Schedule of Study Procedures (**Table 3**).

6.5.2. Serology

Antibodies to HBV and HCV will be measured. Antibodies to HIV will only be measured if clinically indicated.

Patients with a positive HBV surface antigen (HBsAg) test at screening are not eligible for the study.

Patients who are HBsAg and HBV core antibody (HBcAb) negative but are positive for HBsAb may be included in the study provided that all other eligibility criteria are satisfied.

A HBV DNA test will be performed if the patient is HBsAg negative but HBcAb positive (regardless of HBsAb status).

If the HBV DNA test is positive, the patient will be excluded.

If the HBV virus DNA test is negative, the patient may be included in the study.

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

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

6.5.3. Pregnancy testing

For women of childbearing potential, a negative result for serum pregnancy test (β-HCG) must be available at the screening visit, prior to the collection of the tumor biopsy, and prior to each administration of IP. If at any point, the pregnancy test is positive, indicating that the patient is pregnant, no additional IP will be administered, but the patient will be followed for the duration of the study and beyond to determine the outcome of the pregnancy (with the patient's consent).

6.5.4. Physical examination

A complete physical examination will be performed at screening and follow-up visits and will include an assessment of the following: general appearance, respiratory, CV, abdomen, skin (for signs of injection site reactions due to MEDI0457 or EP), lymph nodes, abdomen, pelvis, musculo-skeletal, and neurological systems. A targeted physical examination to document changes in any medical condition since the last visit will be performed at all other visits.

6.5.5. WHO/ECOG performance status

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

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

0=Fully active; able to carry out all pre-disease performance without restrictions.
1=Restricted in physically strenuous activity but ambulatory and able to carry out light work or work of a sedentary nature, e.g., light housework, office work.
2=Ambulatory and capable of self-care but unable to carry out any work activities. Up and about more than 50% of waking hours.
3=Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4=Completely disabled. Unable to carry out any self-care and totally confined to bed or chair.
5=Dead

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

6.5.6. Post-treatment reaction assessment

The investigator will assess local and systemic reactions post-treatment (within 30-60 minutes after study treatment). Any reported MEDI0457 local post-treatment reactions and systemic post-treatment reactions will be graded per NCI CTCAE version 4.03 and all must be recorded in the database. See **Appendix E** for more information.

6.5.7. Vital signs

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

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

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

- Prior to the beginning of the infusion (measured once from approximately 30 minutes before up to 0 minutes [i.e., the start of the infusion]).
- Approximately 30 minutes (± 5 minutes) after start of the infusion (half way through the infusion).
- At the end of the infusion (approximately 60 minutes ± 5 minutes).
- A 1 hour (± 15 minutes) observation period is required after the first infusion of durvalumab is administered.

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

6.5.8. Electrocardiogram

An ECG will be performed at screening within 28 days prior to Cycle 1 Day 1 for all patients to determine patient eligibility and as clinically indicated throughout the study. One 12-lead ECG recordings is required at the screening visit.

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

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

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

6.6. Biological Sampling Procedures

A summary of the samples collected and planned analyses for the study is presented in **Table 4**. The approaches to perform these research assays are rapidly evolving in the laboratories at the MD Anderson Cancer Center and across the world. Thus, we will perform these analyses with the current state-of-the-art assays available at the time of analysis.

Table 4. Summary of Samples, Target, and Assays

Sample	Target	Assay
Tumor (Archival/Biopsy)	HPV-16/HPV-18 genotyping	HPV16/18 assay
Tumor (Biopsy)	HPV-16/HPV-18 DNA sequence	DNA sequencing
Tumor (Biopsy)	PD-L1, p16 expression and exploratory biomarkers	IHC, Nanostring, RNAseq, or Affymetrix expression analysis
Serum	HPV-16/HPV-18 E6/E7 antibodies, PK, ADA	Serology assays
PBMCs	HPV-16/HPV-18 E6/E7 T-cells	IFN-γ ELISPOT and FACS
Plasma	HLA type, Tumor cell DNA and HPV-16/HPV-18 DNA	High resolution class I HLA, PCR and DNA sequencing

6.6.1. Tumor biopsies

Patients will have a pre-treatment tumor biopsy if it can be done safely (as judged by the investigator) during screening. Week 10 Day 1 (± 3 days) tumor biopsies will be required until 10 subjects who completed a pre-treatment biopsy have successfully been biopsied again, and then the Week 10 biopsy will be made optional. Optional biopsies upon confirmed PD will be collected if clinically feasible (i.e., repeat biopsy does not pose unacceptable medical risk to a subject as determined by the investigator). If additional clinically indicated biopsies will be performed (e.g., for mixed responses), additional tissue will be collected for research purposes (optional). All optional biopsies will be discussed with the subject at the time of initial consent.

To confirm eligibility, tumor tissue from the subject must be confirmed positive for HPV-16 or HPV-18 according to the institutionally approved HPV 16/18 assay. Archival tissue, if available, may be used for this assay, else tissue from the screening tumor biopsy will be used.

Fresh tumor biopsies should be preferentially obtained from tumor tissues that are safely accessible as determined by the investigator and are not obtained from sites that require significant risk procedures, which include, but are not limited to, biopsies of the brain, lung, mediastinum, pancreas, or endoscopic procedures extending beyond the esophagus, stomach, or bowel wall.

The biopsied tumor lesion should not be used as a RECIST target lesion. When feasible and depending on the tumor volume, up to 5 cores (18 GA or larger) will be obtained and processed in the following preferential order: 1) FFPE, 2) fresh frozen, 3) FFPE, 4) fresh frozen, and 5) fresh frozen.

6.6.2. Research Blood

Research blood sample will be collected at the time points listed in the Schedule of Procedures (**Table 3**). These samples will be used for pharmacokinetics, pharmacogenetics, ADA, biomarker, and other analyses as described in **Section 6.6**.

6.6.2.1. Immune Profiling and HPV serology

At the time points listed in **Table 3**, up to 70 mL of blood will be collected in vacutainer tubes (containing heparin and/or serum separating agent) for the isolation of PBMCs, plasma, and serum.

6.6.2.2. PK and ADA

At the time points listed in **Table 3**, up 10 mL of blood will be collected in vacutainer tubes (containing serum separating agent) for the isolation of serum for PK and ADA analyses.

6.6.3. Withdrawal of informed consent for donated biological samples

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

6.7. Management of IP-related Toxicities

6.7.1. Dose Management

Either treatment may be stopped by the investigator while the other treatment continues. MEDI0457 doses should not be modified.

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

- Treat each of the toxicities with maximum supportive care (including holding durvalumab).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care. If medically appropriate, dose modifications are permitted for durvalumab.
- All dose modifications should be documented with clear medical reasoning and documentation of the approach taken.

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

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

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing irAEs during the conduct of this study. Potential irAEs include immune-mediated dermatitis, hepatitis/hepatotoxicity, endocrinopathy (hypothyroidism, hyperthyroidism, hypophysitis, and adrenal insufficiency), neuropathy/neuromuscular toxicity, nephritis, pancreatitis (elevated lipase/amylase), pneumonitis, and colitis. Patients should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of dermatitis, hepatitis/hepatotoxicity, endocrinopathy

(hypothyroidism, hyperthyroidism, hypophysitis, and adrenal insufficiency), neuropathy/neuromuscular toxicity, nephritis, pancreatitis (elevated lipase/amylase), pneumonitis, and colitis should be considered to be immune-related.

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

Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered prior to infusion at the discretion of the investigator for primary prophylaxis against infusion-related reactions. In the event of Grade ≤ 2 infusion-related reaction, the infusion rate of durvalumab 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. In patients experiencing Grade ≤ 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. If a patient experiences an infusion-related reaction, acetaminophen and/or an antihistamine (e.g., diphenhydramine) and/or corticosteroid or equivalent medications per institutional standard may be administered prior to subsequent infusions at the discretion of the investigator for secondary prophylaxis of infusion-related reactions. If the infusion-related reaction is Grade 3 or higher in severity, treatment with durvalumab will be discontinued.

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

6.7.2. Dose-limiting Toxicities

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

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

a. Any Grade 4 irAE is a DLT.
b. Any ≥ Grade 3 colitis is a DLT.
c. Any ≥ Grade 3 non-infectious pneumonitis irrespective of duration is a DLT.
d. Any Grade 2 pneumonitis that does not resolve to ≤ Grade 1 within 3 days of the initiation of maximal supportive care is a DLT.
e. Any ≥ Grade 3 neurotoxicity (to include but not limited to limbic encephalitis, autonomic neuropathy, including peripheral neuromotor syndromes such as myasthenia gravis and Guillain-Barré) irrespective of duration is a DLT.
f. Any ≥ Grade 3 cardiotoxicity (to include but not limited to arrhythmias, myocarditis with cardiomyopathy, ventricular dysfunction) irrespective of duration is a DLT.
g. Any ≥ Grade 3 ocular toxicity (including but not limited to iritis, uveitis, significant vision changes) irrespective of duration is a DLT.

h. Any ≥ Grade 3 irAE, excluding colitis or pneumonitis or neurotoxicity or cardiotoxicity and ocular toxicity as mentioned above, that does not downgrade to Grade 2 within 3 days after onset of the event despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days.
i. AST or ALT elevation > 8 × ULN or TBL > 5 × ULN.
j. Any ≥ Grade 3 non-irAE, except for the exclusions listed below.
k. Grade 3 or greater injection site reaction that is persistent beyond 5 days or does not downgrade to ≤ Grade 1 in 14 days.
l. Grade 3 or greater fever, not associated with above listed events (a to f), assessed by Principal Investigator as related to study treatment.
m. Grade 3 or greater systemic symptoms, not associated with above listed events (a to e), assessed by Principal Investigator as related to study treatment.
n. Any Grade 3 or greater anaphylaxis related to study treatment.
o. Death that is at least possibly related to the study treatment.

The DLT definition excludes the following conditions:

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

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

7. SAFETY REPORTING

7.1. 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 preexisting 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 (i.e., occurring after initial receipt of IP) 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 IP.

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.

7.2. Serious Adverse Event Reporting

An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or the MDACC IND Office, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

1. Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the MDACC IND Office.
2. All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in "The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices". Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).
3. All life-threatening or fatal events, that are unexpected, and related to the study drug, must have a written report submitted within 24 hours (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
4. Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
5. Serious adverse events will be captured from the time of the first protocol-specific intervention, until 90 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
6. Additionally, any serious adverse events that occur after the 90-day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

7.3. Assessment of Safety Parameters

7.3.1. 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. 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.

7.3.2. Relationship

The investigator will provide an assessment of relationship of AEs and SAEs to the IP.

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

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

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

7.4. Recording and Reporting of AEs and SAEs

The investigator (or physician designee) is responsible for verifying and providing source documentation for all AEs and assigning the attribution for all AEs for subjects enrolled.

AEs and SAEs will be recorded according to the NCI suggested criteria as listed below.

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

7.4.1. Study recording period and follow-up for AEs and SAEs

AEs and SAES will be recorded from time of first protocol-specific intervention throughout the treatment period and including the follow-up period (90 days after the last dose of Durvalumab and/or MEDI0457). For physical exams, only abnormal findings will be recorded.

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

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

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

7.4.2. Follow-up of unresolved adverse events

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

AstraZeneca 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.

7.4.3. Reporting to FDA

Serious adverse events will be forwarded to FDA by the MDACC IND Office (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's and supporting companies' guidelines, and Institutional Review Board policy.

7.4.4. Investigator Communications with AstraZeneca

A copy of the SAE report must be sent to AstraZeneca at the time the event is reported to the FDA. SAE report forms should be forwarded with supporting relevant source documents (e.g. history and physical [H&P], hospital discharge summary, autopsy report when available, results of relevant diagnostic tests completed to evaluate the event) to AstraZeneca's designated mailbox: AEMailboxClinicalTrialTCS@astrazeneca.com.

Transmission of the SAE report Form should be confirmed by the site personnel submitting the report.

Follow-up information for SAEs and information on non-serious AEs that become serious should also be reported to AstraZeneca as soon as it is available; these reports can be submitted using the MD Anderson eSAE Report Form.

7.5. Adverse Events of Special Interest

An AESI is of scientific and medical interest specific to understanding of the IP and may require close monitoring and rapid communication by the investigator to the supporting companies. An AESI may be serious or non-serious. The rapid reporting of AESIs allows ongoing surveillance of these events in order to characterize and understand them in association with the use of this IP.

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

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

- 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, type 1 diabetes, and hyper- and hypothyroidism),
- Dermatitis,
- Nephritis,
- Pancreatitis (or laboratory tests suggestive of pancreatitis - increased serum lipase, increased serum amylase),
- Infusion-related reactions, and
- Administration site reactions.

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

Further information on these risks (e.g., presenting symptoms) can be found in the subsections below and the current versions of the IBs. More specific guidelines for their evaluation and treatment are described in detail in **Appendix D**.

7.5.1. Colitis

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

7.5.2. Pneumonitis

AEs of pneumonitis are also of interest for the Supporter. Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended. Guidelines for management of patients with pneumonitis are outlined in **Appendix D**.

7.5.3. Hypersensitivity reactions

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

reactions may include hypotension, dyspnea, cyanosis, respiratory failure, urticaria, pruritus, angioedema, hypotonia, urticaria, arthralgia, bronchospasm, wheeze, cough, dizziness, fatigue, headache, hypertension, myalgia, vomiting and unresponsiveness. Guidelines for management of patients with hypersensitivity reactions (including anaphylactic reactions) are outlined in **Appendix D**.

7.5.4. Infusion-related reactions

AEs of infusion reactions (also termed infusion-related reactions) are of special interest to the supporting companies and are defined, for the purpose of this protocol, as all AEs occurring from the start of the study treatment infusion up to 48 hours after the infusion start time. All infusion reactions should be documented in the database, and all infusions-related reaction SAEs should be reported as described in Section 7.4. Guidelines for management of patients with infusion-related reactions are outlined in **Appendix D**.

7.5.5. Administration site reactions

Adverse events of administration site reactions are of special interest to the supporting company. These are defined, for the purpose of this protocol, as all AEs occurring as a result of the administration of the study treatment (vaccine and/or EP) of grade ≥ 3 pair or any other administration site reaction. Guidelines for the grading and management of administration site reactions are outlined in **Appendix E**.

7.6. Other events requiring reporting

7.6.1. Overdose

An overdose is defined as a subject receiving a dose of Durvalumab and/or MEDI0457 in excess of that specified in the IB, unless otherwise specified in this protocol.

Any overdose of a study patient with IP, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the supporting companies' designee and the MDACC IND Office. If the overdose results in an AE, the AE must also be recorded as an AE.

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. There is currently no specific treatment in the event of an overdose of either MEDI0457 or durvalumab.

The investigator will use clinical judgment to treat any overdose.

7.6.2. 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, i.e., 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.

7.6.3. Paternal Exposure

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

Pregnancy of the patients' partners is not considered to be an AE. However, the outcome of all pregnancies (spontaneous miscarriage, elective termination, normal birth, or congenital abnormality) should be followed up and documented.

If any pregnancy occurs in the course of the study, then investigators or other site personnel must inform the appropriate AstraZeneca representatives within 1 or 5 days.

7.6.4. Hepatic Function Abnormality

Hepatic function abnormality (i.e., TBL, ALT, or AST outside of the levels defined in the inclusion criteria) in a study patient, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the MDACC IND Office and supporting companies or designee unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to IP has been confirmed.

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

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

7.6.5. Hy's Law

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

7.6.6. Events requiring reporting within 72 hours

The following events must be reported to MDACC IND Office and supporting companies within 72 hours of the occurrence of the event to discuss whether further administration should continue for the participant.

- Grade 3 or greater injection site reaction.
- Grade 3 or greater fever, not associated with above listed events (a to f) in Section 6.7.2, assessed by Principal Investigator as related to study treatment.
- Grade 3 or greater systemic symptoms, not associated with above listed events (a to e) in Section 6.7.2, assessed by Principal Investigator as related to study treatment.

8. STATISTICAL ANALYSES

8.1. Statistical Considerations

Summary statistics will be provided to summarize response, toxicity, and other clinical and demographic variables. Objective response rate and disease control rate by RECIST 1.1 criteria will be estimated with 95% confidence interval. Progression free survival and OS will be summarized using the method of Kaplan and Meier and Cox proportional hazards models. All analysis will be done across all cohorts along with subset analysis within each cohort.

8.1.1. Sample size estimate

Up to 77 evaluable patients will be enrolled in this study.

The design requires a maximum of 34 evaluable subjects per cohort. Nine subjects will be treated in the first stage. If 1 or fewer responses are seen, enrollment into that cohort will be stopped for futility. If there are 2 or more responses, an additional 25 subjects will be enrolled into the second stage. If there are 9 or more responses out of 34, the combination will be deemed worthy of further study. The two cohorts with the best response rates after completion of accrual into stage 1 for all 3 cohorts will move on to stage 2. The maximum total sample size is 77 (9 x 1 cohorts + 34 x 2 cohorts) evaluable subjects.

After each cohort completes accrual to stage I, only the two cohorts with the most responses will move on to stage 2. Therefore, accrual to stage 2 will not start till all three cohorts have completed stage I. However, if a single cohort has a high response rate (≥4 responses out of 9 patients), the second stage of accrual may proceed prior to other cohorts completing stage I.

8.1.2. Efficacy futility assessments

We will use a Simon's two-stage optimal design targeting an alternative hypothesis ORR of 0.35 versus a null hypothesis ORR of 0.15 with 80% power and a one-sided 0.05 significance level. This will be conducted independently in each of the three cohorts. ORR will be assessed every 8 weeks and will be defined using RECIST 1.1 criteria. During the interim, the accrual will be halted until the go/no-go decision can be made.

8.1.3. Toxicity monitoring

DLT will be monitored continuously in cohorts of 6 subjects for all 34 subjects to ensure safety using the methods by Thall et al. Cohorts will be monitored independently. The trial will be stopped early for toxicity if the Pr(DLT > 30% | data) > 0.90 using a prior of beta(0.6, 1.4) for toxicity. Stopping boundaries corresponding to this probability criterion are to halt the trial if (# of patients with DLT) / (# patients evaluated) ≥ 4/6, 6/12, 9/18, 11/24, and 13/30. The operating characteristics of this rule is found in table below.

Table 5. Operating Characteristics of Stopping Rules for Toxicity

True toxicity	P(stop)	p10	p25	p50	p75	p90	Avg # subjects	Avg # toxicities
0.10	0.002	34	34	34	34	34	33.9	3.4
0.20	0.035	34	34	34	34	34	33.2	6.7
0.30	0.196	12	34	34	34	34	29.9	9.0
0.40	0.549	6	12	30	34	34	23.2	9.2
0.50	0.877	6	6	12	24	34	15.5	7.8

The Investigator is responsible for completing toxicity/efficacy summary reports and submitting them to the IND office Medical Affairs and Safety Group for review. These should be submitted as follows:

Toxicity Assessment: After the first 6 evaluable patients per cohort, complete 4 weeks of study treatment, and every 6 evaluable patients thereafter.

Efficacy Assessment: After the first 9 evaluable patients per cohort, complete 8 weeks of study treatment, and every 5 evaluable patients thereafter, until enrollment is complete. On every report submission, the response information from previous reported patients will need to be updated.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

8.2. Definitions of Analysis Sets

The analysis of data will be based on different subsets according to the purpose of the analysis, i.e., efficacy, safety and pharmacokinetic, respectively.

8.2.1. Efficacy analysis set

Response-evaluable Population: The co-primary endpoint of ORR by RECIST v1.1 will be based on the Response-evaluable Population. This population will include all patients with confirmed HPV-16 or HPV-18 associated disease who have received any dose of both study drugs, have a baseline scan with measurable disease, and have at least one follow-up scan (includes discontinuations due to disease progression or death without follow-up scan) with ≥ 16 weeks follow-up.

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

Table 6 provides a summary of the efficacy endpoints with their corresponding methods of assessment and populations.

Table 6. A Summary of Efficacy Endpoints with Corresponding Methods of Assessment and Populations

Type of efficacy endpoint	Endpoint	Method	Population(s)
Primary	ORR	RECIST version 1.1	Response-evaluable
Secondary	ORR	RECIST version 1.1	As-treated
	ORR	irRECIST	Response-evaluable and As-treated
	DCR-24w	RECIST version 1.1	Response-evaluable and As-treated
	PFS	RECIST version 1.1	Response-evaluable and As-treated
	OS	Kaplan-Meier	Response-evaluable and As-treated

8.2.2. Safety analysis set

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

8.2.3. Pharmacokinetics analysis set

The pharmacokinetic analysis set will include all patients who receive at least one dose of durvalumab and have any post-dose data available and have at least one post dose plasma concentration measurement at a scheduled time point without any important protocol deviations or violations thought to significantly affect the pharmacokinetic of the drug.

8.3. Outcome Measures

8.3.1. Primary

The primary objective will be measured by ORR by RECIST v1.1. The ORR will be estimated along with corresponding 95% confidence interval. All analysis will be done within each cohort as well as across all cohorts.

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

At each visit, patients will be assigned a RECIST version 1.1 visit response of CR, PR, SD, or PD depending on the status of their disease compared with baseline and previous assessments by the investigator. Baseline will be assessed within the 28 days prior to enrollment. If a patient has had a tumor assessment that cannot be evaluated, then the patient will be assigned a visit response of not evaluable (unless there is evidence of progression in which case the response will be assigned as PD).

8.3.2. Secondary

The secondary objectives will be measured by the following:

- AEs/SAEs;
- Collection of hematology, serum chemistry, urinalysis, creatine phosphokinase, thyroid function testing and pregnancy test;
- Electrocardiograms. The following parameters will be recorded for each electrocardiogram: date and time of electrocardiogram, heart rate (beats/min), PR, QRS, RR interval, QT (ms), QTcF (ms), sinus rhythm (yes/no), and overall evaluation (normal/abnormal);
- Vital signs;
- Physical examinations;
- Concomitant medications;
- OS;
- PFS as assessed by RECIST v1.1;
- ORR by RECIST v1.1;
- Immune-related RECIST; and
- Disease control rate at 24 weeks by RECIST v1.1.

Safety will be summarized by the percentage of patients with AEs, with grading(according to CTCAE v4.03) and attribution. Summary statistics will also be provided for serious AEs, hematology, urinalysis, CPK, thyroid function testing, pregnancy test, ECG, vital sign, physical examinations and concomitant medications.

8.3.2.1. Objective Response Rate (ORR)

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

8.3.2.2. Progression Free Survival (PFS)

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

All study evaluations for disease response must be based on RECIST v1.1.

Progression free survival will be defined as the time from the date of start of IP treatment until the date of objective disease progression or death (+1 day) (by any cause) whichever occurs first. Patients who have not progressed or died at the time of the analysis will be censored at the time of the latest date of assessment from their last evaluable RECIST version 1.1 assessment. However, if the patient progresses or dies after two or more missed visits, the patient will be censored at the time of the latest evaluable RECIST version 1.1 assessment prior to two missed visits.

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

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

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

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

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

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

8.3.2.3. Disease Control Rate (DCR)

Disease control rate is defined as N (%) patients with CR, PR, or SD by 24 weeks on study using RECIST version 1.1. For SD determination for DCR, the patient must have lack of progression for the first 24 weeks on study. Disease control rate will be assessed in the Response-evaluable and As-treated populations.

8.3.2.4. Overall Survival (OS)

OS is defined as the time from the date of start of IP treatment until death (+1 day) due to any cause. Any patient not known to have died at the time of analysis will be censored based on the

last recorded date on which the patient was known to be alive. OS will be assessed in the Response-evaluable and As-treated populations.

8.3.3. Exploratory

The exploratory objectives as detailed in Section 6.6 will be analyzed descriptively with summary statistic generation and correlation to survival or other statistics as appropriate.

9. ETHICAL AND REGULATORY REQUIREMENTS

9.1. 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.

9.2. Ethics and Regulatory Review

This study will be subject to subject to local IRB and federal oversight.

9.3. Informed Consent

All participants must be provided a consent form describing this study and providing sufficient information for participants to make an informed decision about their participation in this study. The formal consent of a participant, using the IRB approved consent form, must be obtained before the participant is involved in any study-related procedure. The consent form must be signed and dated by the participant or the participant's legally authorized representative, and by the person obtaining the consent. The participant must be given a copy of the signed and dated consent document. The original signed copy of the consent document must be retained in the medical record or research file.

9.4. Changes to the Protocol and Informed Consent Form

This protocol, the proposed informed consent and all forms of participant information related to the study (e.g., advertisements used to recruit participants) and any other necessary documents must be submitted, reviewed and approved by the IRB and AstraZeneca. Any changes made to the protocol must be submitted as amendments and must be approved by the IRB and AstraZeneca prior to implementation. Any changes in study conduct must be reported to the IRB and AstraZeneca.

9.5. Protocol Review and Monitoring

The study team, including the PI, research nurse, and data coordinator, will perform monthly reviews of case histories and regulatory documents.

The MD Anderson IND Office will monitor this study.

10. STUDY DATABASE MANAGEMENT

10.1. Study Data

Clinical study data for this trial will be collected and managed using the Prometheus database system.

10.2. Data Management

To maintain confidentiality, all laboratory specimens, evaluation forms, reports, and other records transmitted outside the clinical site will be identified by a subject's identification number or coded number and age. All study records, source medical records, and code sheets or logs linking a subject's name to an SID number will be kept in a secure location. Study records may be maintained electronically and require the same security and confidentiality as paper. Clinical information will not be released without written permission of the subject/legal representative, except as specified in the ICF(s) (e.g., necessary for monitoring by regulatory authorities or the MDACC IND Office of the clinical study). The investigator must also comply with all applicable privacy regulations (e.g., HIPAA 1996, EU Data Protection Directive 95/46/EC).

Study documents (including subject records, copies of data submitted to the MDACC IND Office, study notebook, and pharmacy records) must be kept secured in accordance with the specific data retention periods that are described in the clinical study site agreement and based upon local requirements. Study documents must not be destroyed without prior written approval of the MDACC IND Office.

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APPENDIX A. INTERNATIONAL AIRLINE TRANSPORTATION ASSOCIATION (IATA) 6.2 GUIDANCE DOCUMENT

Labeling and shipment of biohazard samples

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

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

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

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

UN 3373 – Biological Substance, Category B

Are to be packed in accordance with UN3373 and IATA 650

Exempt - all other materials with minimal risk of containing pathogens

Clinical trial samples will fall into Category B or exempt under IATA regulations.

Clinical trial samples will routinely be packed and transported at ambient temperature in IATA 650 compliant packaging.

Biological samples transported in dry ice require additional dangerous goods specification for the dry ice content.

IATA compliant courier and packaging materials should be used for packing and transportation and packing should be done by an IATA certified person, as applicable.

Samples routinely transported by road or rail are subject to local regulations which require that they are also packed and transported in a safe and appropriate way to contain any risk of infection or contamination by using approved couriers and packaging/containment materials at all times. The IATA 650 biological sample containment standards are encouraged wherever possible when road or rail transport is used.

APPENDIX B. ACTIONS REQUIRED IN CASES OF INCREASES IN LIVER BIOCHEMISTRY AND EVALUATION OF HY'S LAW

Introduction

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

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

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

Definitions

Potential Hy's Law

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

Hy's Law

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

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

Identification of Potential Hy's Law Cases

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

ALT ≥ 3 x ULN

AST ≥ 3 x ULN

TBL ≥ 2 x ULN

When a patient meets any of the identification criteria, in isolation or in combination, the central laboratory will immediately send an alert to the investigator.

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

Request a repeat of the test (new blood draw) by the central laboratory.

Complete the appropriate unscheduled laboratory database module(s) with the original local laboratory test result.

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

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

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

Determine whether the patient meets PHL criteria (see Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits. Definitions within this Appendix for definition) by reviewing laboratory reports from all previous visits.

Promptly enter the laboratory data into the database.

Follow-up

Potential Hy's Law Criteria not Met

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

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

Potential Hy's Law Criteria Met

If the patient does meet PHL criteria the investigator will:

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

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

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

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

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

Review and Assessment of Potential Hy's Law Cases

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

No later than 3 weeks after the biochemistry abnormality was initially detected, the Study Physician contacts the investigator in order to review available data and agree on whether there is an alternative explanation for meeting PHL criteria other than DILI caused by the IP.

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

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

If the alternative explanation is **not** an AE, record the alternative explanation database.

If the alternative explanation is an AE/SAE, record the AE/SAE in the database accordingly.

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

Report an SAE (report term 'Hy's Law') according to MD Anderson IRB/DSMB standard processes.

The 'Medically Important' serious criterion should be used if no other serious criteria apply.

As there is no alternative explanation for the HL case, a causality assessment of 'related' should be assigned.

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

Report an SAE (report term 'Potential Hy's Law') applying serious criteria and causality assessment as per above.

Continue follow-up and review according to agreed plan. Once the necessary supplementary information is obtained, repeat the review and assessment to determine whether HL criteria are met. Update the SAE report according to the outcome of the review.

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

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

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

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

If there is no significant change no action is required

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

Actions Required for Repeat Episodes of Potential Hy's Law

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

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

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

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

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

If Yes:

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

If there is no significant change no action is required.

If there is a significant change follow the process described in **Appendix D**, **Table 7**.

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

References

FDA Guidance for Industry (issued July 2009) 'Drug-induced liver injury: Premarketing clinical evaluation':
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM174090.pdf

APPENDIX C. CELLECTRA®5P ERROR REPORTING FORM

Please complete the form and fax to (267) 440-4242 or scan the form to EPerror@inovio.com
Protocol#_____ Site#_____ Patient ID_____ Week#_____ Visit Date_____

DEVICE INFORMATION
CELLECTRA®5P Serial No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the front cover
CELLECTRA®5P Applicator Serial No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the handle
CELLECTRA® Array Lot No: ☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐☐
Located on label on the package

Time of Electroporation (EP): _____

Location of Treatment/EP: ☐ Deltoid **R**ight/**L**eft _____

☐ Other Location, specify:_____

IM-5P, was the EP Guide used? ☐ YES ☐ NO

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

Was injection successful? ☐ YES ☐ NO
If NO, please provide reason and include needle gauge and syringe volume used.

Did the display on the device read Electroporation successful? ☐ YES ☐ NO
If NO, please check all complications that led to failure and describe complication below
☐ Impedance Test Error message displayed, fill out Impedance Test Error section below
☐ Electroporation Error message displayed, fill out Electroporation Error section below
☐ EP aborted by trigger or keypad error message displayed
☐ Battery level too low for EP message displayed
☐ Difficulty inserting array into muscle or skin
☐ Other, please specify below
Describe device complication below (continue on back if necessary):

Total # of arrays used: _____

Impedance Test Error

Was the array inserted in patient's arm? ☐ YES ☐ NO Total # of attempts: _____
Were all attempts performed on the same day? ☐ YES ☐ NO
(provide other date(s):_____)
Was a different location used for each attempt? ☐ YES ☐ NO
Was a new array used for each attempt? ☐ YES ☐ NO
Please provide any additional information below (continue on back if necessary):

Electroporation Error

Were there 3 (IM) or 4 (ID) involuntary muscle contractions? ☐ YES ☐ NO (how many_____
Was the array fully inserted in the patient's arm? ☐ YES ☐ NO
Was the array inserted perpendicular to the patient's skin? ☐ YES ☐ NO
Did the needles of the array appear damaged in any way? ☐ YES ☐ NO
If you were provided a sharps shuttle, please eject the array into a shuttle and ship to Inovio.
Please provide any additional information below (continue on back if necessary):

APPENDIX D. DURVALUMAB DOSE MODIFICATION FOR TOXICITY MANAGEMENT

Table 7. Treatment Modification and Toxicity Management Guidelines for Immune-related Adverse Events (Durvalumab)

Event	Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Immune-related adverse events (overall management for toxicities not noted below)		Drug administration modifications of study drug/study regimen will be made to manage potential immune-related adverse events (irAEs) 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 Common Terminology Criteria (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 adverse event (AE) following resumption of dosing.	It is recommended that management of irAEs follow the guidelines presented in this table • Subjects 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 oral 1-2 mg/kg/day or intravenous (IV) equivalent. • If symptoms recur or worsen during corticosteroid tapering 28 days of taper), increase the corticosteroid dose (prednisone dose [e.g. up to 2-4 mg/kg/day or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (≥ 28 days of taper). • More potent immunosuppressives such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab) – (also refer to the individual sections of the irAE 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 tumor 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 subject.
	Grade 1	No dose modification	
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as	

		Grade 3 or Grade 4 • If toxicity improves to baseline, then treat at next scheduled treatment date Study drug/study treatment can be resumed at the next scheduled dose once event stabilizes to Grade ≤ 1 and 5-7 days have passed after completion of steroid taper. Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per Investigator or treating physician's clinical judgment, and 3) doses of prednisone are at less than or equal to 10 mg/day or equivalent.	
	Grade 3	Depending on the individual toxicity, may permanently discontinue study drug/study regimen. Please refer to guidelines below.	
	Grade 4	Permanently discontinue study drug/study regimen.	
	Note: For Grade 3 and above asymptomatic amylase or lipase levels hold study drug/regimen and if complete work-up shows no evidence of pancreatitis, may continue or resume study drug/regimen		
Pneumonitis/ interstitial lung disease (ILD)	Grade of pneumonitis (CTCAE version 4.03)	Any Grade	• Monitor subjects for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Subjects should be evaluated with imaging and pulmonary function tests including other diagnostic procedures as described below. • Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up and high-resolution computed tomography (CT) scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only,	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.

	intervention not indicated)		
	Grade 2 (symptomatic, medical intervention indicated, limiting instrumental activities of daily living [ADL])	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study treatment can be resumed based upon treating physician's clinical judgment at the next scheduled dose once event stabilizes to Grade ≤ 1 or baseline and 5-7 days have passed after completion of steroid taper.	• For Grade 2 (mild to moderate new symptoms) – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1-2 mg/kg/day or IV equivalent). – Reimaging as clinically indicated. – If no improvement within 3-5 days, additional work-up should be considered and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – If still no improvement within 3-5 days despite IV methylprednisone at 2-4 g/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: Important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once improving, gradually taper steroids over ≥ 4 weeks and consider prophylactic antibiotics, antifungal or anti-pneumocystis pneumonia (anti PCP) treatment (refer to current National Comprehensive Cancer Network (NCCN) guidelines for treatment of cancer-related infections (Category 2B recommendation)[1]. – Consider pulmonary and infectious disease consult. – Consider as necessary discussing with Study Physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated Grade 4: life threatening respiratory compromise, urgent intervention indicated [e.g.	Permanently discontinue study drug/study regimen.	• For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life threatening) – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain pulmonary and infectious disease consult. – Hospitalize the subject. – Supportive Care (oxygen, etc). – If no improvement within 3-5 days, additional work-up should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks dose) started. Caution: rule out sepsis and refer to infliximab label for

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

	tracheostomy or intubation])		general guidance before using infliximab. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and in particular, anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections (Category 2B recommendation)[2].
Diarrhea/ enterocolitis	Grade of diarrhea (CTCAE version 4.03)	Any grade	• Monitor for symptoms that may be related to diarrhea/enterocolitis (abdominal pain, cramping, or changes in bowel habits such as increased frequency over baseline or blood in stool) or related to bowel perforation (such as sepsis, peritoneal signs and ileus). • Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, infections including testing for Clostridium difficile toxin, and stool for ova and parasites (O+P).etc.). • Steroids should be considered in the absence of clear alternative etiology, even for low grade events, in order to prevent potential progression to higher grade event. • Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1 diarrhea (stool frequency of < 4 over baseline per day)	No dose modification	• For Grade 1 diarrhea: – Close monitoring for worsening symptoms. – Consider symptomatic treatment including hydration, electrolyte replacement, dietary changes (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 will be based upon treating physician's clinical judgment Study drug/study treatment can be resumed based upon treating physician's clinical judgment at the next scheduled	• 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, gastrosintestinal (GI) consult should be obtained for consideration of further work-up such as imaging and/or

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

		dose once event stabilizes to Grade ≤ 1 or baseline and 5-7 days have passed after completion of steroid taper.	colonoscopy to confirm colitis and rule out perforation, and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – If still no improvement within 3-5 days despite 2-4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as (infliximab at 5 mg/kg once every 2 weeks[3]). Caution: important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consult Study Physician if no resolution to ≤ Grade 1 in 3-4 days. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
	Grade 3 or 4 diarrhea (Grade 3: stool frequency of ≥ 7 over baseline per day Grade 4: life threatening consequences)	Permanently discontinue study drug/study regimen.	• For Grade 3 or 4 diarrhea: – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3-5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). – Caution: ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Once 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 liver	Grade of liver function test		• Monitor and evaluate liver function test: aspartate aminotransferase (AST), alanine aminotransferase (ALT),

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

function tests [LFTs]) **Infliximab should not be used for management of immune-related hepatitis**	elevation (CTCAE version 4.03) Any grade Grade 1 (AST or ALT > upper limit of normal [ULN] to 3 times ULN and/or TBL > ULN to 1.5 times ULN)	No dose modification. If it worsens, treat as Grade 2 event.	alkaline phosphatase (ALP), and total bilirubin (TBL) • Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications). • For Grade 1 AST or ALT and/or TBL elevation – Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT > 3 to 5 times ULN and/or TBL > 1.5-3.0 times ULN)	Hold study drug/study regimen dose until Grade 2 resolution to ≤ Grade 1 • If toxicity worsens then treat as Grade 3 or Grade 4 Study drug/study treatment can be resumed based upon treating physician's clinical judgment at the next scheduled dose once event stabilizes to Grade ≤ 1 or baseline and 5-7 days have passed after completion of steroid taper.	• For Grade 2 AST or ALT and or TBL 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 1-2 mg/kg/day or IV equivalent. – If still no improvement within 3-5 days despite 1-2 mg/kg/day of prednisone or IV equivalent, consider additional work-up and prompt treatment with IV methylprednisolone 2-4 mg/kg/day started. – If still no improvement within 3-5 days despite 2-4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (mycophenolate mofetil)[4]. Discuss with Study Physician if mycophenolate mofetil is not available. **Infliximab should NOT be used**. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]).
	Grade 3 (AST or ALT > 5-20 times ULN and/or TBL > 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	• For Grade 3 or 4 AST or ALT and/or TBL 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,

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

		• Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline • Permanently discontinue study drug/study regimen if the elevations do not downgrade to ≤ Grade 1 For elevations in transaminases > 8 × ULN or elevations in bilirubin > 5 × ULN, discontinue study drug/study regimen • Permanently discontinue study drug/study regimen for any case meeting Hy's Law criteria (ALT > 3 × ULN + bilirubin > 2 × ULN without initial findings of cholestasis (i.e., elevated alkaline P04) and in the absence of any alternative cause[5]	promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with Study Physician if mycophenolate is not available. **Infliximab should NOT be used.** – Hepatology consult, abdominal work-up, 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 TBL > 10 times ULN)	Permanently discontinue study drug/study regimen.	
Nephritis or renal dysfunction (elevated serum creatinine)	Grade of elevated serum creatinine (CTCAE version 4.03) Any grade		• Consult with nephrologist. • Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum blood urea nitrogen and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, proteinuria, etc). • Subjects 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 > 1-1.5 × baseline; > ULN to 1.5 × ULN]	No dose modification	• For Grade 1 elevated creatinine: – Monitor serum creatinine weekly and any accompanying symptom • If creatinine returns to baseline, resume its regular monitoring per study protocol.

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

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

Rash (excluding bullous skin formations)	Grade of skin rash (please refer to NCI CTCAE v4.03 for definition of severity/grade depending on type of skin rash)	Any grade	• Monitor for signs and symptoms of dermatitis (rash and pruritus) – **IF THERE IS ANY BULLOUS FORMATION, THE STUDY PHYSICIAN SHOULD BE CONTACTED **AND STUDY DRUG DISCONTINUED****
	Grade 1	No dose modification	• For Grade 1: – Consider symptomatic treatment including oral antipruritics (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 or baseline 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 • Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline	• For Grade 3 or 4: – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). – Discuss with Study Physician.
	Grade 4	Permanently discontinue study drug/study	

		regimen.	
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, hypopituitarism, adrenal insufficiency, etc.)	Any grade (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity)		• Consult Endocrinologist. • Monitor subjects for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, hypotension and weakness. • Subjects should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, infections, etc). • Monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free triiodothyronine and free thyroxine (T_4) and other relevant endocrine labs depending on suspected endocrinopathy. • If a subject experiences an AE that is thought to be possibly of autoimmune nature (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 v4.03 for defining the CTC Grade 1)	No dose modification	• For Grade 1: (including those with asymptomatic TSH elevation) – Monitor subject with appropriate endocrine function tests – If TSH < 0.5 × lower limit of normal, or TSH > 2 × ULN or consistently out of range in 2 subsequent measurements, include free T_4 at subsequent cycles as clinically indicated and consider endocrinology consult.
	Grade 2 (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 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	• 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 subjects with abnormal endocrine work-up, except for those with isolated hypothyroidism, consider short-term, corticosteroids (e.g., 1-2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., levothyroxine, hydrocortisone, or sex hormones).

		• Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1) the event stabilizes and is controlled, 2) the subject is clinically stable as per Investigator or treating physician's clinical judgment, and 3) doses of prednisone are at less than or equal to 10mg/day or equivalent.	– Once improving, gradually taper steroids over ≥ 28 days and consider prophylactic antibiotics, antifungals and anti PCP treatment (please refer to current NCCN guidelines for treatment of cancer-related infections [Category 2B recommendation]). – For subjects with normal endocrine work-up (laboratory or magnetic resonance imaging [MRI] scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4 (depending on the type of endocrinopathy, refer to NCI CTCAE v4.03 for defining the CTC grade/severity 3 or 4)	• For Grade 3 or 4 endocrinopathy other than hypothyroidism, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled • Resume study drug/study regimen administration if controlled at the next scheduled dose • Study drug/study treatment can be resumed based upon treating physician's clinical judgment at the next scheduled dose once event stabilizes to Grade ≤ 1 or baseline and 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 IV 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	Grade of neurotoxicity Depending on the type of neurotoxicity, refer to NCI CTCAE v4.03 for defining the CTC grade/ severity		
	Any grade		• Subjects should be evaluated to rule out any alternative etiology

gravis and Guillain-Barré)			(e.g., disease progression, infections, metabolic syndromes and medications, etc). • Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness). • Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). • Symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications	– See "Any Grade" recommendations above.
	Grade 2	• For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to ≤ Grade 1 • For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to ≤ Grade 1. – If toxicity worsens then treat as Grade 3 or Grade 4 – If toxicity improves to baseline then treat at next scheduled treatment date • Study drug/study regimen can be resumed at the next scheduled dose once event stabilizes to Grade ≤ 1 and 5-7 days have passed after completion of steroid taper	• 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 1-2 mg/kg/day or IV equivalent. • If no improvement within 3-5 days despite 1-2 mg/kg/day prednisone or IV equivalent consider additional work-up and promptly treat with additional immunosuppressive therapy (e.g., IVIG).
	Grade 3	• Hold study drug/study regimen dose until resolution to ≤ Grade 1 • Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline	• For Grade 3 or 4: – Discuss with Study Physician. – Obtain Neurology Consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 3-5 days despite IV corticosteroids, consider additional work-up and promptly treat with additional immunosuppressants (e.g., IVIG). – Once stable, gradually taper steroids over ≥ 4 weeks.
	Grade 4	Permanently discontinue study drug/study regimen	
Immune-		Any grade	• The prompt diagnosis of immune-mediated peripheral

mediated peripheral neuromotor syndromes, such as Guillain-Barré and myasthenia gravis			neuromotor syndromes is important, since certain subjects 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. • Subjects 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 subjects with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. • Neurophysiologic diagnostic testing (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-Barré is not typically considered effective. Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.
	Grade 1	No dose modification	• Discuss with the Study Physician. • Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above. • Obtain a neurology consult unless the symptoms are very minor and stable.
	Grade 2	• Hold study drug/study regimen dose until resolution to ≤ Grade 1 • Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline	• Grade 2: – Discuss with the Study Physician. – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology Consult. – Sensory neuropathy/neuropathic pain may be managed

			by appropriate medications (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 Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each subject. o If Myasthenia Gravis-like neurotoxicity present, consider starting acetylcholinesterase (AChE) inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ◦ *GUILLAIN-BARRÉ:* o Important to consider here that the use of steroids as the primary treatment of Guillain-Barré is not typically considered effective. Subjects 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 • Resume study drug/study regimen administration at the next scheduled dose if elevations downgrade ≤ Grade 1 or baseline	• For severe or life threatening (Grade 3 or 4) events: – Discuss with Study Physician. – Recommend hospitalization. – Monitor symptoms and obtain neurological consult. ◦ *MYASTHENIA GRAVIS* o Steroids may be successfully used to treat Myasthenia Gravis. It should typically be administered in a monitored setting under supervision of a consulting neurologist. o Subjects unable to tolerate steroids may be candidates for treatment with plasmapheresis or IVIG.
	Grade 4	Permanently discontinue study drug/study regimen.	

			○ If Myasthenia Gravis-like neurotoxicity present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. ◦ *GUILLAIN-BARRÉ*: ○ Important to consider here that the use of steroids as the primary treatment of Guillain-Barré is not typically considered effective. Subjects requiring treatment should be started with IVIG and followed by plasmapheresis if not responsive to IVIG.

Table 8. Treatment Modification and Toxicity Management Guidelines for Infusion-related Reactions (Durvalumab)

Severity Grade	Dose Modifications	Toxicity Management
Any grade		• Management per institutional standard at the discretion of investigator. • Monitor subjects for signs and symptoms of infusion-related reactions (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., intramuscular epinephrine, followed by intravenous diphenhydramine and ranitidine, and intravenous glucocorticoid).

Table 9. Treatment Modification and Toxicity Management Guidelines for Non-immune-mediated Reactions (Durvalumab)

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

APPENDIX E. ADMINISTRATION SITE REACTION GRADING AND MANAGEMENT

Grading:

- Grading should be done using two systems: Common Terminology Criteria for Adverse Event version 4.03 (which should be used for all dose delay/withdrawal decisions) and the system outlined below.

- Table: Administration Site Reaction Grading Scale (adapted from "FDA Guidance for Industry—Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine Clinical Trials")

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

* In addition to grading the measured local reaction at the greatest single diameter, the measurement should be recorded as a continuous variable.

** Induration/Swelling should be evaluated and graded using the functional scale as well as the actual measurement.

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

APPENDIX F. DURVALUMAB WEIGHT-BASED DOSE CALCULATION

For durvalumab dosing done depending on subject weight. Weight-based dosing should be utilized for patients < 30 kg who would have otherwise received a 1500mg fixed dose.

1. Cohort dose: X mg/kg
2. Subject weight: Y kg
3. Dose for subject: XY mg = X (mg/kg) × Y (kg)
4. Dose to be added into infusion bag:

   Dose (mL) = XY mg / 50 (mg/mL)

   where 50 mg/mL is durvalumab nominal concentration.

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

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

Number of vials = Dose (mL) / 10.0 (mL/vial)

Example:

1. Cohort dose: 20 mg/kg
2. Subject weight: 30 kg
3. Dose for subject: 600 mg = 20 (mg/kg) × 30 (kg)
4. Dose to be added into infusion bag:

   Dose (mL) = 600 mg / 50 (mg/mL) = 12.0 mL

5. The number of vials required for dose preparation:

Number of vials = 12.0 (mL) / 10.0 (mL/vial) = 2 vials

Bagarazzi, M. L., Yan, J., Morrow, M. P., Shen, X., Parker, R. L., Lee, J. C., . . . Sardesai, N. Y. (2012). Immunotherapy against HPV16/18 generates potent TH1 and cytotoxic cellular immune responses. *Sci Transl Med, 4*(155), 155ra138. doi:10.1126/scitranslmed.3004414