PROTOCOL AMENDMENT #4

LCCC 1725: A Phase II Study of Durvalumab (MEDI 4736) with Radiotherapy for the adjuvant treatment of Intermediate Risk Head and Neck Squamous Cell Carcinoma

AMENDMENT INCORPORATES (check all that apply):

_X_ Editorial, administrative changes
_X__Scientific changes (IRB approval)
_ __ Therapy changes (IRB approval)
_ ___Eligibility Changes (IRB approval)

The purpose of this amendment is to change accrual for the study to 18 subjects. Statistical considerations in light of this change have been updated to accommodate the new accrual. Dr. Sheth's designation was updated.

Editorial Changes

1. Where appropriate in the header, Dr. Sheth's designation was changed from MD to DO.

Scientific Changes

1. Section 1.1 and Schema have been updated to accommodate new accrual numbers.
2. Section 5.1: Updated Schema to accommodate new accrual numbers.
3. Section 9.2 has been updated to include new statistical descriptions relative to the change in accrual.

THE ATTACHED VERSION DATED June 1, 2021 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #3

LCCC 1725: A Phase II Study of Durvalumab (MEDI 4736) with Radiotherapy for the adjuvant treatment of Intermediate Risk Head and Neck Squamous Cell Carcinoma

AMENDMENT INCORPORATES (check all that apply):

__X__ Editorial, administrative changes
_____Scientific changes (IRB approval)
_____Therapy changes (IRB approval)
__X__Eligibility Changes (IRB approval)

Protocol Amendment 3 was generated to update Appendix 12.1, "Dose Modification and Toxicity Management Guideline for Durvalumab." This update included the incorporation of the revised "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v5.0)." This revised version included general mechanical editing throughout and additional or revised adverse events, severity grade definitions, dose modification guidance and toxicity management, where appropiate. Specific changes in the toxicities and guidelines that were incorporated into the body of the protocol are outlined in the below section. Adverse events were added/modified in the Diarrhea/Colitis, Rash, and Endocrinopathy sections. Clarification was provided for severity grades in the Peripheral neuromotor syndromes, Myocarditis, Diarrhea/Colitis/Large intestine peforation/Intestine perforation and Myositis/Polymyositis sections. Of note, clarification of Grade in the first Hepatitis section was added relative to normal or abnormal baseline levels; and specific grades, generally,were removed in the Hepatitis Section for Patients with HCC (the shaded Hepatitis Section), instead emphasizing the levels in AST, ALT or total bilirubin and subsequent changes resulting from dose modifications. Dose modification language was updated in the General Consideration regarding Immune-Mediated Reactions and both Hepatitis sections. Toxicity management guidance was updated in Diarrhea/Colitis Large intestine perforation/Intestine perforation, the Rash or Dermatitis, Neurotoxicity, Endocrinopathy, and Nephritis or renal dysfunction sections. This Amendment also reduces redundant language in the protocol by removing Sections 7.2-7.5, which reiterates the study table. Language pertinent to those sections was relocated, as necessary, to the time and events table footnotes. The pregnancy schedule has also been amended.

Editorial/Administrative

1. Section 5.3: Links to Sections 12.1.2, 12.2.3, 12.2.4 updated.
2. Section 6.1.7: Inclusion of Large Intestine Perforation/Intestine Perforation as an adverse event including Toxicity Management monitoring language.
3. Section 6.1.7: Inclusion of Dermatitis with Rash adverse event.

4. Section 7.1: Time and Events Table:
    a. Pregnancy Row: Added pregnancy testing at each cycle, removed parenthetical phrase regarding 72 hour requirement.
    b. Footnote 1: Added language from text to clarify timing of events associated within this footnote.
    c. Footnote 2:
        i. Added language from text describing medical history and physical exam details.
        ii. Edited B-HCG to β-HCG
        iii. Clarified that pregnancy tests will performed within 7 days of administration of the first dose of study drug for women of childbearing potential.
    d. Footnote 4: Removed section reference for long-term follow-up as the section does not exist anymore.
    e. Footnote 5: Added language regarding pre-surgical imagining and pathology review.
    f. Added footnotes 11-15, adding language from Sections 7.2-7.5 as appropriate to compensate for the removal of Sections 7.2-7.5.
5. Section 7.2 through Section 7.5 have been removed to reduce redundancy
6. Section 8.2: Mmyocarditis, edited to Myocarditis
7. Section 8.2: Added Intestinal Perforation and thyroiditis as adverse events of special interest.
8. Section 12.1: Dose Modification and Toxicity Management for Durvalumab was updated to reflect the revised "Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v5.0)." This update provided revised adverse events and severity definitions, including dose modifications, and toxicity management as appropriate.
9. Amendment 1 Coversheet: Eligibility Changes: Item 1: The change inadvertantly states a change to 24 days for a pregnancy test, when the change was from 24 days to 3 days.

Eligibility

1. Criterion 4.1.8 was updated to provide a pregnancy test within 7 days prior to administration of treatment.

THE ATTACHED VERSION DATED November 5, 2019 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT #2

LCCC 1725: A Phase II Study of Durvalumab (MEDI 4736) with Radiotherapy for the adjuvant treatment of Intermediate Risk Head and Neck Squamous Cell Carcinoma

AMENDMENT INCORPORATES (check all that apply):

__X__ Editorial, administrative changes
_____Scientific changes (IRB approval)
_____Therapy changes (IRB approval)
__X__ Eligibility Changes (IRB approval)

This protocol amendment is to revise the required antibiotic washout for subjects prior to receiving their 1st dose of durvalumab. Antibiotics are now prohibited to be given less than 7 days prior to the first dose of durvalumab. If a subject receives intravenous antibiotics or has an antibiotic treatment course of greater than 5 days (oral or IV) then the previously required longer washout period of 14 days is required. Language surrounding timing and amounts of radiation therapy was also amended to increase clarity and understanding. Additionally, this amendment is to update the Principal Investigator of the study from Jared Weiss, MD to Siddharth Sheth, DO.

Editorial/Administrative

1. Siddharth Sheth was updated to the Principal Investigator of the study.
2. The study schema, Sections 1.6.1, 5.1, 5.2, 5.2.1, 6.1.3, 6.2, 7.3.1 and the Time and Events Table footnotes were updated to clarify the timing and fraction of radiation therapy.

Eligibility

1. Criteria 4.2.6 updated to prohibit antibiotics within less than 7 days prior to the first dose of durvalumab. If the patient receives either IV antibiotics or >5 day treatment course (oral or IV), then the 1st durvalumab dose should not be given until 14 days of last antibiotic dose.

THE ATTACHED VERSION DATED October 27, 2019 INCORPORATES THE ABOVE REVISIONS

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT # 1

AMENDMENT #1 INCORPORATES:
X Administrative Changes
X Scientific Changes
X Therapy Changes
X Eligibility Changes

Rationale for Amendment:
Due to the recent negative results for the use of tremelimumab in HNSCC, the protocol is being revised to treat subjects with durvalumab and radiation alone, without the addition of tremelimumab. This multi-center, single arm Phase II trial will evaluate the efficacy of combining radiation therapy with durvalumab as adjuvant therapy for patients with intermediate risk HNSCC. A total of 33 subjects will be accrued as depicted in the study schema. The treatment regimen will evaluate Q3 weekly durvalumab (1500 mg) with radiation in cycles 1-3, followed by single agent durvalumab (1500 mg) Q4 weekly for an additional three cycles. The study's objectives, endpoints and data analysis were updated according to the new study schema.

Administrative changes

1. Administrative editorial changes made throughout the protocol, including updates to T&E Table for consistency with Assessments language.
2. Updated references to "UNCCN" to "Multicenter" throughout the protocol.
3. Sections 1.2 and 1.2.1 were updated for clarity.
4. Updated the footnotes to the time and events table to include windows for all study visits that were previously provided elsewhere in the protocol.
5. Updated T&E Table footnote #6 to include a reference to a section in the protocol that details additional assessments that will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis.
6. Clarified that the dental exam in Section 7.2 need only be performed if it is required per institutional standard of care as previously indicated in the footnotes of the T&E table.
7. Clarified the allowed windows for Sections 7.3.1, 7.3.2 and 7.4.
8. Updated Sections 8.1.4 and 8.5.1 to clarify that a pregnancy within 90 days of the last dose of durvalumab should be reported as an important medical event.
9. Removed references to Tremelimuab in Sections 8.2, 8.3, 8.5.2, 8.5.2.1, 8.5.2.2, 8.5.2.5 and 8.6.
10. Updated Section 8.5.3 to be consistent with updated protocol template language for FDA reporting.
11. Updated Section 8.6 to reflect current UNC job titles.
12. Updated Section 10.3 to reflect current registration procedures.
13. Updated Section 10.4 to reflect current monitoring and auditing procedures.

14. Updated Section 10.6 to reflect current multicenter amendment procedures.
15. Version 1.1 of this Amendment includes the FACT Head and Neck Questionnaire, Version 4, in Section 12.5.

Scientific changes

1. Section 1.1 was updated to support the change in study design.
2. Sections 1.3, 1.3.2, 1.5.1, 1.7 and 7.6.1 were updated to remove references to CTLA4 combination therapy.
3. Sections detailed CTLA4 Inhibition, Combination of PD1/PDL1 with CTLA4 inhibition and Combination Durvalumab with Tremelimumab were removed as they are no longer applicable to the study design.
4. Section 1.5.1.1 Rationale for Fixed Dosing of Durvalumab, Section 1.5.1.2 Durvalumab Dosing Scheduling and Section 1.6.1 Dose Rationale were updated to remove references to fix dosing of tremelimumab.
5. Section 1.6 Rationale for Clinical Study was updated to provide a rationale for durvalumab monotherapy in combination with radiation therapy.
6. Co-Primary Objectives, Secondary Objectives, Exploratory Objectives, Co-Primary Endpoints, Secondary Endpoints and Exploratory Endpoints were updated to reflect the change in study design to durvalumab monotherapy in combination with radiation therapy.
7. Removed section referencing drug-specific information about Tremelimumab.
8. Updated Section 9.0-9.3 Statistics to reflect the changes in study design, primary endpoints, secondary endpoints and exploratory endpoints.

Therapy changes

1. The study was updated to remove combination therapy with tremelimumab including Sections 1.1, 5.1, 5.2, 5.2.1, 5.3, 5.4, 5.5, 5.6, 5.7, 5.9, 6.0, 6.1.3, 7.1, 7.3.1 and 7.3.2.
2. The study was updated to have combination durvalumab/radiation therapy Cycles 1-3 as opposed to Cycles 2-4 including Sections 1.1, 5.1, 5.2, 5.2.1, 6.1.3, 6.2, 7.1, 7.3.1 and 7.3.2.
3. The study was updated to have durvalumab monotherapy transition to Q4 weekly for Cycles 4-6 including Sections 1.1, 5.1, 5.2, 5.2.1, 6.1.3, 7.1 and 7.3.3.
4. The definition of dose limiting toxicity was removed from Section 5.3 as the study will no longer have a dose escalation.
5. In Version 1.1 of this Amendment 1, Footnote 9 of the Time and Events Table (in regard to blood draws) has been modified to add "…and 24 mL of blood in ACD."

Eligibility changes

1. Eligibility criterion 4.1.8 was updated to clarify that the serum pregnancy test should be conducted within 3 days prior to treatment.
2. Eligibility criteria 4.1.9, 4.1.10, 4.2.7, 4.2.8 and 4.2.14 were updated to remove references to combination therapy with durvalumab and tremelimumab.
3. Eligibility criterion 4.2.5 was updated to clarify that the timeframe is whichever specified timeframe is shortest.

4. Eligibility criterion 4.2.13 was updated to only prohibit subjects from enrolling with "uncontrolled" liver disease.

The attached version dated May 24, 2019 incorporates the above revisions

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

LCCC 1725: A Phase II Study of Durvalumab (MEDI 4736) with Radiotherapy for the adjuvant treatment of Intermediate Risk Head and Neck Squamous Cell Carcinoma

Principal Investigator
Siddharth Sheth, DO
Division of Hematology/Oncology
3115 Physicians Office Bldg
170 Manning Dr, CB# 7305
Chapel Hill, NC 27599-7305
919-843-7709 (PHONE)
919-966-6735 (FAX)
Email: Siddharth.Sheth@med.unc.edu

Biostatistician
Allison Deal, MS
Allison_Deal@med.unc.edu
Phone: 919-966-1387
Fax: 919-966-4244

Clinical Protocol Office
Lineberger Comprehensive Cancer Center
The University of North Carolina at Chapel Hill
450 West Drive, 3rd Floor, CB# 7295
Chapel Hill, NC 27599-7295

CPO Multicenter Project Manager:
Phone: 919-966-7359
Fax: 919-966-4300
Email: CPOMulticenter@med.unc.edu

Sponsor: Lineberger Comprehensive Cancer Center

Funding Source: AstraZeneca
Version: Protocol Amendment #4 Version 4.0
Version date: June 1, 2021

LCCC 1725: A Phase II Study of Durvalumab (MEDI 4736) with Radiotherapy for the adjuvant treatment of Intermediate Risk Head and Neck Squamous Cell Carcinoma

Principal Investigator
Siddharth Sheth, DO
Division of Hematology/Oncology
3115 Physicians Office Bldg
170 Manning Dr, CB# 7305
Chapel Hill, NC 27599-7305
919-843-7709 (PHONE)
919-966-6735 (FAX)
Email: Siddharth.Sheth@med.unc.edu

Signature Page

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this trial will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable U.S. federal regulations and ICH guidelines.

Principal Investigator (PI) Name:_____

PI Signature: _____

Date:_____

Amendment: 4
Version: 4.0
Version date: June 1, 2021

LIST OF ABBREVIATIONS

ACD	Acid Citrate Dextrose
AE	Adverse event
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
β-HCG	Beta-human chorionic gonadotropin
BUN	Blood urea nitrogen
C	Celsius
CBC	Complete blood count
CD	Cluster of differentiation
CL	Chloride
CLIA	Clinical Laboratory Improvement Amendments
CO2	Bicarbonate
CPO	Clinical Protocol Office
CT	Computer tomography
CTLA-4	Cytotoxic T lymphocyte associated antigen 4
CTV60	Clinical target volume 60 Gy
D1	Day 1
DFS	Disease-free survival
dL	Deciliter
DLT	Dose limiting toxicity
DNA	Deoxyribonucleic acid
DSMC	Data safety monitoring committee
ECE	Extracapsular extension
eCRF	Electronic case report form
ECOG	Eastern Cooperative Oncology Group
EDTA	Ethylenediaminetetraacetic acid
EORTC	European Organization for Research and Treatment of Cancer
F	Fahrenheit
FACT	Functional assessment of cancer therapy
Fc	Constant fragment
FDA	Food and Drug Administration
G or gm	Gram
GCP	Good clinical practice
GMP	Good Manufacturing Practice
Gy	Gray
HBs-Ag	Hepatitis B surface antigen
HBc	Hepatitis B core
Hgb	Hemoglobin
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health insurance portability act
HIV	Human immunodeficiency virus
HL	Hodgkin's lymphoma
HNSCC	Head and neck squamous cell carcinoma
HPV	Human papilloma virus
IC	Immune cells
ICH	International Conference on Harmonization
ICOS	Immune costimulator
IDS	Investigational drug service

IFN	Interferon
IGRT	Image guidance radiation therapy
Ig	Immunoglobulin
IHC	Immunohistochemistry
ILD	Interstitial lung disease
imAE	Immune-mediated adverse event
IMRT	Intensity-modulated radiation therapy
IND	Investigational new drug
IO	Immuno-oncology
irAE	Immune-related adverse event
IRB	Institutional Review Board
IV	Intravenous
K	Potassium
Kg	Kilograms
LCCC	Lineberger Comprehensive Cancer Center
LDH	Lactate dehydrogenase
mAB	Monoclonal antibody
Mg	Magnesium
Mg/m^2 or mL or mm^3	Milligrams per meter squared or milliliter or cubic millimeter
MHC	Major histocompatibility complex
MRI	Magnetic resonance Imaging
MTD	Maximum Tolerated Dose
Na	Sodium
NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NF-κB	Nuclear factor kappa light-chain enhancer of activated B cells
NHL	Non-Hodgkin's lymphoma
NIH	National Institute of Health
NK	Natural killer
NSCLC	Non-small cell lung cancer
OHRE	Office of Human Research Ethics
OS	Overall survival
PBMC	Peripheral blood mononuclear cells
PCR	Polymerase chain reaction
PD	Progressive disease
PD-1/PDL-1	Program cell death receptor 1/Programmed cell death ligand 1
PET	Positron Emission Tomography
PFS	Progression free survival
PK	Pharmacokinetic
PHI	Personal health information
PRC	Protocol review committee
QOL	Quality of life
QW/Q2W/Q4W	Once weekly/Once every 2 weeks/Once every 4 weeks
RBC	Red blood cell
RNA	Ribonucleic acid
RTOG	Radiation Oncology Group
SAE	Serious adverse event
SCID	Severe combined immunodeficiency
SD	Stable disease
SOC	Standard of care
SOP	Standard operating procedure
SPO2	Saturation of peripheral oxygen

SUSAR	Serious unexpected adverse reaction
T3/T4	Thyroxine 3 or 4
TC	Tumor cells
TCR	T-cell receptor
TIL	Tumor infiltrating lymphocytes
TNF/TNFR	Tumor necrosis factor/Receptor
TPF	Tissue procurement facility
TSH	Thyroid stimulating hormone
TUNEL	Terminal deoxynucleotidyl dUTP tranferase nick end labeling (dUTP = deoxyuridine triphosphate)
µl or µM	Microliter or micromolar
ULN	Upper limit of normal
UNC	University of North Carolina
WT	Weight
WOCBP	Woman of childbearing potential
XRT	Radiation
Yr or yrs	Year or years

TABLE OF CONTENTS

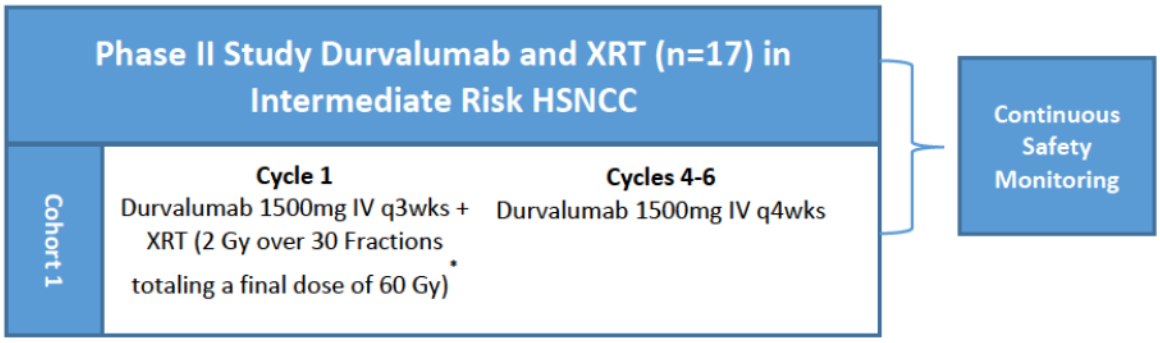
1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

Currently, there is no standard of care for those diagnosed with intermediate risk head and neck squamous cell carcinoma (HNSCC), defined as locally advanced disease with risk features other than extracapsular extension (ECE) or positive margins. Most commonly they are treated with either radiotherapy alone or with concurrent chemo-radiotherapy (cCRT) in the post-surgical setting, with no high level evidence to define which should have chemotherapy added to adjuvant radiotherapy. In patients receiving cCRT, cisplatin is most commonly used. The clinical benefit of cisplatin with radiation therapy in this patient population is questionable and the rate of serious toxicity is high. To address the unmet need for improving systemic treatment options, this multi-center, single arm Phase II trial will evaluate the feasibility of combining radiation therapy with durvalumab as adjuvant therapy for patients with intermediate risk HNSCC.

A total of 18 evaluable subjects will be accrued as depicted in the study schema. The treatment regimen will administer Q3 weekly flat dosing durvalumab (1500 mg) with radiation therapy in cycles 1-3, followed by single agent durvalumab (1500 mg) Q4 weekly for an additional three cycles. Our hypothesis is that durvalumab combined with radiation will have improved 3-year disease free survival (DFS) compared to historical control. Secondarily, we predict there will be fewer Grade 3-5 acute toxicities compared to the combination of radiation therapy and cisplatin. Tissue and blood based correlative studies will characterize the tumor microenvironment both at pre-treatment and in the event of recurrence.

Study Schema



*Radiation therapy is administered per standard radiation oncology regimens, on a daily basis and/or as scheduling during a Monday-Friday work week. Radiation therapy is given concurrently with durvalumab during Cycles 1-3. Durvlumab treatment Cycles 1-3 are 3-week long cycles (total of 9 weeks). Radiation therapy will be delivered at a dose of 2 Gy over 30 fractions totaling a final dose of 60 Gy. Radiation treatment will take 6 weeks (Monday-Friday) or 30 days and occurs for 6 of 9 weeks that define Cycles 1-3. However, due to delays or missed appointments, completion of those

30 fractions may take longer than the allotted 6 weeks and this is allowed. Radiation therapy must be scheduled and completed within Cycels 1-3 and should not extend into Cycle 4.

1.2 Postoperative Treatment in Head and Neck Cancer: Cisplatin and Radiation as Standard of Care (SOC)

In the modern era, HNSCC has been divided into virally driven cancers due to the human papilloma virus (HPV) and non-HPV cancers, which are typically mediated by smoking and heavy alcohol use. Locally advanced HNSCC is treated with either concurrent cCRT therapy or surgery followed by adjuvant therapy. Commonly, HPV-driven cancers are treated with cCRT and the prognosis is excellent. In contrast, surgery is generally reserved for non-HPV driven cancers or high-risk HPV-positive tumors, both of which are associated with inferior prognosis. Unsurprisingly, postoperative outcomes in HNSCC are poor. In the pre-adjuvant therapy era, local and regional recurrence occurred in 30% of patients and distant recurrence in 25% [1]. Adjuvant radiotherapy (XRT) improves outcomes, however less than 50% patients are disease free at five years.

Two phase 3 studies attempted to improve outcomes for post-operative HNSCC patients by adding cisplatin chemotherapy to adjuvant radiotherapy. RTOG 9501 randomized patients with histologic evidence of invasion of two or more regional lymph nodes, extracapsular extension of nodal disease, or microscopically- involved mucosal margins of resection to either radiotherapy alone or radiotherapy plus three cycles of cisplatin at 100 mg/m^2 [2, 3]. A second study, EORTC 22931, had a similar randomization, but different inclusion criteria -- pT3 or pT4 and any nodal stage (except T3N0 of the larynx, with negative resection margins), or a tumor stage of 1 or 2 with a nodal stage of 2 or 3 or stage T1/T-N0/1 with unfavorable pathological findings (extranodal spread, positive resection margins, perineural involvement, or vascular tumor embolism) or oral-cavity or oropharyngeal tumors with involved lymph nodes at level IV or V [4].

A combined analysis of these two trials showed that clear benefit from the addition of cisplatin to radiation therapy was restricted to only patients with extracapsular extension (ECE) or positive surgical margins. This benefit was statistically significant in subgroup analysis in EORTC with a strong trend towards significance in RTOG [5]. Similarly, in long-term follow up (at 9.4 years) of the RTOG study, only patients with ECE or positive margins had a benefit in terms of locoregional failure and disease free survival (DFS). Critically, 10-year disease-free survival (DFS) was poor in cisplatin and radiation treated patients (18%) and only slightly improved compared to patients treated with radiation alone (12%). Perhaps most importantly, no overall survival advantage was noted when comparing cCRT to XRT alone (27% vs 20%, P=0.07) [3]. Thus, the treatment advantage offered by the addition of cisplatin is marginal and there is a low threshold to evaluate experimental therapeutics with the hope of superiority.

Nevertheless, high risk patients, with either ECE or positive surgical margins on their surgical pathology, should receive cisplatin and radiation therapy. In the treatment of patients with intermediate risk factors, defined as having unfavorable pathological factors in the absence of ECE or positive margins, there remains widespread practice variation. These patients may receive either no adjuvant therapy, XRT alone or cCRT, depending on institution, patient, and provider preferences. Importantly, intermediate risk patients who received radiation therapy alone had a locoregional failure risk of 15-35% [6]. To date, there are no published studies comparing radiation therapy versus concurrent systemic therapy plus radiation in this study population. As a result, there is an opportunity to evaluate experimental therapeutics in the intermediate risk population, which may improve outcomes.

1.2.1 Cisplatin with Radiation Therapy: A Highly Toxic Standard of Care

In RTOG 9501 study, the rate of grade 3-5 acute toxicities with radiotherapy alone was 34.4%. This rate rose to 77% with the addition of cisplatin to radiotherapy [7]. In clinical practice, long-term otopathy, nephropathy and neuropathy are also commonly seen in patients treated with cisplatin alone [8]. Finally, many HNSCC patients are considered poor candidates for cisplatin due advanced age, baseline renal dysfunction, known auditory deficits including hearing loss and/or tinnitus, and poor performance status [9]. The combination of poor efficacy and highly toxic side effects with cisplatin opens the door for investigating alternative treatment strategies.

1.3 Immunotherapy

It is increasingly understood that cancers are recognized by the immune system, and, under some circumstances, the immune system may control or even eliminate tumors [10, 11]. Inhibitory pathways, also known as immune checkpoints, control the duration and extent of immune system activity and deliver negative signals to prevent immune reactions by the host. PD-1 is a well-studied inhibitory pathway that leads to down regulation of T cell activation. Therefore, impaired immune recognition occurs when a high percentage of PD-1 T cells are expressed by the tumor or found in the tumor microenvironment [12]. Immunomodulatory agents have been developed to target the inhibitory pathways with the goal of re-activating T cells and producing improved antitumor immune response.

1.3.1 PD1 and PDL1 inhibition

PD-L1 is a member of the B7 family of ligands that inhibit T-cell activity through binding to the PD-1 receptor and to CD80. PD-L1 expression is an adaptive response that helps tumors evade detection and elimination by the immune system. Expression of PD-L1 protein is induced by inflammatory signals that are typically associated with an adaptive immune response (e.g. IFNγ) and can be found on both tumor cells (TC) and tumor infiltrating immune cells (IC). The binding of PD-L1 to PD-1 on activated T cells delivers an inhibitory signal to the T cells, preventing them from killing target TC, and protecting the tumor from immune elimination

[13]. PD-L1 may also inhibit T cells through binding to CD80, although the exact mechanism is still not elucidated [14, 15].

The inhibitory mechanism described above is co-opted by tumors that express PD-L1 as a way of evading immune detection and elimination. The binding of an anti-PD-L1 agent to the PD-L1 receptor inhibits the interaction of PD-L1 with the PD-1 and CD80 receptors expressed on immune cells. This activity overcomes PD-L1–mediated inhibition of antitumor immunity. While functional blockade of PD-L1 results in T-cell reactivation, this mechanism of action is different from direct agonism of a stimulatory receptor such as CD28 [16].

In vivo studies have shown that durvalumab inhibits tumor growth in xenograft models via a T cell-dependent mechanism [17]. PD-L1 is expressed in a broad range of cancers. Based on these findings, an anti-PD-L1 antibody could be used therapeutically to enhance antitumor immune responses in patients with cancer. Results of non-clinical and clinical studies of monoclonal antibodies (mAbs) targeting the PD-L1/PD-1 pathway have shown evidence of clinical activity and a manageable safety profile, supporting the hypothesis that an anti-PD-L1 antibody could be used to therapeutically enhance antitumor immune response in cancer patients with responses that tend to be more pronounced in patients with tumors that express PD-L1 [18]. In addition, high mutational burden, for example in bladder carcinoma, may contribute to the responses seen with immune therapy [19].

1.3.2 Combining Immunotherapy with Radiation Therapy

Radiation therapy remains a backbone in the treatment of HNSCC in definitive, palliative, and adjuvant setting. The rationale for postoperative radiation is to target microscopic deposits of cancer cells that may remain after resection [20]. If untreated, these cells may eventually lead to a local–regional recurrence. Immunologically, radiotherapy induces antigen release from the tumor and danger signals activating both the host's innate and adaptive immune system [21]. This may lead to reverse the tolerance to weakly immunogenic tumor-associated antigens and elicit both local and distant anticancer immune response.

Radiation therapy has been shown to have a synergistic effect with various immunomodulating agents [22]. Additionally upregulation of PD-L1 expression leads to T cell exhaustion, which causes resistance to treatment from radiotherapy [23]. This provides a rationale for the combination of PD-L1 inhibitors with radiation therapy and is currently being evaluated in multiple clinical trials.

1.4 PD1 and PDL1 inhibition in metastatic/recurrent HNSCC

Immunotherapy has made substantial advances in the care of incurable HNSCC, with the recent FDA approval of the immune checkpoint inhibitors pembrolizumab and nivolumab in the second-line setting for patients with disease progression or recurrence after first line platinum-based chemotherapy. In phase II study, response rate (RR) to pembrolizumab in unselected and mostly highly pretreated patients

was 16% and overall survival (OS) was 8 months, results significantly superior to that expected with standard therapy [24]. Nivolumab was compared in phase III study to standard of care treatment with investigator's choice of docetaxel, methotrexate or cetuximab and showed superior survival [25]. Durvalumab was evaluated in 62 patients with recurrent or metastatic HNSCC and had an overall response rate of 12% [26]. Of note, in each of these studies, the toxicity profile of immunotherapy was notably superior to that seen in major studies of cisplatin. Critically for consideration of these agents in the adjuvant context, survival advantages seen in these studies and in clinical practice include a real proportion of long-term survivors.

1.5 Study Agent

1.5.1 Durvalumab

Durvalumab is a human monoclonal antibody (mAb) of the immunoglobulin G (IgG) 1 kappa subclass that blocks the interaction of PD-L1 (but not programmed cell death ligand-2) with PD-1 on T cells and CD80 (B7.1) on immune cells. Durvalumab has been engineered to reduce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity. *In vitro* studies demonstrate that durvalumab antagonizes the inhibitory effect of PD-L1 on primary human T cells, resulting in their restored proliferation and release of interferon gamma.

As of July 2019, 5127 patients have been exposed to one or more doses of durvalumab in ongoing open-label AstraZeneca-sponsored or MedImmune-sponsored Phase I-III monotherapy and combination therapy studies across all indications [27].

In patients with recurrent/metastatic HNSCC who received durvalumab monotherapy from Study 1108, overall response rate (ORR) was 7.3% across all patients, 16.7% in patients with PD-L1 high tumors and 2.7% in patients with PD-L1 low/negative tumors. Median OS was 8.4 months and OS at 24 months was 24.2%. In Study D413C0001, HNSCC patients with PD-L1% high, ORR was 16.2%. The median duration of treatment was 3.45 months, while the median OS was 7.1 months [24].

1.5.1.1 Rationale for Fixed Dosing of Durvalumab

A population pharmacokinetic (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 once every 2 weeks (Q2W) or 15 mg/kg once every 3 weeks (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 patients were simulated using body WT distribution of 40–120 kg.

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

A fixed dosing approach is preferred 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 durvalumab (equivalent to 20 mg/kg) will be used at Q3W during cycles 1-3 and Q4W during cycles 4-6 in the current study.

1.5.1.2 Durvalumab Dosing Schedule

Pre-clinical and clinical studies have evaluated the scheduling of durvalumab at two week, three week, and four week cycles. We have decided to proceed with durvalumab Q3W cycles when used in combination with radiation therapy and then Q4W when used as monotherapy following the completion of radiation.

1.5.2 Radiation Therapy + Durvalumab

In a single center subset of patients with solid malignancies, a phase I/II trial of durvalumab in combination with radiotherapy in the palliative setting was shown to be safe. The median duration of exposure to durvalumab was 5.2 months with a median delivery of 11 cycles (range, 4-38 cycles). RT (conformal 3D RT, 79% and intracranial stereotactic RT, 21%) was delivered at 28 Gy (range, 6-92), in a median number of five fractions (range, 1-10) and over a median duration of 6 days (range, 1-14). Five patients (50%) reported an irradiation-related adverse event grade 1 or 2 and one patient had two grade 2 AEs. The most frequently reported AE was grade 2 mucositis. There were no grade three or higher AEs.

1.6 Rationale for Clinical Study

The rationale for combining immuno-oncology (IO) with radiotherapy is multifactorial. In addition to cell death caused by high-dose radiation, radiotherapy has crosstalk with the immune system in three principle ways: (1) induction of immunogenic cell death to recruit antitumor T cells to the irradiated site; (2) upregulation of major histocompatibility complex (MHC) I expression, which was previously downregulated for immune escape; and (3) expansion of the diversity of the T cell receptor (TCR) repertoire to detect tumor antigens [28].

Therefore, the combination of PD-1/PD-L1 inhibitors and radiotherapy has the potential for synergistic properties by (1) reducing the number of MDSCs in the tumor microenvironment; (2) increasing CD8+ to Treg ratio; and (3) enhancing CD8+ infiltration, thereby augmenting the antitumor response. There currently exists data in multiple tumor types showing the positive role of combining PD-1/PD-L1 inhibitors and radiotherapy in different types of tumors.

1.6.1 Dose Rationale

Durvalumab dosing at 1500mg IV q3 and q4 weeks has been previously studied and has minimal toxicities when combined with radiation therapy. The use of 2 Gy over 30 fractions totaling a final dose of 60 Gy is the standard radiation dosing regimen in the adjuvant setting.

1.7 Correlative Studies

The tumor immune microenvironment is a complex mixture of competing cellular phenotypes. Thus, an optimal predictor of response to immunomodulatory therapy will likely include features that describe tumor genetics, tumor-related immunosuppression, and any existent but insufficient anti-tumor immune response. Chronic antigen exposure in the setting of tumor growth and metastasis leads to anergy and dysfunction (exhaustion) of the adaptive immune response, in part through increased engagement of the PD-1 receptor with its ligand (PD-L1). The net result of signaling through this axis is an attenuation of the cytotoxic and cytokine-producing capacity of tumor-infiltrating lymphocytes, leading to ineffective antitumor immune responses. In patients with metastatic melanoma, the fraction of partially exhausted cytotoxic T lymphocytes (peCTLs, tumor-infiltrating CD8+ T cells expressing high levels of cytotoxic T lymphocyte–associated antigen 4 [CTLA-4] and PD-1) strongly correlates with response to anti–PD-1 monotherapy. We plan to assess these parameters in our proposed study.

We hope to characterize the tumor immune microenvironment in multiple settings (1) in pre-treatment, surgically resected tissue, (2) during various times points during treatment with combination IO therapy with radiation therapy, and (3) at time of disease recurrence. Correlative studies will be run in both tumor and blood samples.

Specific aims include: (1) evaluation of the immunosuppressive biomarker PD-L1 on tumor and immune cells using immunohistochemistry analysis at pre-treatment and at disease recurrence. The expression of baseline PD-LI levels will be assessed for its predictive response to recurrence; and (2) measurement of inflammatory/immune signature including CD4, CD8, CD25, FOXP3 and TUNEL/Caspase3 by flow cytometry to better understand the treatment-related changes in the tumor microenvironment.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

2.1.1 To estimate median 3-year disease free survival (DFS) in patients with intermediate-risk HNSCC treated with adjuvant durvalumab with radiotherapy.

2.2 Secondary Objectives

2.2.1 To characterize safety by evaluating Grade 3-4 acute toxicities of adjuvant durvalumab with radiotherapy in intermediate-risk HNSCC patients

2.2.2 To characterize the Grade 3-4 chronic toxicities of adjuvant durvalumab with radiotherapy in intermediate-risk HNSCC patients.

2.2.3 To characterize any-grade chronic toxicities of adjuvant durvalumab with radiotherapy in intermediate-risk HNSCC patients.

2.2.4 To estimate median OS in patients with intermediate-risk HNSCC treated with adjuvant durvalumab with radiotherapy.

2.2.5 To correlate PD-L1 expression with disease free survival

2.3 Exploratory Objectives

2.3.1 [redacted]

[redacted]

3.0 Criteria for Evaluation / Study Endpoints

3.1 Primary Endpoint

3.1.1 3-year DFS will be estimated via the Kaplan-Meier method. DFS is defined as the time from D1 of treatment to time of disease recurrence or death.

3.2 Secondary Endpoints

3.2.1 Grade 3-5 acute toxicity will be evaluated according to guidelines from NCI CTCAE, v5.0 and include toxicity from the first day of treatment with immunotherapy until 30 days after completion of concurrent immunotherapy and radiation. Toxicity will include all toxicity attributed to the total study regimen (inclusive of radiation) not just to durvalumab alone.

3.2.2 Grade chronic 3-5 toxicity will be evaluated according to guidelines from NCI CTCAE, v5.0 and include toxicity continuing or occurring 30 days after completion of concurrent immunotherapy and radiation, and will be followed for up to 6 months.

3.2.3 OS will be estimated via the Kaplan-Meier method. OS is defined as the time from D1 of treatment to death from any cause.

3.2.4 Measure PD-LI expression by immunohistochemistry. Pre-treatment PD-L1 expression will be correlated with disease free survival following treatment of adjuvant durvalumab with radiotherapy

3.3 Exploratory Endpoints

3.3.1 [redacted]

[redacted]

4.0 PATIENT ELIGIBILITY

In order to participate in this study a subject must meet all of the eligibility criteria outlined below.

4.1 Inclusion Criteria

4.1.1 Written informed consent obtained to participate in the study and HIPAA authorization for release of personal health information. Consent for the use of any residual material from biopsy (archival tissue) and serial blood draws will be required for enrollment.

4.1.2 Age ≥ 18 years of age on day of signing informed consent

4.1.3 ECOG Performance Status of 0 or 1 (See Appendix 12.4: ECOG Performance Status)

4.1.4 Histologically confirmed squamous cell carcinoma of the head and neck, including the following subtypes: oral cavity, oropharynx, hypopharynx, larynx

4.1.5 Must have undergone gross total resection of the primary tumor with curative intent within the past 8 weeks with surgical pathology demonstrating ≥ 1 of the following criteria for "intermediate" risk of recurrence:

- perineural invasion
- lymphovascular invasion
- single lymph node > 3 cm or at least 2 nodes without evidence of extracapsular extension
- close margins defined as < 5 mm but not frankly positive (in the case of ambiguous, controversial, or superseded margins, final clinical assessment regarding margin status will prevail)
- pathologically confirmed T3 or T4 primary tumor

4.1.6 No prior therapy to primary tumor prior to surgical resection (no induction therapy or recurrent disease).

4.1.7 Demonstrated adequate organ function as defined in the table below; all screening labs to be obtained within 14 days prior to initiating study treatment

System	Laboratory Value
Hematological*	
Hemoglobin (Hgb)	≥ 8 g/dL (acceptable to reach via transfusion)
Absolute Neutrophil Count (ANC)	≥ 1000 per mm^3
Platelets	≥ 75,000 per mm^3
Renal*	
Calculated creatinine clearance[1]	≥ 40 mL/min using the Cockcroft-Gault formula in Appendix 12.3
Hepatic*	
Bilirubin	≤ 1.5 × upper limit of normal (ULN)
Aspartate aminotransferase (AST)	≤2.5 × ULN
Alanine aminotransferase (ALT)	≤2.5 × ULN

1. Measured creatinine clearance (CL) >40 mL/min or Calculated creatinine clearance CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance

***Note:** Hematology and other lab parameters that are ≤ grade 2 BUT still meet criteria for study entry are allowed. Furthermore, changes in laboratory parameters during the study should not be considered adverse events unless they meet criteria for dose modification(s) of study medication outlined by the protocol and/or worsen from baseline during therapy.

4.1.8 Women of childbearing potential (WOCBP) must have a negative serum pregnancy test within 7 days prior to treatment. NOTE: Females are considered of child bearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for at least 12 consecutive months. Documentation of postmenopausal status must be provided.

4.1.9 WOCBP must be willing to abstain from heterosexual activity or to use at least 1 highly effective method of contraception from the time of informed consent until 90 days after durvalumab monotherapy treatment is discontinued (whichever is longer).

See section 5.6 of the protocol for additional details on contraception requirements for WOCBP and male participants in this trial.

4.1.10 Male patients with female partners must have had a prior vasectomy or agree to use an adequate method of contraception (i.e., double barrier method: condom plus

spermicidal agent) starting with the first dose of study therapy through 90 days after durvalumab monotherapy is discontinued.

4.1.11 Subjects must be willing and able to comply with study procedures based on the judgment of the investigator or protocol designee.

4.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria will not be able to participate in this study:

4.2.1 Is currently participating in or has participated in a study of an investigational agent or an investigational device within 4 weeks of the first dose of treatment.

4.2.2 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.

4.2.3 Has evidence of metastatic disease at time of diagnosis

4.2.4 Is receiving concurrent chemotherapy, investigational drug, biologic, or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non–cancer-related conditions (e.g., hormone replacement therapy) is acceptable.

4.2.5 Treatment with any investigational drug within 28 days or 5 half-lives of Day 1 of treatment on this study, whichever is shortest.

4.2.6 Has not received any antibiotics <7 days prior to 1st dose of durvalumab. If the patient receives either IV antibiotics or >5 day treatment course (oral or IV), then the 1st durvalumab dose should not be given until 14 days of last antibiotic dose. During eligibility screening, subjects who receive any antibiotics within 30 days prior to the proposed initial infusion of durvalumab should be flagged and reviewed by the site's Principle Investigator to determine if the subject is a good candidate to receive durvalumab.

4.2.7 Known allergy or hypersensitivity to durvalumab or any of the study drug excipients.

4.2.8 Prior randomization or treatment in a previous durvalumab clinical study regardless of treatment arm assignment.

4.2.9 Current or prior use of immunosuppressive medication within 14 days before the first dose of durvalumab. The following are exceptions to this criterion:

- Intranasal, inhaled, topical steroids, or local steroid injections (e.g., intra articular injection)

- Systemic corticosteroids at physiologic doses not to exceed 10 mg/day of prednisone or its equivalent
- Steroids as premedication for hypersensitivity reactions (e.g., CT scan premedication)

4.2.10 Has received systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.

4.2.11 Active infection requiring systemic therapy including tuberculosis (clinical evaluation that includes clinical history, physical examination and radiographic findings, and TB testing in line with local practice), hepatitis B (known positive HBV surface antigen (HBsAg) result), hepatitis C, or human immunodeficiency virus (positive HIV 1/2 antibodies).

- 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 hepatitis C (HCV) antibody are eligible only if polymerase chain reaction is negative for HCV RNA**.**

4.2.12 Has a known contraindication to radiation therapy, including inherited syndromes associated with hypersensitivity to ionizing radiation such as Ataxia-Telangiectasia and Nijmegen Breakage Syndrome

4.2.13 Has a history of uncontrolled liver disease (including but not limited to cirrhosis).

4.2.14 Subjects with baseline weight ≤ 40kg (88 lbs).

4.2.15 Female patients who are pregnant or breastfeeding (NOTE: breast milk cannot be stored for future use while the mother is being treated on study) or male or female patients of reproductive potential who are not willing to employ effective birth control from screening to 90 days after the last dose of durvalumab monotherapy.

4.2.16 History of another primary malignancy except for.

- Malignancy treated with curative intent and with no known active disease ≥5 years before the first dose of IP and of low potential risk for recurrence
- Adequately treated non-melanoma skin cancer or lentigo maligna without evidence of disease
- Adequately treated carcinoma *in situ* without evidence of disease

4.2.17 History of leptomeningeal carcinomatosis.

4.2.18 Has an active autoimmune disease (or inflammatory disorders) requiring systemic treatment within the past 3 months or a documented history of clinically severe autoimmune disease, or a syndrome that requires systemic steroids or immunosuppressive agents. Subjects with inflammatory disorders (including inflammatory bowel disease [e.g., 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:

- Subjects with vitiligo or alopecia or resolved childhood asthma/atopy
- Subjects who require intermittent use of bronchodilators or local steroid injections would not be excluded from the study.
- Subjects with hypothyroidism (e.g., following Hashimoto syndrome) stable on hormone replacement or with Sjorgen's syndrome will not be excluded from the study
- Any chronic skin condition that does not require systemic therapy
- Subjects without active HNSCC disease in the last 5 years may be included but only after consultation with the study physician
- Subjects with celiac disease controlled by diet alone

4.2.19 Has a history of non-infectious pneumonitis that required steroids or evidence of interstitial lung disease or current active, non-infectious pneumonitis.

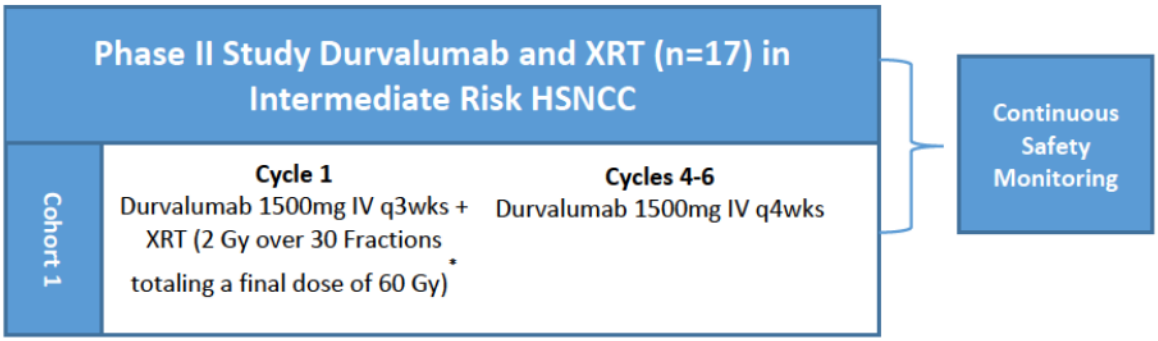
4.2.20 Major surgical procedure (as defined by the Investigator) within 21 days prior to the first dose of investigational product (IP). Note: Local surgery of isolated lesions for palliative intent is acceptable.

4.2.21 Uncontrolled intercurrent illness, including but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, 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.

4.2.22 Receipt of live attenuated vaccine within 30 days prior to the first dose of study drug. Note: Patients, if enrolled, should not receive live vaccine whilst receiving study treatment and up to 30 days after the last dose of study treatment.

5.0 TREATMENT PLAN

5.1 Schema



*Radiation therapy is administered per standard radiation oncology regimens, on a daily basis and/or as scheduling during a Monday-Friday work week. Radiation therapy is given concurrently with durvalumab during Cycles 1-3. Durvlumab treatment Cycles 1-3 are 3-week long cycles (total of 9 weeks). Radiation therapy will be delivered at a dose of 2 Gy over 30 fractions totaling a final dose of 60 Gy. Radiation treatment will take 6 weeks (Monday-Friday) or 30 days and occurs for 6 of 9 weeks that define Cycles 1-3. However, due to delays or missed appointments, completion of those 30 fractions may take longer than the allotted 6 weeks and this is allowed. Radiation therapy must be scheduled and completed within Cycels 1-3 and should not extend into Cycle 4.

5.2 Treatment Dosage

This Phase II trial will evaluate the combination of durvalumab with radiation therapy as post-operative therapy in intermediate risk patients with HNSCC. All patients will receive durvalumab and radiation therapy during cycles 1-3. Radiation therapy is administered per standard radiation oncology regimens, on a daily basis and/or as scheduled during a Monday-Friday working week. Radiation therapy is given concurrently with durvalumab during Cycles 1-3. Durvalumab treatment (1500 mg Q3W) Cycles 1-3 are 3-weeks long cycles (total of 9 weeks). Radiation therapy will be delivered at a dose of 2 Gy over 30 fractions totalling a final dose of 60 Gy. Radiation treatment will take 6 weeks (Mon-Fri) or 30 days and will occur for 6 of 9 weeks that define Cycles 1-3. However, due to delays or missed appointments, completion of those 30 fractions may take longer than the allotted 6 weeks and this is allowed. Radiation therapy must be scheduled and completed within Cycles 1-3 and should not extend into Cycle 4. Please refer to Section 6.2 for additional details and allowances.

During Cycle 4-6, only durvalumab 1500mg Q4W will be given.

5.2.1 Treatment Administration

Agent	Pre-medications	Dose	Route	Schedule
Durvalumab	None required	1500mg	Intravenous (IV)	Day 1, Cycle 1 every 3 weeks for 3 cycles (C1-3) (3-week cycles), followed by every 4 weeks for 3 cycles (C4-6) (4-week cycles)
Radiation Therapy	Per standard of care	2Gy over 30 fractions for a total of 60 Gy *CTV66 may be defined at the discretion of the treating radiation oncologist. This would include regions felt to be at particularly high risk for recurrence (e.g., an area of the ECS or positive margin of resection). Note: A separate boost plan will be created (2 Gy/fx for 3 fractions for a total dose of 6 Gy)	Per standard of care	Administered per standard radiation oncology regimens, on a daily basis and/or as scheduled during a Monday-Friday working week. Radiation treatment will take 6 weeks (Mon-Fri) or 30 days and occur 6 of 9 weeks that define cycles 1-3. However, due to delays or missed appoints, completion of those 30 fractions may take longer than the allotted 6 weeks and this is allowed. Radiation therapy must be scheduled and completed within Cycles 1-3 and should not extend into Cycle 4.

Durvalumab infusion time is 60 minutes (±5 minutes). In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature once the infusion is started.

Radiation therapy will be given per standard of care.

5.3 Toxicities and Dosing Delays/Dose Modifications

Guidelines for the management of immune-mediated reactions, infusion-related reactions, and non-immune-mediated reactions for durvalumab monotherapy are provided in the **Dosing Modification and Toxicity Management Guidelines provided in Appendix 12.1** and relevant subsections.

- **12.1.1 Immune-Mediated Reactions - General**
- **12.1.2 Specific Immune-Mediated Reactions**
- **12.1.3 Non-Immune-Mediated Reactions**

- **12.1.4 Infusion-related Reactions**

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

In addition, there are certain circumstances (e.g., subject's weight falls to ≤ 30 kg/ 66.6 lbs.) in which durvalumab should be permanently discontinued (see Dosing Modification and Toxicity Management Guidelines provided in Appendix 12.0 as noted above).

Dose modifications will be made according to study protocol. Patients should be thoroughly evaluated and appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the immune mediated AEs. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an immune mediated AE diagnosis. In the absence of a clear alternative etiology, events should be considered potentially immune related. All toxicities will be graded according to NCI CTCAE, Version 5.0.

5.4 Concomitant Medications/Treatments/Supportive Care Allowed

The Principal Investigator must be informed as soon as possible about any medication taken from the time of screening until the end of the clinical phase of the study (end of study treatment visit). Any concomitant medication(s), including herbal preparations, taken during the study will be recorded in the eCRF. Refer to Appendix 12.0 for guidance on management of study drug-related toxicities. See section 5.2.1 for above details.

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 provided. 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," in section 5.5, should be used, when necessary for all patients. Inactivated virus vaccines (e.g., influenza vaccine) are permitted. Drugs with laxative properties and herbal or natural remedies for constipation are permitted.

Immunosuppressive medications (e.g., corticosteroids) are allowed for management of the following:

- Durvalumab related adverse events per dose modification guidelines provided in Appendix 12.0
- Use in subjects with contrast allergies
- Use of inhaled, topical, and intranasal corticosteroids is permitted
- A temporary period of steroid use is allowed if clinically indicated and considered to be essential for the management of non-immunotherapy related events experienced by the subject (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc.).

5.5 Prohibited Medications/Treatments

The following medications are prohibited while the subject is on study.

- Any investigational anticancer therapy other than those under investigation in this study
- mAbs against PD-1 or PD-L1 other than those under investigation in this study
- Chemotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment apart from those under investigation in this study
- Immunosuppressive medications including but not limited to systemic corticosteroids at doses ≥10 mg/day or prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers
- Sunitinib
- Tyrosine kinase inhibitors that target EGFR (e.g., erlotinib, gefinitib)
- Live attenuated vaccines – also withhold use for at least 30 days after discontinuing study medications
- Herbal and natural remedies, which have immune-modulating effects (e.g., ginseng, gingko biloba, ganoderma, astragalus, etc.)

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

5.6 Contraception Requirements

Female patient of childbearing potential

Females of childbearing potential who are sexually active with a non-sterilized male partner must use at least 1 highly effective method of contraception (see Table below) from the time of screening and must agree to continue using such precautions for 90 days after the last dose of durvalumab monotherapy . Non-sterilized male partners of a female patient must use male condom plus spermicide throughout this period. Cessation of birth control after this point should be discussed with a responsible physician. Not engaging in sexual activity for the total duration of the drug treatment and the drug washout period is an acceptable practice; however, periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control. Female patients should also refrain from breastfeeding throughout this period.

Male patients with a female partner of childbearing potential:

Non-sterilized males who are sexually active with a female partner of childbearing potential must use a male condom plus spermicide from screening through 90 days after receipt of the final dose of durvalumab monotherapy. Not engaging in sexual activity is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male patients should refrain from sperm donation throughout this period.

Female partners (of childbearing potential) of male patients must also use a highly effective method of contraception throughout this period (Table 1).

Females of childbearing potential are defined as:
Those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or post-menopausal.

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 >1 year ago, had chemotherapy-induced menopause with last menses >1 year ago, or underwent surgical sterilization (bilateral oophorectomy, bilateral salpingectomy or hysterectomy).

Highly effective methods of contraception, defined as one that results in a low failure rate (i.e., less than 1% per year) when used consistently and correctly are described in the Table below.

> **Note**: Some contraception methods are not considered highly effective (e.g., male or female condom with or without spermicide; female cap, diaphragm, or sponge with or without spermicide; non-copper containing intrauterine device; progestogen-only oral hormonal contraceptive pills where inhibition of ovulation is not the primary mode of action [excluding Cerazette/desogestrel which is considered highly effective]; and triphasic combined oral contraceptive pills).
>
> **Highly effective methods of contraception (<1% failure rate). See the table below.**

Barrier/Intrauterine methods	Hormonal Methods
• Copper T intrauterine device • Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	• Implants: Etonogestrel-releasing implants: e.g. Implanon® or Norplant® • Intravaginal: Ethinylestradiol/etonogestrel-releasing intravaginal devices: e.g. NuvaRing® • Injection: Medroxyprogesterone injection: e.g. Depo-Provera® • Combined Pill: Normal and low dose combined oral contraceptive pill • Patch: Norelgestromin/ethinylestradiol-releasing transdermal system: e.g. Ortho Evra® • Minipillc: Progesterone based oral contraceptive pill using desogestrel: Cerazette® is currently the only highly effective progesterone based pill

[a] This is also considered a hormonal method

5.7 Other Modalities or Procedures

Radiation therapy will be given per standard of care.

5.8 Reasons for Early Withdrawal from Study Treatment

Study treatment should continue through completion of the adjuvant immunotherapy and radiation therapy regimen outlined in Section 5.2. Subjects should be withdrawn from study therapy if they experience:

- Disease progression
- Subject weight is ≤ 30 kg (66.6 lbs.)
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s)
- Pregnancy or intent to become pregnant
- Patient decides to withdraw from study treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.
- Patient is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk

- Grade ≥3 infusion reaction
- Patient noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; e.g., refusal to adhere to scheduled visits
- Initiation of alternative anticancer therapy including another investigational agent
- Subject is lost to follow up

5.9 Duration of Follow Up

All patients will be followed for up to 5 years, or until death, whichever occurs first after removal from study treatment for determination of study endpoints. Patients removed from study treatment for unacceptable AEs will be followed for resolution or stabilization of the adverse event(s). All patients (including those withdrawn for AEs) should be followed after removal from study treatment as stipulated in the protocol.

5.10 Study Withdrawal

Patients will be removed from protocol therapy and the PI notified when any of the criteria listed in section 5.8 apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

If a patient decides to withdraw from the study (and not just from protocol therapy) an effort should be made to complete and report study assessments as thoroughly as possible. At the time of withdrawal, the investigator should attempt to establish as completely as possible the reason for the study withdrawal.

- The patient should be asked if they are willing to allow for the abstraction of relevant information from their medical record in order to meet the long term follow up (e.g., survival) objectives outlined in the protocol.
- If a patient withdraws consent, they should be specifically asked if they are withdrawing consent to:
  - all further participation in the study including any further follow up (e.g., survival contact telephone calls)
  - withdrawal of consent to the use of their study generated data
  - withdrawal to the use of any samples
- A complete final evaluation at the time of the patient's study withdrawal should be obtained with an explanation of why the patient is withdrawing from the study.
- If the patient is noncompliant and does not return for an end of study follow up assessment, this should be documented in the eCRF.
- If the reason for removal of a patient from the study is an adverse event, the principal specific event will be recorded on the eCRF.

Excessive patient withdrawals from protocol therapy or from the study can render the study un-interpretable; therefore, unnecessary withdrawal of patients should be avoided.

6.0 DRUG INFORMATION

The investigational drug in this study is durvalumab (Imfinzi™) and will be supplied by AstraZeneca.

6.1 Durvalumab (Imfinzi™)

6.1.1 Description

Durvalumab, a human IgG1κ mAb directed against PD-L1, contains a triple mutation in the constant domain of the IgG1 heavy chain that reduces binding to C1q and the Fcγ receptors. Durvalumab is being developed for the treatment of patients with solid tumors or hematologic malignancies. Durvalumab received accelerated approval in May of 2017 as treatment for patients with locally advanced or metastatic urothelial carcinoma who have progressed during or within 12 months of neoadjuvant or adjuvant platinum-containing chemotherapy.

Full prescribing information for durvalumab is available at:
https://www.azpicentral.com/imfinzi/imfinzi.pdf#page=1

6.1.2 Storage and Handling

Durvalumab will be supplied by AstraZeneca as a 500 mg vial solution for infusion after dilution. The solution contains 50 mg/mL durvalumab, 26 mM histidine/histidine-hydrochloride, 275 mM trehalose dihydrate, and 0.02% weight/volume (w/v) polysorbate 80; it has a pH of 6.0 and density of 1.054 g/mL. The nominal fill volume is 10.0 mL. Investigational product vials are stored at 2°C to 8°C (36°F to 46°F) and must not be frozen.

6.1.3 Dosage and Administration

Patients will receive durvalumab (1500mg Q3W) for cycles 1-3, followed by durvalumab 1500 mg Q4W for 3 additional cycles (i.e., cycles 4-6). Concomitant radiotherapy (2 GY in 30 fractions for a total of 60 Gy) will begin in cycle 1and may continue into cycle 3. Radiation therapy will take 6 weeks (Monday-Friday) or 30 days and occur 6 of 9 weeks that define Cycles 1-3. However, due to delays or missed appoints, completion of those 30 fractions may take longer than the allotted 6 weeks and this is allowed. Radiation therapy must be scheduled and completed within Cycles 1-3 and should not extend into Cycle 4. Please refer to Section 6.2 for additional details and allowances. Subjects will continue on study therapy as described unless there is unacceptable toxicity, withdrawal of consent, or another discontinuation criterion is met as outlined in section 5.8.

The immunotherapy regimens will be instituted approximately 3-5 weeks after surgery.

- Standard infusion time for durvalumab is 60 minutes (±5 minutes). Less than 55 minutes is considered a deviation.

- In the event that there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

- Durvalumab does not contain preservatives, and any unused portion must be discarded.

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

6.1.4 Durvalumab Preparation

Preparation of durvalumab doses for administration with an IV bag

Total time from needle puncture of the durvalumab vial to the start of administration should not exceed:

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

A dose of 1500 mg (for patients >30kg in weight) will be administered using an IV bag containing 0.9% (w/v) saline or 5% (w/v) dextrose, with a final durvalumab concentration ranging from 1 to 15 mg/mL, and delivered through an IV administration set with a 0.2- or 0.22-µm in-line filter.

Add 30.0 mL of durvalumab (i.e., 1500 mg of durvalumab) to the IV bag. The IV bag size should be selected such that the final concentration is within 1 to 15 mg/mL. Mix the bag by gently inverting to ensure homogeneity of the dose in the bag.

The IV line will be flushed with a volume of IV diluent equal to the priming volume of the infusion set used after the contents of the IV bag are fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

6.1.5 Drug Accountability

The investigator or designee is responsible for keeping accurate records of the clinical supplies received from the company sponsor or designee, the amount dispensed to the subjects and the amount remaining at the conclusion of the trial. An accurate and current accounting of the dispensing and return of investigational study drug for each subject will be maintained on an ongoing basis by a member of the study site staff. The amount of study drug dispensed and returned by the subject will be recorded in the Investigational Drug Accountability Record.

6.1.6 Return and Retention of Study Drug

Upon completion or termination of the study, all unused investigational product will be destroyed at the site per institutional policy (e.g., UNC IDS drug destruction policy). It is the Investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established

according to applicable federal, state, local and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

Handling and Disposal: Local requirements for disposal of hazardous drugs should be followed at each participating clinical site.

Please see UNC policy on hazardous drugs:
http://news.unchealthcare.org/empnews/att/2011/nov/admin0188/.

6.1.7 Adverse Events Associated with Durvalumab

The following immune mediated adverse events are associated with durvalumab.

- Pneumonitis or interstitial lung disease: Evaluate patients with suspected pneumonitis with radiographic imaging and manage with treatment modifications and corticosteroids
- Hepatitis: Monitor patients with abnormal liver tests each cycle during treatment; manage immune-mediated hepatitis with treatment modifications and corticosteroids
- Colitis: Monitor patients for signs and symptoms of colitis or diarrhea during treatment; manage immune-mediated colitis with treatment modifications, anti-diarrheal agents, and corticosteroids
- Large intestine perforation/intestine perforation: When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay.
- Endocrinopathies: Monitor patients for thyroid disorders, adrenal insufficiency, type 1 diabetes mellitus and hypophysitis/hypopituitarism
- Rash or Dermatitis (including Pemphigoid): Monitor patients for immune-mediated rash and vitiligo. Manage with treatment modifications and corticosteroids
- Immune thrombocytopenic purpura: Monitor patients for thrombocytopenic purpura. This led to one death related to durvalumab. The patient received high-dose corticosteroids, human IgG, and rituximab
- Nephritis: Monitor patients for abnormal renal function prior to each cycle during treatment; manage nephritis with treatment modifications and corticosteroids
- Infection: Severe infections, including sepsis, necrotizing fasciitis, and osteromyelitis, occurred in patients receiving durvalumab. Monitor patients for signs/symptoms of infection and treat with anti-infectives for suspected or confirmed infections
- Infusion-related reactions: Monitor patients for signs and symptoms of infusion-related reaction. Interrupt or slow the rate of infusion in patients with mild or moderate reactions. Permanently discontinue durvalumab in patients with Grade 3 or 4 reactions
- Myocarditis: Monitor patients for signs/symptoms of myocarditis. Manage myocarditis with treatment modifications and immunosuppressive therapy

including corticosteroids and in TNF-alpha inhibitors. Permanently discontinue durvalumab in patients with Grade 3 or 4 myocarditis.

- Embryo-fetal toxicity: Durvalumab can cause fetal harm when administered to pregnant woman. WOCBP must use contraception during treatment and for at least 3 months after the last dose of durvalumab.

Please consult the durvalumab investigator's brochure and package insert for additional information.

6.2 Radiation Therapy

Patients will receive radiation therapy concomitantly with durvalumab starting at Cycle 1. Institutional guidelines for delivery of standard of care radiation therapy to the head and neck patients will be followed.

Localization, Simulation, and Immobilization

Patients must have an immobilization device for the head and neck (shoulders optional) (eg, aquaplast mask) made prior to the treatment planning CT scan that is required for all patients. The treatment planning CT scan can be performed with or without IV contrast. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be a maximum of 3 mm.

Daily image guidance (IGRT) is recommended but not required. Weekly verification imaging is required.

Treatment Planning/Target Volumes

- Clinical target volume of 60 Gy (CTV60): This volume will receive 2 Gy per day. CTV60 will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, pathologic findings) plus regions of grossly involved lymphadenopathy. CTV60 may include the broader operative resection bed in the region of gross primary and nodal disease. The entire nodal regions in the involved hemi-neck may be included in CTV60 at the discretion of the investigator for perceived higher-risk cancers. CTV60 will include the ipsilateral pathologically positive hemineck (if both sides of the neck are proven pathologically positive, CTV60 will include both sides).
- CTV54: This will include all other lesser risk regions in the operative bed (that were involved with surgery in any way) or regional nodes but felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV60. This volume will receive 1.8 Gy per day. CTV60 and CTV54 will be in one intensity-modulated radiation therapy (IMRT) plan with the dose painted.
- CTV66 Optional: This volume may be defined at the discretion of the treating radiation oncologist. This would include regions felt to be at

particularly high risk for recurrence (e.g., an area of the ECS or positive margin of resection). Note: A separate boost plan will be created (2 Gy/fx for 3 fractions for a total dose of 6 Gy).

- Planning Target Volumes (PTVs): In general, the PTV should not extend beyond the skin surface, except if the skin was involved with tumor. If it does extend beyond the skin surface, the application of bolus material over this portion of the PTV may be considered. CTV to PTV expansion will be 3 to 5 mm.

IMRT Dose Prescription to PTVs: Dose will be prescribed to the PTV's so that 95% of the dose covers 100% of the volume.
Dose Constraints

- PTV66, PTV60, PTV54
  - 100% of the prescription should cover 95% of the PTV
  - No more than 10% of the PTV should receive ≥ 110% of the prescribed dose
  - No more than 1% of the PTV should receive ≤ 93% of the prescribed dose
- Non-target Tissue
  - No more than 1% of the tissue outside the PTV should receive ≥ 110% of the prescribed dose
- PRV
  - Spinal Cord: 0.1cc ≤ 50 Gy
  - Brainstem: 0.1cc ≤ 54 Gy
  - Parotid: Mean dose < 26 Gy and/or 50% < 30 Gy
  - Cochlea: Mean dose < 45 Gy
  - Larynx: Mean dose < 41 Gy and/or 60 Gy to < 20%
  - Optic structures: 0.1cc ≤ 54Gy

PTV coverage should not be compromised to meet the dose constraints of the parotid, cochlea, or larynx. Sparing of these structures is left at the discretion of the treating radiation oncologists. The dose constraints for the spinal cord and brainstem must be satisfied. This may be done at the cost of altering the PTV.

7.0 EVALUATIONS AND ASSESSMENTS

7.1 Time and Events Table

Assessments	Screening[2, 3]	Study Treatment[3]						End of Treatment [4]	3&6 months after completion of study therapy[3]	At Time Disease Recurs[3]	Long Term Follow-up[3,4,14]
		C1 D1	C2 D1	C3 D1	C4 D1	C5 D1	C6 D1				
Informed Consent	X										
Dental Exam [1]	X										
Physical Exam and Medical History[2]	X	X	X	X	X	X	X	X	X		X
ECOG Performance status	X	X	X	X	X	X	X	X	X		X
Pregnancy Test [15]	X	X	X	X	X	X	X				
CBC with Differential	X	X	X	X	X	X	X	X	X		
Serum Chemistries and LFTs[12]	X	X	X	X	X	X	X	X	X		
Amylase and Lipase	X							X			
Thyroid Studies[7]	X[7]		X[7]	X[7]	X[7]	X[7]	X[7]	X[7]	X[7]		
Uric Acid	X		X								
Creatinine Clearance[13]	X	X	X	X	X	X	X	X			
Concomitant Medicine Review	X	X	X	X	X	X	X	X	X		X
Durvalumab 1500mg IV Q3W		X	X	X							
Durvalumab 1500mg IV Q4W					X	X	X				
Radiation Therapy (Daily, Mon-Friday)		X[10]	X[10]	X[10]							
Tumor Assessment[5]	X								X		X
Pneumonitis (ILD) Assessment[6, 8]			X	X	X	X	X	X	X		X
Clinical Toxicity Assessment[6]	X	X	X	X	X	X	X	X	X		X
FACT-H&Nv4 (QOL Assessment)		X	X	X	X			X	X		
Standard of care imaging (PET/CT/MRI)					X						
Blood draw to study immune system[9]		X			X			X	X	X	X
Request for Archival Tissue[11]	X										
Surgical biopsy at recurrence										X	
Progression and Survival								X	X		X

Footnotes to Time and Events Table

1. As required per institutional standard of care. Should be obtained 3 weeks before Day 1 if it is required per institutional standard of care.
2. History and physical exam may be performed within 6 weeks prior to day 1 of study treatment. Complete medical history and physical examination (including height, weight, and vital signs) for pre-study assessment; focused medical history and physical examination (including weight) at subsequent assessments. Other evaluations except for pregnancy test and baseline imaging must be performed within 6 weeks prior to Day 1 of study treatment. Serum β-HCG must be performed within 7 days prior to first dose of study medication for women of child-bearing potential. Initial baseline imaging must be within 4 weeks of Cycle 1 day 1.
3. A window of +/- 3 and +7 days applies to all study visits unless otherwise specified. The visits occurring 3 months and 6 months after completion of study therapy have a window of +/-15 days. Long-term follow-up visits will occur per standard of care (SOC). Also note, cycles 1-3 are 3 week cycles and cycles 4-6 are 4 week cycles.
4. The end of treatment visit should only occur when patients permanently stop study treatment and should be performed within 7 days (+/-7 days) after the last dose of study medication. Patients who have an ongoing ≥grade 2 or serious AE (SAE) at this visit will continue to be followed until the event is resolved or deemed irreversible by the investigator.
5. Pre-surgical imaging will be reviewed. CT or MRI scan of the neck, results from physical examination head and neck, and chest imaging (x-ray or CT scan at discretion of physician). Pathology report for surgery will be reviewed. Baseline tumor assessment at a minimum must include imaging of neck and chest (CT, MRI, and/or PET). Ongoing tumor assessment may be performed per institutional standard of care and may include imaging of neck and chest, nasopharyngolaryngoscopy, and/or physical examination. The study recommends initial assessment at least every 3 months x 1 year then every 6 months x 1 year then annually.
6. Toxicity assessed per NCI-CTCAEv5.0. Changes in the severity of AEs from baseline should be recorded in the eCRF during the trial and assessed for their relationship to study therapy. If pneumonitis or suspected pneumonitis occurs, please refer to Section 8.2 for additional assessments that will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis.
7. Free T3 or free T4 will only be measured if TSH is abnormal or if there is a clinical suspicion of an AE related to the endocrine system.
8. Pneumonitis (ILD) Assessment: per section 8.2, including physical examination, O2, and additional studies per discretion of study investigator
9. Blood draws for immune correlate studies will include 10 mL of whole blood in a single standard venous blood collection tube with EDTA additive, and 24 mL of blood in collection tubes with ACD additive.
10. Radiation therapy is administered per standard radiation oncology regimens, on a daily basis and/or as scheduling during a Monday-Friday working week. Radiation therapy is given concurrently with durvalumab during Cycles 1-3. Durvalumab treatment Cycles 1-3 are 3-week long cycles (total of 9 weeks). Radiation therapy will be delivered at a dose of 2 Gy over 30 fractions totaling a final dose of 60 Gy. Radiation treatment will take 6 weeks (Monday-Friday) or 30 days and occur for 6 of 9 weeks

that define Cycles 1-3. However, due to delays or missed appointments, completion of those 30 fractions may take longer than the allotted 6 weeks and this is allowed. Radiation therapy must be scheduled and completed within Cycles 1-3 and should not extend into Cycle 4. Please refer to Section 6.2 for additional details and allowances.

11. Obtain archival tissue from surgery for correlative studies if available. If insufficient tissue available, patient can still participate in the clinical trial.
12. Serum chemistries include sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin. Liver function tests (LFTs) include total bilirubin, alkaline phosphatase, AST, ALT)
13. Based on Cockroft Gault see Appendix 12.3
14. Laboratory evaluations are performed per standard of care. The only study required evaluation is the blood draw for immune correlates.
15. Serum pregnancy test in women of childbearing potential (Note: pregnancy test to be performed within 7 days of day 1 of each treatment cycle)

7.2 Correlative Studies

The state of the art for biomarker testing in immunotherapy is rapidly evolving at the timing of protocol generation. We suspect that biomarkers of relevance for predicting treatment efficacy and for future study development will be substantially different at the time of study conclusion than they are at the time of study initiation. Subjects will be consented for biomarker testing of blood and tissue samples collected. No subject will be refused study entry for lack of tissue, but subjects will be required to allow use of any pre-treatment tissue remaining (i.e., archival and/or fresh tissue) for research purposes. In addition, subjects will be required, if consent is provided, to allow use of operative tissue at time of disease recurrence for research purposes (see below).

7.2.1 Collection of Post-Surgical Tissue for Correlative Studies

All subjects will be asked to provide consent for analysis of post-surgical tissue. Additionally, in the event of disease recurrence, subjects may be offered an optional second biopsy to obtain a sample of tumor tissue. Blood samples will be collected per above and used for future unspecified research if the patient provides consent.

Post-surgical tissue will be evaluated for the immunosuppressive biomarker PD-L1 on tumor cells using the Ventana PD-L1 (SP263) assay, which is a qualitative IHC assay. IHC expression analyses consider the marker intensity and staining pattern including distribution (percentage of positive cells) and intensity in the form of H-score. IHC analysis and scoring will be performed by a certified pathologist using image analysis software.

Outcome from the analysis will be calculated according to the H-score. The H-score ranges from 0 to 300, and it considers both intensity of the IHC (from 0 to 3) and distribution (percentage of the target cells positive, from 0 to 100). Hematoxylin/eosin and PD-L1-stained sections will be reviewed by a pathologist and the quantity and location of PD-L1 staining will be quantified. The presence and type of intratumoral lymphocytic infiltration as determined by but not limited to CD4, CD8, CD25, FOXP3 will be quantified from tissue specimens per below. Expression of PD-L1 will be prioritized.

7.2.2 Post-surgical Tissue by Flow Cytometry

Post-surgical tissue will be evaluated for the expression level and localization of markers of inflammatory/immune signature that may include but not be limited to CD4, CD8, CD25, FOXP3 and TUNEL/Caspase3 by flow cytometry.

7.3 Handling of Biospecimens Collected for Correlative Research

Biospecimens collected for this study will be stored in the Lineberger Comprehensive Cancer Center (LCCC) Tissue Procurement Facility (TPF), or if needed, in a secure off-site storage facility. All biospecimen samples will be obtained in accordance with procedures outlined in the LCCC 1725 Study Laboratory Manual and stored in containers with controlled access. Each sample

will be assigned a unique code number and no identifiable personal health information (PHI) will be on the specimen label. Information about the patient's disease will be linked to the specimens stored in the repository database. TPF-associated research staff, LCCC Bioinformatics staff who support the TPF database and the LCCC Data Warehouse, and researchers with IRB-approval for access to PHI for each subject in this study will be able to link specimens to relevant medical information. Some results from laboratory analyses that occurred during the patient's participation in the clinical study may also be included. This information may be important for understanding how the patient's cancer developed and responded to treatment.

Storage Time:

- The biospecimen will be used first and foremost for research purposes outlined within the confines of this protocol. Samples will be discarded/destroyed after relevant data are collected for this study, unless consent was obtained from the patient to use tissue for other research purposes (e.g., TPF consent form was signed by the patient). In this circumstance, there is no time limit on how long biospecimens may be stored.
    - The investigator must agree to abide by policies and procedures of the TPF facility and sign a letter of research agreement for ethical and appropriate conduct of their research that utilizes specimens obtained from the TPF facility (e.g., Use of leftover specimens will require a protocol outlining the research plan for biospecimen use).

7.4 Compliance Statement

Biospecimen collection for this study will be conducted in full accordance with all applicable University of North Carolina (UNC) Research Policies and Procedures and all applicable Federal and state laws and regulations including 45 CFR 46, and the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule. Any episode of noncompliance will be documented.

The investigators will perform the study in accordance with this protocol, will obtain consent and assent (unless a waiver is granted), and will report unexpected problems in accordance with The UNC IRB Policies and Procedures and all federal requirements. Collection, recording, and reporting of data will be accurate and will ensure the privacy, health, and welfare of research subjects during and after the study.

7.5 Assessment of Safety

Any patient who receives at least one dose of study therapy on this protocol will be evaluable for toxicity. Each patient will be assessed periodically for the development of any toxicity according to the Time and Events table. Toxicity will be assessed according to the NCI CTCAEv5.0.

7.6 Assessment of Efficacy

Disease free survival will be assessed by either physical exam or at pre-specified interval imaging as a dichotomous variable based on evidence of tumor recurrence (yes or no) per clinician's assessment. Overall survival will be assessed at follow up visits as a dichotomous variable (yes or no).

8.0 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event (AE)

An adverse event (AE) is any untoward medical occurrence (e.g., an abnormal laboratory finding, symptom, or disease temporally associated with the use of a drug) 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 related to the medicinal product.

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

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) need not be considered AEs and should not be recorded as an AE. Disease progression should not be recorded as an AE, unless it is attributable by the investigator to the study therapy.

8.1.2 Suspected Adverse Reaction (SAR)

A suspected adverse reaction (SAR) is any AE for which there is a *reasonable possibility* that the drug is the cause. *Reasonable possibility* means that there is evidence to suggest a causal relationship between the drug and the AE. A suspected adverse reaction implies a lesser degree of certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Causality assessment to a study drug is a medical judgment made in consideration of the following factors: temporal relationship of the AE to study drug exposure, known mechanism of action or side effect profile of study treatment, other recent or concomitant drug exposures, normal clinical course of the disease under investigation, and any other underlying or concurrent medical conditions. Other factors to consider in considering drug as the cause of the AE:

- Single occurrence of an uncommon event known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome)
- One or more occurrences of an event not commonly associated with drug exposure, but otherwise uncommon in the population (e.g., tendon rupture); often more than once occurrence from one or multiple studies would be

needed before the sponsor could determine that there is *reasonable possibility* that the drug caused the event.

- An aggregate analysis of specific events observed in a clinical trial that indicates the events occur more frequently in the drug treatment group than in a concurrent or historical control group

8.1.3 Unexpected AE or SAR

An AE or SAR is considered unexpected if the specificity or severity of it is not consistent with the applicable product information (e.g., Investigator's Brochure (IB) for an unapproved investigational product or package insert/summary of product characteristics for an approved product). Unexpected also refers to AEs or SARs that are mentioned in the IB as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

8.1.4 Serious AE or SAR

A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drug: An AE or SAR is considered serious if, in the view of either the investigator or sponsor, it results in any of the following outcomes:

- Death;
- Is life-threatening (places the subject at immediate risk of death from the event as it occurred);
- Requires inpatient hospitalization (>24 hours) or prolongation of existing hospitalization;*
- Results in congenital anomaly/birth defect;
- Results in a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions;
- 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 the definition. For reporting purposes, also consider the occurrences of pregnancy as an event which must be reported as an important medical event.

*Hospitalization for anticipated or protocol specified procedures such as administration of chemotherapy, central line insertion, metastasis interventional therapy, resection of primary tumor, or elective surgery, will not be considered serious adverse events.

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

Pregnancy that occurs within 90 days of the last dose of durvalumab must also be reported as an important medical event.

8.2 Durvalumab AEs of Special Interest

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

AESIs for durvalumab 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, immune-suppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy. An immune-mediated adverse event (imAE) is defined as an AESI 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 imAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the imAE.
If the Investigator has any questions in regard to an event being an imAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab include:

- Diarrhea / Colitis
- Intestinal perforation
- Pneumonitis / ILD
- Hepatitis / transaminase increases Neuropathy / neuromuscular toxicity (e.g. Guillain-Barré, and myasthenia gravis)
- Endocrinopathies (i.e. events of hypophysitis, hypopituitarism adrenal insufficiency, diabetes insipidus, hyper- and hypothyroidism, thyroiditis, and type I diabetes mellitus)
- Rash / Dermatitis
- Nephritis / Blood creatinine increases
- Pancreatitis/serum lipase and amylase increases
- Myocarditis
- Myositis / Polymyositis
- Other inflammatory responses that are rare / less frequent with a potential immune-mediated aetiology include, but are not limited to, pericarditis, sarcoidosis, uveitis and other events involving the eyeskin, haematological and rheumatological events, vasculitis, non-infectious meningitis and non-infectious encephalitis

In addition, infusion-related reactions and hypersensitivity/anaphylactic reactions with a different underlying pharmacological etiology are also considered AESIs. Further information on these risks (e.g. presenting symptoms) can be found in the current version of the durvalumab Investigator's Brochure. More specific guidelines for their evaluation and treatment are described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 12.0). These guidelines have been prepared by the Sponsor to assist the Investigator in the exercise of his/her clinical judgment in treating these types of toxicities. These guidelines apply to AEs considered causally related to the study drug/study regimen by the reporting investigator.

If new or worsening pulmonary symptoms (e.g. dyspnea) or radiological abnormality suggestive of pneumonitis/interstitial lung disease is observed, toxicity management as described in detail in the Dosing Modification and Toxicity Management Guidelines (see Appendix 12.0) will be applied. The results of the full diagnostic workup (including high-resolution computed tomography (HRCT), blood and sputum culture, hematological parameters etc.) will be captured in the eCRF. It is strongly recommended to perform a full diagnostic workup, to exclude alternative causes such as lymphangitic carcinomatosis, infection, allergy, cardiogenic edema, or pulmonary hemorrhage. In the presence of confirmatory HRCT scans where other causes of respiratory symptoms have been excluded, a diagnosis of pneumonitis (ILD) should be considered and the Dosing Modification and Toxicity Management Guidelines should be followed.

Pneumonitis (ILD) investigation

The following assessments, and additional assessments if required, will be performed to enhance the investigation and diagnosis of potential cases of pneumonitis. The results of the assessment will be collected.

- Physical examination
  - Signs and symptoms (cough, shortness of breath and pyrexia, etc.) including auscultation for lung field will be assessed.

- SpO2
  - Saturation of peripheral oxygen (SpO2)

- Other items
  - When pneumonitis (ILD) is suspected during study treatment ILD markers and tumor markers may be obtained if felt appropriate by study investigators

Additional Clinical chemistry: c-reactive protein and lactate dehydrogenase (CRP, LDH)

8.3 Documentation of non-serious AEs or SARs

For non-serious AEs or SARs, documentation must begin from time of signature of informed consent, throughout the treatment period and including the follow-up period (90 days after the last dose of durvalumab).

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

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.

The investigator is responsible for following all SAEs until resolution, until the patient 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.

Collected information should be recorded in the Case Report Forms (CRF) for that patient. Please include a description of the event, its severity or toxicity grade, onset and resolved dates (if applicable), and the relationship to the study drug. Documentation should occur at least monthly.

Adverse events will be recorded using a recognized medical term or diagnosis that accurately reflects the event (CTCAE 5.0 Meddra terms). AEs will be assessed by the investigator for severity, relationship to the investigational product, possible etiologies, and whether the event meets criteria of an SAE and therefore requires immediate notification to AstraZeneca/MedImmune Patient Safety.

The following variables will be collected for each AE:

- AE (verbatim)
- The date when the AE started and stopped
- The maximum CTCAE grade reported
- Changes in CTCAE grade
- Whether the AE is serious or not
- Investigator causality rating against the IPs (yes or no)
- Action taken with regard to IPs
- Administration of treatment for the AE
- Outcome

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

- Date the AE met criteria for SAE
- Date the Investigator became aware of the SAE
- Seriousness criteria fulfilled

- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Whether an autopsy was performed
- Causality assessment in relation to study procedure(s)
- Causality assessment in relation to other medication
- Description of the SAE

The grading scales found in the revised NCI CTCAE version 5.0 will be utilized for all events with an assigned CTCAE grading. For those events without assigned CTCAE grades, the recommendation in the CTCAE criteria that converts mild, moderate, and severe events into CTCAE grades should be used. A copy of the CTCAE version 5.0 can be downloaded from the Cancer Therapy Evaluation Program website (http://ctep.cancer.gov).

8.3.1 Hy's Law

Cases where a patient shows elevations in liver biochemistry may require further evaluation and occurrences of AST or ALT ≥3 × ULN together with total bilirubin ≥2 × ULN may need to be reported as SAEs.

8.4 SAEs or Serious SARs

8.4.1 Timing

After informed consent but prior to initiation of study medications, only SAEs caused by a protocol-mandated intervention will be collected (e.g. SAEs related to invasive procedures such as biopsies, medication washout).

For any other experience or condition that meets the definition of an SAE or a serious SAR, recording of the event must begin from day 1 of study treatment and continue through the 90 day follow-up period after treatment is discontinued.

8.4.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within Oncore™ for that patient within 24 hours of learning of its occurrence. Additionally, the Multicenter Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

8.5 Adverse Event Reporting

8.5.1 IRB Reporting Requirements:

UNC:

- The UNC-IRB will be notified of all SAEs that qualify as an Unanticipated Problem as per the UNC IRB Policies using the IRB's web-based reporting

system within 7 days of the Investigator becoming aware of the problem. Please note, these events must be reported to the sponsor within 24 hours of learning of the occurrence.

Multicenter sites:

- For multicenter sites using a local IRB of record, please submit adverse events per local IRB policy.

Pregnancy

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on study, or within 90 days of the subject's last dose of study should be recorded as important medical events. The patient is to be discontinued immediately from the study.

For multicenter sites, the pregnancy, suspected pregnancy, or positive pregnancy test must be reported to the Multicenter Project Manager immediately (within 24 hours) via email (preferable) to CPOMulticenter@med.unc.edu or facsimile to 919-966-4300. The Multicenter Project Manager will then report the event to the Funding Source (see requirements below). The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must document the outcome of the pregnancy (either normal or abnormal outcome) and report the condition of the fetus or newborn to the Multicenter Project Manager. If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

8.5.2 AstraZeneca Reporting Requirements:

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

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

The investigator and/or sponsor must inform the FDA, via a MedWatch/AdEERs form, of any serious or unexpected adverse events that occur in accordance with

the reporting obligations of 21 CFR 312.32, and will concurrently forward all such reports to AstraZeneca. A copy of the MedWatch/AdEERs report must be emailed to AstraZeneca at the time the event is reported to the FDA. It is the responsibility of the sponsor to compile all necessary information and ensure that the FDA receives a report according to the FDA reporting requirement timelines and to ensure that these reports are also submitted to AstraZeneca at the same time.
* A ***cover page*** should accompany the ***MedWatch/AdEERs*** form indicating the following:

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR 17-12741)

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

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

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

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

8.5.2.1 Reporting of deaths to AstraZeneca

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

- Death that is clearly the result of disease progression should be documented but should not be reported as an SAE.
- Where death is not due (or not clearly due) to progression of the disease under study, the AE causing the death must be reported to AstraZeneca as a SAE within **24 hours**. The report should contain a comment regarding the co-involvement of progression of disease, if appropriate, and should assign main and contributory causes of death.
- Deaths with an unknown cause should always be reported as a SAE.

8.5.2.2 Overdose

Use of durvalumab in doses in excess of that specified in the protocol is considered to be an overdose. There is currently no specific treatment in the event

of overdose of durvalumab b and possible symptoms of overdose are not established.

- An overdose with associated AEs will be recorded as the AE diagnosis or symptoms in the relevant AE modules of the eCRF and in the Overdose eCRF module.
- An overdose without associated symptoms will only be reported in the Overdose eCRF module.

If an overdose of an AstraZeneca IP occurs in the course of the study, then the Investigator or other site personnel will inform appropriate AstraZeneca representatives immediately, or **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.

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

8.5.2.3 Pregnancy

All pregnancies and outcomes of pregnancy should be reported to AstraZeneca except for pregnancy discovered before the study patient has received any study drugs.

8.5.2.4 Maternal exposure

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

Pregnancy itself is not regarded as an AE unless there is a suspicion that the IP under study may have interfered with the effectiveness of a contraceptive medication. Congenital abnormalities 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.

8.5.2.5 Paternal exposure

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

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

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

8.5.2.6 Medication error

For the purposes of this clinical study a medication error is an unintended failure or mistake in the treatment process for an AstraZeneca study drug that either causes harm to the patient or has the potential to cause harm to the patient. A medication error is not lack of efficacy of the drug, but rather a human or process related failure while the drug is in control of the study site staff or patient.

Medication error includes situations where an error:

- Occurred
- Was identified and intercepted before the patient received the drug
- Did not occur, but circumstances were recognized that could have led to an error
- Examples of events to be reported in clinical studies as medication errors:
    - Drug name confusion
    - Dispensing error e.g. medication prepared incorrectly, even if it was not actually given to the patient
    - Drug not administered as indicated, for example, wrong route or wrong site of administration
    - Drug not taken as indicated e.g. tablet dissolved in water when it should be taken as a solid tablet
    - Drug not stored as instructed e.g. kept in the fridge when it should be at room temperature
    - Wrong patient received the medication
    - Wrong drug administered to patient

- Examples of events that do not require reporting as medication errors in clinical studies:
  - Patient accidentally missed drug dose(s) e.g. forgot to take medication
  - Accidental overdose (will be captured as an overdose)
  - Patient failed to return unused medication or empty packaging
  - Errors related to background and rescue medication, or standard of care medication in open label studies, even if an AstraZeneca product
- Medication errors are not regarded as AEs but AEs may occur as a consequence of the medication error.

If a medication error occurs in the course of the study, then the Investigator or other site personnel informs 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 works with the Investigator to ensure that all relevant information is completed within 1 or 5 calendar days if there is an SAE associated with the medication error and within 30 days for all other medication errors.

8.5.3 FDA Expedited Reporting requirements for studies conducted under an IND:

A sponsor must report any suspected adverse reaction (SARs) that is both serious and unexpected to the FDA. Please refer to Section 8.1.2 for the definition of an SAR.

The sponsor must submit each IND safety report on FDA Form 3500A.

Timing

FDA must be notified of potential serious risks within 15 calendar days after the sponsor determines the event requires reporting. FDA must be notified of unexpected fatal or life-threatening suspected adverse reactions as soon as possible but in no case later than 7 calendar days after the sponsor's initial receipt of the information. The sponsor must be notified of the SAE by the investigator within 24 hours of the event and thus the Multicenter Project Manager must be notified within 24 hours of the event. If the results of a sponsor's investigation show that an adverse event not initially determined to be reportable is reportable, the sponsor must report such suspected adverse reaction in an IND safety report as soon as possible, but in no case later than 15 calendar days after the determination is made.

Follow-up

The sponsor must promptly investigate all safety information it receives. Relevant follow-up information to an IND safety report must be submitted as soon as the information is available.

Notification of Investigators
The sponsor must notify all participating investigators (i.e., all investigators to whom the sponsor is providing drug under its INDs or under any investigator's IND) in an IND safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

Process
If the sponsor deems that an event is both a serious adverse reaction (SAR) AND unexpected, it must also (in addition to OnCore™) be recorded on the MedWatch Form 3500A as per 21 CFR 312.32. Unexpected adverse events or adverse reaction refers to an event or reaction that is not listed in the investigator's brochure or is not listed at the specificity or severity that has been observed; or if an investigator's brochure is not required or available, is not consistent with the risk information described in the general investigation plan or elsewhere in the current IND application.

The MedWatch form should be submitted on MedWatch by the study coordinator.

The MedWatch form should be emailed faxed to the Multicenter Project Manager at CPOMulticenter @med.unc.edu or 919-966-4300 along with supporting documentation defining the event and causality. The Multicenter Project Manager will then send the report to the Funding Source. The MedWatch 3500A form can be accessed at:
http://www.fda.gov/Safety/MedWatch/HowToReport/DownloadForms/default.htm.

(Please be sure and access form 3500A, and not form 3500).

The Multicenter Project Manager will also be responsible for informing each multicenter site of all serious and unexpected SARs reported to the FDA as soon as possible.

Additional Reporting Requirements
The following additional items must be reported via IND safety report:

- *Findings from other studies.* The sponsor must report any findings from epidemiological studies, pooled analysis of multiple studies, or clinical studies, whether or not conducted under an IND, and whether or not conducted by the sponsor, that suggest a significant risk to humans exposed to the drug.
- *Findings from animal or in vitro testing.* The sponsor must report any findings from animal or *in vitro* testing, whether or not conducted by the

sponsor, that suggest a significant risk in humans exposed to the drug, such as reports of mutagenicity, teratogenicity, or carcinogenicity, or reports of significant organ toxicity at or near the expected human exposure.

- *Increased rate of occurrence of serious suspected adverse reactions.*

Additional Guidance

Please refer to 21CFR312.32 and "Guidance for Industry and Investigators: Safety Reporting Requirements for INDs and BA/BE Studies" for additional information and reporting requirements. All IND Safety Reports will be submitted in accordance with these regulations/guidances.

8.6 Data and Safety Monitoring Plan

The Principal Investigators will provide continuous monitoring of subject safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC). The Principal Investigators responsible for the care of all subjects in this study will also oversee the conduct of safety data review meetings on a regular basis. Bi-weekly safety review meetings will be instituted upon study enrollment. as soon as a subject(s) enters the study, has received treatment with durvalumab and radiation therapy during Cycles 1-3, and the during the post-treatment evaluation period. These meetings will include the investigators as well as study coordinators, data coordinators, regulatory associates, clinical data management associates, and any other relevant personnel the principal investigators may deem appropriate. At these meetings, the research team will discuss all issues relevant to study progress, including enrollment, safety, regulatory issues, data collection, etc. An agenda and minutes will be generated for each meeting to document attendees and subject data reviewed.

Meeting summaries will be available for inspection when requested by any of the regulatory bodies charged with the safety of human subjects and the integrity of data including, but not limited to, the oversight (Office of Human Research Ethics (OHRE) Biomedical IRB, the Oncology Protocol Review Committee (PRC) or the North Carolina TraCS Institute Data and Safety Monitoring Board (DSMB).

The UNC LCCC Data and Safety Monitoring Committee (DSMC) will review the study on a regular (quarterly to annually) basis, with the frequency of review based on risk and complexity as determined by the UNC Protocol Review Committee. The UNC PI will be responsible for submitting the following information for review: 1) safety and accrual data including the number of patients treated; 2) significant developments reported in the literature that may affect the safety of participants or the ethics of the study; 3) preliminary response data; and 4) summaries of team meetings that have occurred since the last report. Findings of the DSMC review will be disseminated by memo to the UNC PI, PRC, and the UNC IRB and DSMB.

9.0 STATISTICAL CONSIDERATIONS

9.1 Study Design/Study Endpoints

Primary endpoint is to estimate median 3 year disease free survival (DFS) in patients with intermediate-risk HNSCC treated with adjuvant durvalumab with radiotherapy.

9.2 Sample Size, Accrual and Duration of Accrual

Our evaluable study sample size (N_{total}) is 17, and we will enroll 18 to allow for possible non-evaluable patients. Based on a historical control of 10yr DFS is 19% (Cooper, RTOG 1016), the 3 year DFS is approximated to be 60.8%. Based on this calculation, we will need a sample size of 17 patients, to detect a 23% difference in 3 year DFS with 80% power (table below) and one-sided alpha of 0.1.

Difference from Historical Control	10%	**20%**	23%	25%
Test significance level, □	0.050	**0.050**	0.010	0.050
1 or 2 sided test?	1	**1**	1	1
Null hypothesis proportion, $_0$	0.608	**0.608**	0.608	0.608
Alternative proportion, $_A$	0.708	**0.808**	0.838	0.858
Power (%)	80	**80**	80	80
n	141	**33**	17	20

9.3 Data Analysis Plans

Analytic plan for secondary objective:

The rate of grade 3-5 acute toxicity will be tabulated as described above to determine whether the criterion for safety has been met. A confidence interval for this rate will be calculated based on the methods of Koyoma T, and Chen H. Rates of individual types/grades of toxicities will also be reported [30].

Median DFS will be estimated using the Kaplan Meier method.

***Analytic plan for additional secondary objective*:**

1. Grade 3-5 chronic toxicities will be tabulated by type and grade.

2. Median OS will be estimated using the Kaplan Meier method.

3. PD-LI expression will be measured from baseline tumor sample using IHC. Expression will be correlated with DFS using the Kaplan Meier method. A

Log-rank test will compare DFS between those with and without PD-L1 expression.

Analytic plan for exploratory Objectives:

1. HPV status will be measured per institutional SOC, typically p16 and/or HPV FISH. The Kaplan Meier method will be used and a Log-rank test will compare DFS between HPV positive/negative patients.

2. Tumor infiltrating level (TIL) expression will be measured by flow cytometry at baseline and if possible at tumor recurrence. These levels will be compared at these time points using paired t-tests (pre vs final post assessment) or longitudinal models that account for repeated assessments when available. These models can be broadened to allow for comparisons to be made across the 4-response groups (CR/PR/SD/PD) using analysis of covariance models with baseline assessments being the covariate in the model.

10.0 STUDY MANAGEMENT

10.1 Institutional Review Board (IRB) Approval and Consent

It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

In obtaining and documenting informed consent, the investigator should comply with the applicable regulatory requirement(s), and should adhere to Good Clinical Practice (GCP) and to ethical principles that have their origin in the Declaration of Helsinki.

Before recruitment and enrollment onto this study, the patient will be given a full explanation of the study and will be given the opportunity to review the consent form. Each consent form must include all the relevant elements currently required by the FDA Regulations and local or state regulations. Once this essential information has been provided to the patient and the investigator is assured that the patient understands the implications of participating in the study, the patient will be asked to give consent to participate in the study by signing an IRB-approved consent form.

Prior to a patient's participation in the trial, the written informed consent form should be signed and personally dated by the patient and by the person who conducted the informed consent discussion.

10.2 Required Documentation

Before the study can be initiated at any site, the following documentation must be provided to the Clinical Protocol Office (CPO) at the University of North Carolina.

- A copy of the official IRB approval letter for the protocol and informed consent
- IRB membership list
- CVs and medical licensure for the principal investigator and any sub-investigators who will be involved in the study.
- Form FDA 1572 appropriately filled out and signed with appropriate documentation
- Financial Disclosures
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

10.3 Registration Procedures

Within 24 hours of subject consent, all subjects are registered in OnCore and all informed consent documentation uploaded into the OnCore Subject Console by a designee from the participating institution. Upon subject registration completion, the designee must email CPOMulticenter@med.unc.edu or call 919-966-7359 (M-F 8:30AM – 5:00PM EST) to alert the UNC LCCC Multicenter Office for initial review and assignment. Complete eligibility packets (institutionally-signed eligibility checklist and full source documentation confirming eligibility) are uploaded by the institutional designee into the OnCore Subject Console and the LCCC Multicenter Office concurrently alerted by email or phone (CPOMulticenter@med.unc.edu; 919-966-7359) to begin review. All subjects must have final eligibility verified by the UNC Multicenter Project Manager on behalf of the UNC PI prior to starting treatment. Please allow 24 hours for source to be reviewed and notification of subject eligibility released. All subjects must maintain eligibility from the time of this notification through the beginning of treatment.

10.4 Data Management and Monitoring/Auditing

The CPO Multicenter Office of the UNC LCCC will serve as the coordinating center for this trial. Data will be collected through a web based clinical research platform, OnCore®. Other study institutions will be given a password to directly enter their own data onto the web site via electronic case report forms (eCRFs). Multicenter personnel will coordinate and manage data for quality control assurance and integrity.

All data will be collected and entered into OnCore® by the multicenter study teams at participating institutions. The investigators at each site will allow monitors to review all source documents supporting data entered into OnCore®. The Multicenter Data Coordinator can be reached at 919-843-2742 or 1-877-668-0683.

All data will be monitored and source data will be verified on selected subjects. Queries will be issued on an ongoing basis on all subjects. Participating sites should respond to data queries within 14 days of receipt. The LCCC

Compliance Committee or their designee will audit trial sites every twelve months while still enrolling or subjects are still on treatment. Participating sites must send source and regulatory documents to LCCC upon request, for remote monitoring and/or audit review.

10.5 Adherence to the Protocol

Except for an emergency situation in which proper care for the protection, safety, and well-being of the study patient requires alternative treatment, the study shall be conducted exactly as described in the approved protocol.

10.5.1 Emergency Modifications

UNC and multicenter site investigators may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to trial subjects without prior UNC or their respective institution's IRB/IEC approval/favorable opinion.

For Institutions Relying on UNC's IRB:
For any such emergency modification implemented, a UNC IRB modification form must be completed by UNC Research Personnel within five (5) business days of making the change.

For Institutions Relying on Their Own IRB:
For multicenter site investigators relying on their own institution's IRB, as soon as possible after the modification has been made, the implemented deviation or change and the reasons for it should be submitted to:

- The UNC Principal Investigator for agreement
- The multicenter institution's IRB for review and approval. (Once IRB's response is received, this should be forwarded to the Multicenter Regulatory Associate).

10.5.2 Single Patient/Subject Exceptions

Eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials under any circumstances. Other types of single subject exceptions may be allowed if proper regulatory review has been completed in accordance with Lineberger Comprehensive Cancer Center's Single Subject Exceptions Policy.

10.5.3 Other Protocol Deviations/Violations

According to UNC's IRB, a protocol deviation is any unplanned variance from an IRB approved protocol that:

- Is generally noted or recognized after it occurs
- Has no substantive effect on the risks to research participants

- Has no substantive effect on the scientific integrity of the research plan or the value of the data collected
- Did not result from willful or knowing misconduct on the part of the investigator(s).

An unplanned protocol variance is considered a violation if the variance meets any of the following criteria:

- Has harmed or increased the risk of harm to one or more research participants.
- Has damaged the scientific integrity of the data collected for the study.
- Results from willful or knowing misconduct on the part of the investigator(s).
- Demonstrates serious or continuing noncompliance with federal regulations, State laws, or University policies.

If a deviation or violation occurs please follow the guidelines below:

For Institutions Relying on UNC's IRB:
Protocol Deviations: UNC or multicenter site personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies.

Protocol Violations: Violations should be reported by UNC personnel within one (1) week of the investigator becoming aware of the event using the same IRB online mechanism used to report Unanticipated Problems.

For Institutions Relying on Their Own IRB:
In addition to adhering to the policies regarding protocol compliance set forth by your institution's IRB, the following is also required:

Protocol Deviations: In the event a deviation from protocol procedures is identified, record the deviation in OnCore®.

Protocol Violations: Any protocol violation that occurs must be reported to your IRB per institutional policies and reported to the Multicenter Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the patient and integrity of the data. Once your institution's IRB response is received, please forward to the Multicenter Regulatory Associate.

Unanticipated Problems:
UNC

Any events that meet the criteria for "Unanticipated Problems" as defined by UNC's IRB must be reported by the study personnel using the IRB's web-based reporting system.

Multicenter Sites:
Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the Multicenter Project Manager. The Multicenter Regulatory Associate will submit reportable events to the UNC IRB using the IRB's web-based reporting system. Examples of such UPs include a lost or stolen laptop computer that contains sensitive study information.

10.6 Amendments to the Protocol

Should amendments to the protocol be required, the amendments will be originated and documented by the Principal Investigator at UNC. It should also be noted that when an amendment to the protocol substantially alters the study design or the potential risk to the patient, a revised consent form might be required.

For Institutions Relying on UNC's IRB:
The written amendment, and if required the amended consent form, must be sent to UNC's IRB for approval prior to implementation.

For Institutions Relying on Their Own IRB:
Investigators must submit the amendment to their institution's IRB for approval. For multi-center studies, any multicenter site must submit their informed consent revisions to the Multicenter Regulatory Associate prior to submission to their IRB.

10.7 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor correspondence to Investigators, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed patient consent forms).

Source documents include all recordings of observations or notations of clinical activities and all reports and records necessary for the evaluation and reconstruction of the clinical research study.

Government agency regulations and directives require that all study documentation pertaining to the conduct of a clinical trial must be retained by the study investigator. In the case of a study with a drug seeking regulatory approval and marketing, these documents shall be retained for at least two years after the last approval of marketing application in an International Conference on Harmonization (ICH) region. In all other cases, study documents should be kept on file until three years after the completion and final study report of this investigational study.

10.8 Obligations of Investigators

The Principal Investigator is responsible for the conduct of the clinical trial at the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study patients. The Principal Investigator must assure that all study site personnel, including sub-investigators and other study staff members, adhere to the study protocol and all FDA/GCP/NCI regulations and guidelines regarding clinical trials both during and after study completion.

The Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the eCRFs. Periodically, monitoring visits will be conducted and the Principal Investigator will provide access to his/her original records to permit verification of proper entry of data. At the completion of the study, all eCRFs will be reviewed by the Principal Investigator and will require his/her final signature to verify the accuracy of the data.

11.0 REFERENCES

1. Laramore, G.E., et al., *Adjuvant chemotherapy for resectable squamous cell carcinomas of the head and neck: report on Intergroup Study 0034.* Int J Radiat Oncol Biol Phys, 1992. **23**(4): p. 705-13.
2. Cooper, J.S., et al., *Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck.* N Engl J Med, 2004. **350**(19): p. 1937-44.
3. Cooper, J.S., et al., *Long-term follow-up of the RTOG 9501/intergroup phase III trial: postoperative concurrent radiation therapy and chemotherapy in high-risk squamous cell carcinoma of the head and neck.* Int J Radiat Oncol Biol Phys, 2012. **84**(5): p. 1198-205.
4. Bernier, J., et al., *Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer.* N Engl J Med, 2004. **350**(19): p. 1945-52.
5. Bernier, J., et al., *Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (# 9501).* Head Neck, 2005. **27**(10): p. 843-50.
6. Tupchong, L., et al., *Randomized study of preoperative versus postoperative radiation therapy in advanced head and neck carcinoma: long-term follow-up of RTOG study 73-03.* Int J Radiat Oncol Biol Phys, 1991. **20**(1): p. 21-8.
7. Trotti, A., et al., *Mucositis incidence, severity and associated outcomes in patients with head and neck cancer receiving radiotherapy with or without chemotherapy: a systematic literature review.* Radiother Oncol, 2003. **66**(3): p. 253-62.
8. Rivelli, T.G., et al., *Cisplatin based chemoradiation late toxicities in head and neck squamous cell carcinoma patients.* Discov Med, 2015. **20**(108): p. 57-66.
9. Bonner, J.A., et al., *Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck.* N Engl J Med, 2006. **354**(6): p. 567-78.
10. Disis, M.L., *Immune regulation of cancer.* J Clin Oncol, 2010. **28**(29): p. 4531-8.
11. Dunn, G.P., L.J. Old, and R.D. Schreiber, *The three Es of cancer immunoediting.* Annu Rev Immunol, 2004. **22**: p. 329-60.
12. Keir, M.E., et al., *PD-1 and its ligands in tolerance and immunity.* Annu Rev Immunol, 2008. **26**: p. 677-704.
13. Zou, W. and L. Chen, *Inhibitory B7-family molecules in the tumour microenvironment.* Nat Rev Immunol, 2008. **8**(6): p. 467-77.
14. Butte, M.J., et al., *Programmed death-1 ligand 1 interacts specifically with the B7-1 costimulatory molecule to inhibit T cell responses.* Immunity, 2007. **27**(1): p. 111-22.
15. Paterson, A.M., et al., *The programmed death-1 ligand 1:B7-1 pathway restrains diabetogenic effector T cells in vivo.* J Immunol, 2011. **187**(3): p. 1097-105.
16. Talmadge, J.E., M. Donkor, and E. Scholar, *Inflammatory cell infiltration of tumors: Jekyll or Hyde.* Cancer Metastasis Rev, 2007. **26**(3-4): p. 373-400.
17. Stewart, R., et al., *Identification and Characterization of MEDI4736, an Antagonistic Anti-PD-L1 Monoclonal Antibody.* Cancer Immunol Res, 2015. **3**(9): p. 1052-62.

18. Gangadhar, T.C. and A.K. Salama, *Clinical applications of PD-1-based therapy: a focus on pembrolizumab (MK-3475) in the management of melanoma and other tumor types.* Onco Targets Ther, 2015. **8**: p. 929-37.
19. Kim, J., et al., *Invasive Bladder Cancer: Genomic Insights and Therapeutic Promise.* Clin Cancer Res, 2015. **21**(20): p. 4514-24.
20. Mendenhall, W.M., et al., *Postoperative radiotherapy for squamous cell carcinoma of the head and neck.* Clin Med Res, 2006. **4**(3): p. 200-8.
21. Park, B., C. Yee, and K.M. Lee, *The effect of radiation on the immune response to cancers.* Int J Mol Sci, 2014. **15**(1): p. 927-43.
22. Ferrara, T.A., J.W. Hodge, and J.L. Gulley, *Combining radiation and immunotherapy for synergistic antitumor therapy.* Curr Opin Mol Ther, 2009. **11**(1): p. 37-42.
23. Spiotto, M., Y.X. Fu, and R.R. Weichselbaum, *The intersection of radiotherapy and immunotherapy: mechanisms and clinical implications.* Sci Immunol, 2016. **1**(3).
24. Bauml, J., et al., *Pembrolizumab for Platinum- and Cetuximab-Refractory Head and Neck Cancer: Results From a Single-Arm, Phase II Study.* J Clin Oncol, 2017. **35**(14): p. 1542-1549.
25. Ferris, R.L., et al., *Nivolumab for Recurrent Squamous-Cell Carcinoma of the Head and Neck.* N Engl J Med, 2016. **375**(19): p. 1856-1867.
26. Levy, A., et al., *Concurrent irradiation with the anti-programmed cell death ligand-1 immune checkpoint blocker durvalumab: Single centre subset analysis from a phase 1/2 trial.* Eur J Cancer, 2016. **68**: p. 156-162.
27. AstraZeneca, *Durvalumab (MEDI4736) Investigator's Brochure* 2017.
28. Formenti, S.C. and S. Demaria, *Combining radiotherapy and cancer immunotherapy: a paradigm shift.* J Natl Cancer Inst, 2013. **105**(4): p. 256-65.
29. Ivanova, A., B.F. Qaqish, and M.J. Schell, *Continuous toxicity monitoring in phase II trials in oncology.* Biometrics, 2005. **61**(2): p. 540-5.
30. Koyama, T. and H. Chen, *Proper inference from Simon's two-stage designs.* Stat Med, 2008. **27**(16): p. 3145-54.

12.0 APPENDICES

12.1 Dose Modification & Toxicity Management Guidelines for Durvalumab

Toxicity grades per NCI-CTCAE criteria version 5.0.

12.1.1 Immune-Mediated Reactions - General

See next page for details. Note that recommended dose holds may result in lack of planned synchrony between radiation and systemic therapy. In the case that a patient requires a hold of dose due to toxicity, which recovers to grade 1 or less and the patient is eligible to restart therapy, this will be allowed. **The lack of synchrony will not be considered a deviation. Imaging timing will be potentially delayed due to such a situation and this will also not be a deviation.**

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v5.0)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
Drug administration modifications of study drug/study regimen will be made to manage potential immune-related AEs based on severity of treatment-emergent toxicities graded per NCI CTCAE v5.0. In addition to the criteria for permanent discontinuation of study drug/study regimen based on CTC grade/severity (table below), permanently discontinue study drug/study regimen for the following conditions: • Inability to reduce corticosteroid to a dose of ≤10 mg of prednisone per day (or equivalent) **within 12 weeks** of the start of the immune-mediated adverse event (imAE) • Grade 3 recurrence of a previously experienced treatment-related imAE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution toGrade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per Investigator or treating physician's clinical judgement. 3. Doses of prednisone are at ≤10 mg/day or equivalent. **Grade 3** Depending on the individual toxicity, study drug/study regimen may be permanently discontinued. Please refer to guidelines below.	It is recommended that management of immune-mediated adverse events (imAEs) follows the guidelines presented in this table: – It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs, some of them not noted specifically in these guidelines. – Whether specific immune-mediated events (and/or laboratory indicators of such events) are noted in these guidelines or not, patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, concomitant medications, and infections) to a possible immune-mediated event. In the absence of a clear alternative etiology, all such events should be managed as if they were immune related. General recommendations follow. – Symptomatic and topical therapy should be considered for low-grade (Grade 1 or 2, unless otherwise specified) events. – For persistent (>3 to 5 days) low-grade (Grade 2) or severe (Grade ≥3) events, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Some events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – should progress rapidly to high dose IV corticosteroids (methylprednisolone at 2 to 4 mg/kg/day) even if the event is Grade 2, and if clinical suspicion is high and/or there has been clinical confirmation. Consider, as necessary, discussing with the study physician, and promptly pursue specialist consultation. – If symptoms recur or worsen during corticosteroid tapering (28 days of taper), increase the corticosteroid dose (prednisone dose [e.g., up to 2 to 4 mg/kg/day PO or IV equivalent]) until stabilization or improvement of symptoms, then resume corticosteroid tapering at a slower rate (>28 days of taper). – More potent immunosuppressives such as TNF inhibitors (e.g., infliximab; also refer to the individual sections of the imAEs for specific type of immunosuppressive) should be considered for events not responding to

Dosing Modification and Toxicity Management Guidelines for Immune-Mediated, Infusion-Related, and Non-Immune–Mediated Reactions (MEDI4736 Monotherapy or Combination Therapy with Tremelimumab or Tremelimumab Monotherapy) 17 October 2019 Version (CTCAE v5.0)

General Considerations regarding Immune-Mediated Reactions

Dose Modifications	Toxicity Management
Grade 4 Permanently discontinue study drug/study regimen. Note: For asymptomatic amylase or lipase levels of >2X ULN, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. Note: Study drug/study regimen should be permanently discontinued in Grade 3 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines. Similarly, consider whether study drug/study regimen should be permanently discontinued in Grade 2 events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when they do not rapidly improve to Grade <1 upon treatment with systemic steroids and following full taper Note: There are some exceptions to permanent discontinuation of study drug for Grade 4 events (i.e., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus).	systemic steroids. Progression to use of more potent immunosuppressives should proceed more rapidly in events with high likelihood for morbidity and/or mortality – e.g., myocarditis, or other similar events even if they are not currently noted in the guidelines – when these events are not responding to systemic steroids. – With long-term steroid and other immunosuppressive use, consider need for *Pneumocystis jirovecii* pneumonia (PJP, formerly known as *Pneumocystis carinii* pneumonia) prophylaxis, gastrointestinal protection, and glucose monitoring. – Discontinuation of study drug/study regimen is not mandated for Grade 3/Grade 4 inflammatory reactions attributed to local tumor response (e.g., inflammatory reaction at sites of metastatic disease and lymph nodes). Continuation of study drug/study regimen in this situation should be based upon a benefit-risk analysis for that patient.

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

12.1.2 Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of pneumonitis or ILD (new onset or worsening shortness of breath or cough). Patients should be evaluated with imaging and pulmonary function tests, including other diagnostic procedures as described below. – Initial work-up may include clinical evaluation, monitoring of oxygenation via pulse oximetry (resting and exertion), laboratory work-up, and high- resolution CT scan.
	Grade 1 (asymptomatic, clinical or diagnostic observations only; intervention not indicated)	No dose modifications required. However, consider holding study drug/study regimen dose as clinically appropriate and during diagnostic work-up for other etiologies.	**For Grade 1 (radiographic changes only):** – Monitor and closely follow up in 2 to 4 days for clinical symptoms, pulse oximetry (resting and exertion), and laboratory work-up and then as clinically indicated. – Consider Pulmonary and Infectious Disease consults.
	Grade 2 (symptomatic; medical intervention indicated; limiting instrumental ADL)	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper.	**For Grade 2 (mild to moderate new symptoms):** – Monitor symptoms daily and consider hospitalization. – Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated. – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started – If still no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is

			important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections)[a] – Consider Pulmonary and Infectious Disease consults. – Consider, as necessary, discussing with study physician.
	Grade 3 or 4 (Grade 3: severe symptoms; limiting self-care ADL; oxygen indicated) (Grade 4: life-threatening respiratory compromise; urgent intervention indicated [e.g., tracheostomy or intubation])	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or new symptoms, new/worsening hypoxia, life-threatening):** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious Disease consults; consider, as necessary, discussing with study physician. – Hospitalize the patient. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks' dose) started. Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and, in particular, anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Diarrhea/Colitis **Large intestine perforation/Intestine perforation**	**Any Grade**	**General Guidance**	**For 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).

		- When symptoms or evaluation indicate a perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections), including testing for clostridium difficile toxin, etc. – Steroids should be considered in the absence of clear alternative etiology, even for low-grade events, in order to prevent potential progression to higher grade event, including perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
Grade 1 (Diarrhea: stool frequency of <4 over baseline per day) (Colitis: asymptomatic; clinical or diagnostic observations only; intervention not indicated)	No dose modifications.	**For Grade 1:** – Monitor closely for worsening symptoms. – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide. Use probiotics as per treating physician's clinical judgment.
Grade 2 (Diarrhea: stool frequency of 4 to 6 over baseline per day; limiting instrumental ADL) (Colitis: abdominal	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 Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, dietary changes (e.g., American Dietetic Association colitis diet), and loperamide and/or budesonide. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, GI consult should be obtained for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out

pain; mucus or blood in stool) (Perforation: invasive intervention not indicated)		perforation, and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg once every 2 weeks[a]. **Caution:** it is important to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. – Consider, as necessary, discussing with study physician if no resolution to Grade ≤1 in 3 to 4 days. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 3 or 4 (Grade 3 Diarrhea: stool frequency of ≥7 over baseline per day; limiting self care ADL; Grade 4 Diarrhea: life threatening consequences) (Grade 3 Colitis: severe abdominal pain, fever; ileus; peritoneal signs; Grade 4 Colitis: life-threatening consequences, urgent intervention indicated) (Grade 3 Perforation: invasive intervention indicated; Grade 4 Perforation:	**Grade 3** Permanently discontinue study drug/study regimen for Grade 3 if toxicity does not improve to Grade ≤1 within 14 days; study drug/study regimen can be resumed after completion of steroid taper. **Grade 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 2 to 4 mg/kg/day or equivalent. – Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 3 to 5 days of IV methylprednisolone 2 to 4 mg/kg/day or equivalent, promptly start further immunosuppressives (e.g., infliximab at 5 mg/kg once every 2 weeks). **Caution**: Ensure GI consult to rule out bowel perforation and refer to infliximab label for general guidance before using infliximab. If perforation is suspected, consult a surgeon experienced in abdominal surgery immediately without any delay . – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

life-threatening consequences; urgent intervention indicated)	

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **PLEASE SEE shaded area immediately below this section to find guidance for management of "Hepatitis (elevated LFTS)" in HCC patients**	**Any Grade**	**General Guidance**	**For Any Grade** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications).
	Grade 1 (AST or ALT >ULN and ≤3.0×ULN if baseline normal, 1.5-3.0×baseline if baseline abnormal; and/or TB >ULN and ≤1.5×ULN if baseline normal, >1.0-1.5×baseline if baseline abnormal)	• No dose modifications. • If it worsens, then treat as Grade 2.	– Continue LFT monitoring per protocol.
	Grade 2 (AST or ALT >3.0×ULN and ≤5.0×ULN if baseline normal, >3-5×baseline if baseline abnormal; and/or TB >1.5×ULN and ≤3.0×ULN if baseline normal, >1.5-3.0×baseline if baseline abnormal)	• Hold study drug/study regimen dose until resolution to Grade≤1. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade≤1, resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Regular and frequent checking of LFTs (e.g., every 1 to 2 days) until elevations of these are improving or resolved. – If no resolution to ≤Grade 1 in 1 to 2 days, consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional work up and start prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, promptly start immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and

		anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 3 (AST or ALT >5.0×ULN and ≤20×ULN if baseline normal, >5-20× baseline if baseline abnormal; and/or TB >3.0×ULN and ≤10.0×ULN if baseline normal, >3.0-10.0× baseline if baseline abnormal)	For elevations in transaminases ≤8×ULN, or elevations in TB ≤5×ULN: • Hold study drug/study regimen dose until resolution to Grade≤1 • Resume study drug/study regimen if elevations downgrade to Grade≤1 within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to Grade≤1 within 14 days. For elevations in transaminases >8×ULN or elevations in bilirubin >5×ULN, permanently discontinue study drug/study regimen. Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria (AST and/or ALT >3×ULN + bilirubin >2×ULN without initial findings of cholestasis [i.e., elevated alkaline P04] and in the absence of any alternative cause).[b]	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If still no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with immunosuppressive therapy (i.e., mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Request Hepatology consult, and perform abdominal workup and imaging as appropriate. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 4 (AST or ALT >20×ULN if baseline normal, >20×baseline if baseline abnormal; and/or TB >10×ULN if baseline normal, >10.0×baseline if baseline abnormal)		

Hepatitis (elevated LFTs) Infliximab should not be used for management of immune-related hepatitis. **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** See instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	**Any Elevations of AST, ALT, or TB as Described Below**	**General Guidance**	**For Any Elevations Described:** – Monitor and evaluate liver function test: AST, ALT, ALP, and TB. – Evaluate for alternative etiologies (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – For HBV+ patients: evaluate quantitative HBV viral load, quantitative HBsAg, or HBeAg – For HCV+ patients: evaluate quantitative HCV viral load – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral medications for any patient with an elevated HBV viral load >2000 IU/ml – Consider consulting hepatologist/Infectious Disease specialist regarding change/implementation in/of antiviral HCV medications if HCV viral load increased by ≥2-fold – For HCV+ with HBcAB+: Evaluate for both HBV and HCV as above
	Isolated AST or ALT >ULN and ≤5.0×ULN, whether normal or elevated at baseline	• No dose modifications. • If ALT/AST elevations represents significant worsening based on investigator assessment, then treat as described for elevations in the row below. For all transaminase elevations, see instructions at bottom of shaded area if transaminase rise is not isolated but (at any time) occurs in setting of either **increasing bilirubin or signs of DILI/liver decompensation**	

Isolated AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline **Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • If toxicity worsens, then treat as described for elevations in the rows below. If toxicity improves to AST or ALT ≤5.0×ULN, resume study drug/study regimen after completion of steroid taper.	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved. – Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with study physician. – If event is persistent (>3 to 5 days) or worsens, and investigator suspects toxicity to be immune-mediated AE, recommend to start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 3 to 5 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup and treatment with IV methylprednisolone 2 to 4 mg/kg/day. – If still no improvement within 3 to 5 days despite 2 to 4 mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting immunosuppressives (i.e., mycophenolate mofetil).[a] Discuss with study physician if mycophenolate mofetil is not available. **Infliximab should NOT be used.**
Isolated AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline **Isolated AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline**	• Hold study drug/study regimen dose until resolution to AST or ALT ≤5.0×ULN. • Resume study drug/study regimen if elevations downgrade to AST or ALT ≤5.0×ULN within 14 days and after completion of steroid taper. • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days Permanently discontinue study drug/study regimen for any case meeting Hy's law	– Regular and frequent checking of LFTs (e.g., every 1-2 days) until elevations of these are improving or resolved. – Consult hepatologist (unless investigator is hepatologist); obtain abdominal ultrasound, including Doppler assessment of liver perfusion; and consider liver biopsy. – Consider, as necessary, discussing with study physician. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylprednisolone at 1 to 4 mg/kg/day or equivalent. – If no improvement within 3 to 5 days despite 1 to 4 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with immunosuppressive therapy (mycophenolate mofetil). Discuss with study physician if mycophenolate is not available. **Infliximab should NOT be used.** – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and

		criteria, in the absence of any alternative cause.[b]	anti-PCP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
	Isolated AST or ALT >20×ULN, whether normal or elevated at baseline	Permanently discontinue study drug/study regimen.	**Same as above (except would recommend obtaining liver biopsy early)**
If transaminase rise is not isolated but (at any time) occurs in setting of either increasing total/direct bilirubin (≥1.5×ULN, if normal at baseline; or 2×baseline, if >ULN at baseline) or signs of DILI/liver decompensation (e.g., fever, elevated INR): **- Manage dosing for each level of transaminase rise as instructed for the next highest level of transaminase rise** **- For example, manage dosing for second level of transaminase rise (i.e., AST or ALT >5.0×ULN and ≤8.0×ULN, if normal at baseline, or AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline) as instructed for the third level of transaminase rise (i.e., AST or ALT >8.0×ULN and ≤20.0×ULN, if normal at baseline, or AST or ALT >12.5×ULN and ≤20.0×ULN, if elevated >ULN at baseline)** **- For the third and fourth levels of transaminase rises, permanently discontinue study drug/study regimen**			
Nephritis or renal dysfunction (elevated serum creatinine)	**Any Grade**	**General Guidance**	**For Any Grade:** – Consult with nephrologist. – Monitor for signs and symptoms that may be related to changes in renal function (e.g., routine urinalysis, elevated serum BUN and creatinine, decreased creatinine clearance, electrolyte imbalance, decrease in urine output, or proteinuria). – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression or infections). – Steroids should be considered in the absence of clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade event.

Grade 1 (serum creatinine >ULN to 1.5×ULN)	No dose modifications.	**For Grade 1:** – Monitor serum creatinine weekly and any accompanying symptoms. • If creatinine returns to baseline, resume its regular monitoring per study protocol. • If creatinine worsens, depending on the severity, treat as Grade 2, 3, or 4. – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – If baseline serum creatinine is elevated above normal, and there is a rise to > 1 to 1.5 × baseline, consider following recommendations in this row.
Grade 2 (serum creatinine >1.5 to 3.0×baseline; >1.5 to 3.0×ULN)	Hold study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3 or 4. • If toxicity improves to Grade ≤1 or baseline, then resume study drug/study regimen after completion of steroid taper.	**For Grade 2:** – Consider symptomatic treatment, including hydration, electrolyte replacement, and diuretics. – Carefully monitor serum creatinine every 2 to 3 days and as clinically warranted. – Consult nephrologist and consider renal biopsy if clinically indicated. – If event is persistent (>3 to 5 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone at 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – When event returns to baseline, resume study drug/study regimen and routine serum creatinine monitoring per study protocol.
Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Carefully monitor serum creatinine on daily basis.

	(Grade 3: serum creatinine >3.0×baseline; >3.0 to 6.0×ULN) (Grade 4: serum creatinine >6.0×ULN)		– Consult nephrologist and consider renal biopsy if clinically indicated. – Promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If event is not responsive within 3 to 5 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Rash or Dermatitis (including Pemphigoid)	**Any Grade** (refer to NCI CTCAE v 5.0 for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For 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 IF SUSPECT STEVENS-JOHNSON SYNDROME OR TOXIC EPIDERMAL NECROLYSIS.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream).
	Grade 2	For persistent (>1 to 2 weeks) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity worsens, then treat as Grade 3. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper.	**For Grade 2:** – Obtain Dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., urea cream). – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 to 5 days or is worsening despite symptomatic treatment and/or use of moderate strength topical steroid, consider, as necessary, discussing with study physician and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV

			equivalent. If > 30% body surface area is involved, consider initiation of systemic steroids promptly. – Consider skin biopsy if the event is persistent for >1 to 2 weeks or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If temporarily holding the study drug/study regimen does not provide improvement of the Grade 3 skin rash to Grade ≤1 or baseline within 30 days, then permanently discontinue study drug/study regimen. **For Grade 4 (or life-threatening):** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (or life-threatening):** – Consult Dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – Consider, as necessary, discussing with study physician.
Endocrinopathy (e.g., hyperthyroidism, thyroiditis, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency; exocrine event of amylase/lipase increased	**Any Grade** (depending on the type of endocrinopathy, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Consider consulting an endocrinologist for endocrine events. – Consider, as necessary, discussing with study physician. – Monitor patients for signs and symptoms of endocrinopathies. Non-specific symptoms include headache, fatigue, behavior changes, changed mental status, vertigo, abdominal pain, unusual bowel habits, polydipsia, polyuria, hypotension, and weakness. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: TSH, free T3 and free T4 and

also included in this section)			other relevant endocrine and related labs (e.g., blood glucose and ketone levels, HgA1c). – For asymptomatic elevations in serum amylase and lipase >ULN and <3×ULN, corticosteroid treatment is not indicated as long as there are no other signs or symptoms of pancreatic inflammation. – If a patient experiences an AE that is thought to be possibly of autoimmune nature (e.g., thyroiditis, pancreatitis, hypophysitis, or diabetes insipidus), the investigator should send a blood sample for appropriate autoimmune antibody testing.
	Grade 1	No dose modifications.	**For Grade 1 (including those with asymptomatic TSH elevation):** – Monitor patient with appropriate endocrine function tests. – For suspected hypophysitis/hypopituitarism, consider consultation of an endocrinologist to guide assessment of early-morning ACTH, cortisol, TSH and free T4; also consider gonadotropins, sex hormones, and prolactin levels, as well as cosyntropin stimulation test (though it may not be useful in diagnosing early secondary adrenal insufficiency). – If TSH < 0.5 × LLN, or TSH >2 × ULN, or consistently out of range in 2 subsequent measurements, include free T4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2	For Grade 2 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until patient is clinically stable. • If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid	**For Grade 2 (including those with symptomatic endocrinopathy):** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, consider short-term corticosteroids (e.g., 1 to 2 mg/kg/day methylprednisolone or IV equivalent) and prompt initiation of treatment with relevant hormone replacement (e.g., hydrocortisone, sex hormones). – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids.

		replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement. 3. Doses of prednisone are ≤10 mg/day or equivalent.	– Isolated Type 1 diabetes mellitus (DM) may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a] – For patients with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
	Grade 3 or 4	For Grade 3 or 4 endocrinopathy other than hypothyroidism and Type 1 diabetes mellitus, hold study drug/study regimen dose until endocrinopathy symptom(s) are controlled. Study drug/study regimen can be resumed once event stabilizes and after completion of steroid taper. Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 3 or 4:** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. Hospitalization recommended. – For all patients with abnormal endocrine work up, except those with isolated hypothyroidism or Type 1 DM, and as guided by an endocrinologist, promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent, as well as relevant hormone replacement (e.g., hydrocortisone, sex hormones). – For adrenal crisis, severe dehydration, hypotension, or shock, immediately initiate IV corticosteroids with mineralocorticoid activity. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated Type 1 diabetes mellitus may be treated with appropriate diabetic therapy, without study drug/study regimen interruption, and without corticosteroids. – Once patients on steroids are improving, gradually taper immunosuppressive steroids (as appropriate and with guidance of endocrinologist) over ≥28 days and consider prophylactic

		3. Doses of prednisone are ≤10 mg/day or equivalent.	antibiotics, antifungals, and anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Neurotoxicity (to include but not be limited to limbic encephalitis and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	**Any Grade** (depending on the type of neurotoxicity, refer to NCI CTCAE v5.0 for defining the CTC grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor patient for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with Neurology consult as appropriate. –

	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above. – Treat mild signs/symptoms as Grade 1 (e.g. loss of deep tendon reflexes or paresthesia)
	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 4. Study drug/study regimen can be resumed once event improves to Grade ≤1 and after completion of steroid taper.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Obtain Neurology consult. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). – Promptly start systemic steroids prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If no improvement within 3 to 5 days despite 1 to 2 mg/kg/day prednisone PO or IV equivalent, consider additional workup and promptly treat with additional immunosuppressive therapy (e.g., IV IG).
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days. **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing 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 to 5 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG). – Once stable, gradually taper steroids over ≥28 days.
Peripheral neuromotor syndromes	**Any Grade**	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain patients may

(such as Guillain-Barre and myasthenia gravis)		unpredictably experience acute decompensations that can result in substantial morbidity or in the worst case, death. Special care should be taken for certain sentinel symptoms that may predict a more severe outcome, such as prominent dysphagia, rapidly progressive weakness, and signs of respiratory insufficiency or autonomic instability. – Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes or medications). It should be noted that the diagnosis of immune-mediated peripheral neuromotor syndromes can be particularly challenging in patients with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a Neurology consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a Neurology consultation. – It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 1 (Guillain-Barre [GB]: mild symptoms) (Myasthenia gravis [MG]: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated)	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult.

Grade 2 (GB: moderate symptoms; limiting instrumental ADL) (MG: moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL)	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor patients for sentinel symptoms of a potential decompensation as described above. – Obtain a Neurology consult – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine). *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. It is important to consider that steroid therapy (especially with high doses) may result in transient worsening of myasthenia and should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. Such decisions are best made in consultation with a neurologist, taking into account the unique needs of each patient. o If myasthenia gravis-like neurotoxicity is present, consider starting AChE inhibitor therapy in addition to steroids. Such therapy, if successful, can also serve to reinforce the diagnosis. *GUILLAIN-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Grade 3 or 4 (Grade 3 GB: severe	**For Grade 3:**	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with study physician.

	symptoms; limiting self care ADL; Grade 4 GB: life-threatening consequences; urgent intervention indicated; intubation) (Grade 3 MG: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of existing hospitalization indicated; limiting self care ADL; Grade 4 MG: life-threatening consequences; urgent intervention indicated)	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability. **For Grade 4:** Permanently discontinue study drug/study regimen.	– Recommend hospitalization. – Monitor symptoms and obtain Neurology consult. *MYASTHENIA GRAVIS:* o Steroids may be successfully used to treat myasthenia gravis. They should typically be administered in a monitored setting under supervision of a consulting neurologist. o Patients unable to tolerate steroids may be candidates for treatment with plasmapheresis or IV IG. o 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-BARRE:* o It is important to consider here that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. o Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider, as necessary, discussing with the study physician. – Monitor patients for signs and symptoms of myocarditis (new onset or worsening chest pain, arrhythmia, shortness of breath, peripheral edema). As some symptoms can overlap with lung toxicities, simultaneously evaluate for and rule out pulmonary toxicity as well as other causes (e.g., pulmonary embolism, congestive heart failure, malignant pericardial effusion). A Cardiology consultation should be obtained early, with prompt

	assessment of whether and when to complete a cardiac biopsy, including any other diagnostic procedures. – Initial work-up should include clinical evaluation, BNP, cardiac enzymes, ECG, echocardiogram (ECHO), monitoring of oxygenation via pulse oximetry (resting and exertion), and additional laboratory work-up as indicated. Spiral CT or cardiac MRI can complement ECHO to assess wall motion abnormalities when needed. – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections)

Grade 1 (asymptomatic or mild symptoms*; clinical or diagnostic observations only; intervention not indicated) *Treat myocarditis with mild symptoms as Grade 2.	No dose modifications required unless clinical suspicion is high, in which case hold study drug/study regimen dose during diagnostic work-up for other etiologies. If study drug/study regimen is held, resume after complete resolution to Grade 0.	**For Grade 1 (no definitive findings):** - Monitor and closely follow up in 2 to 4 days for clinical symptoms, BNP, cardiac enzymes, ECG, ECHO, pulse oximetry (resting and exertion), and laboratory work-up as clinically indicated. - Consider using steroids if clinical suspicion is high.
Grade 2, 3 or 4 (Grade 2: Symptoms with moderate activity or exertion) (Grade 3: Severe with symptoms at rest or with minimal activity or exertion; intervention indicated; new onset of symptoms*) (Grade 4: Life-threatening consequences; urgent intervention indicated (e.g., continuous IV therapy or mechanical hemodynamic support))	- If Grade 2 -- Hold study drug/study regimen dose until resolution to Grade 0. If toxicity rapidly improves to Grade 0, then the decision to reinitiate study drug/study regimen will be based upon treating physician's clinical judgment and after completion of steroid taper. If toxicity does not rapidly improve, permanently discontinue study drug/study regimen. If Grade 3-4, permanently discontinue study drug/study regimen.	**For Grade 2-4:** – Monitor symptoms daily, hospitalize. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day or equivalent after Cardiology consultation has determined whether and when to complete diagnostic procedures including a cardiac biopsy. – Supportive care (e.g., oxygen). – If no improvement within 3 to 5 days despite IV methylprednisolone at 2 to 4 mg/kg/day, promptly start immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

	* Consider "new onset of symptoms" as referring to patients with prior episode of myocarditis.		
Myositis/Polymyositis ("Poly/myositis")	**Any Grade**	**General Guidance**	**For Any Grade:** – Monitor patients for signs and symptoms of poly/myositis. Typically, muscle weakness/pain occurs in proximal muscles including upper arms, thighs, shoulders, hips, neck and back, but rarely affects the extremities including hands and fingers; also difficulty breathing and/or trouble swallowing can occur and progress rapidly. Increased general feelings of tiredness and fatigue may occur, and there can be new-onset falling, difficulty getting up from a fall, and trouble climbing stairs, standing up from a seated position, and/or reaching up. – If poly/myositis is suspected, a Neurology consultation should be obtained early, with prompt guidance on diagnostic procedures. Myocarditis may co-occur with poly/myositis; refer to guidance under Myocarditis. Given breathing complications, refer to guidance under Pneumonitis/ILD. Given possibility of an existent (but previously unknown) autoimmune disorder, consider Rheumatology consultation. – Consider, as necessary, discussing with the study physician. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, LDH, BUN/creatinine, erythrocyte sedimentation rate or C-reactive protein level, urine myoglobin, and additional laboratory work-up as indicated, including a number of possible rheumatological/antibody tests (i.e., consider whether a rheumatologist consultation is indicated and could guide need for rheumatoid factor, antinuclear antibody, anti-smooth muscle, antisynthetase [such as anti-Jo-1], and/or signal-recognition particle antibodies). Confirmatory testing may include electromyography, nerve conduction studies, MRI of the muscles, and/or a muscle biopsy. Consider Barium swallow for evaluation of dysphagia or dysphonia. Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections).

Grade 1 (mild pain)	- No dose modifications.	**For Grade 1:** – Monitor and closely follow up in 2 to 4 days for clinical symptoms and initiate evaluation as clinically indicated. – Consider Neurology consult. – Consider, as necessary, discussing with the study physician.
Grade 2 (moderate pain associated with weakness; pain limiting instrumental activities of daily living [ADLs])	Hold study drug/study regimen dose until resolution to Grade ≤1. - Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency.	**For Grade 2:** – Monitor symptoms daily and consider hospitalization. – Obtain Neurology consult, and initiate evaluation. – Consider, as necessary, discussing with the study physician. – If clinical course is rapidly progressive (particularly if difficulty breathing and/or trouble swallowing), promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant – If clinical course is *not* rapidly progressive, start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent); if no improvement within 3 to 5 days, continue additional work up and start treatment with IV methylprednisolone 2 to 4 mg/kg/day – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]
Grade 3 or 4 (Grade 3: pain associated with severe weakness; limiting self-care ADLs	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve	**For Grade 3 or 4 (severe or life-threatening events):** – Monitor symptoms closely; recommend hospitalization. – Obtain Neurology consult, and complete full evaluation. – Consider, as necessary, discussing with the study physician.

Grade 4: life-threatening consequences; urgent intervention indicated)	to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	– Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 3 to 5 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg every 2 weeks). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. – Consider whether patient may require IV IG, plasmapheresis. – Once the patient is improving, gradually taper steroids over ≥28 days and consider prophylactic antibiotics, antifungals, or anti-PJP treatment (refer to current NCCN guidelines for treatment of cancer-related infections).[a]

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

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

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

12.1.3 Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline.	Treat accordingly, as per institutional standard.
Grade 3	Hold study drug/study regimen until resolution to ≤Grade 1 or baseline. For AEs that downgrade to ≤Grade 2 within 7 days or resolve to ≤Grade 1 or baseline within 14 days, resume study drug/study regimen administration. Otherwise, discontinue study drug/study regimen.	Treat accordingly, as per institutional standard.
Grade 4	Discontinue study drug/study regimen (Note: For Grade 4 labs, decision to discontinue should be based on accompanying clinical signs/symptoms, the Investigator's clinical judgment, and consultation with the Sponsor.).	Treat accordingly, as per institutional standard.

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

12.1.4 Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 5.0)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor patients for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (e.g., generalized urticaria, angioedema, wheezing, hypotension, or tachycardia).
Grade 1 or 2	**For 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 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.	**For Grade 1 or 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. – Steroids should not be used for routine premedication of Grade ≤2 infusion reactions.
Grade 3 or 4	**For Grade 3 or 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Manage severe infusion-related reactions per institutional standards (e.g., IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

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

12.2 Patient Handout Prohibited Medications

The study medication(s) you are receiving during this clinical trial is immunotherapy (durvalumab). It is important for you to tell your doctor if you stop taking any regular medicine, or if you start taking a new medicine while you take part in this study. When you talk about your medicine with your study doctor, include medicine you buy without a prescription at the drug store (over-the counter remedy), or anything that you buy from the health food store or grocery store (herbal supplement). Many health care prescribers can write prescriptions. You must also tell your other prescribers (doctors, physicians' assistants or nurse practitioners) that you are taking part in a clinical trial. **Bring this paper with you**.

- **While receiving durvalumab avoid the following:**
  - Any investigational anticancer therapy other than those under investigation in this study
  - mAbs against CTLA-4, PD-1, or PD-L1 other than those under investigation in this study
  - Chemotherapy, immunotherapy, or biologic or hormonal therapy for cancer treatment apart from those under investigation in this study
  - Immunosuppressive medications including but not limited to systemic corticosteroids at doses ≥10 mg/day or prednisone or equivalent, methotrexate, azathioprine, and tumor necrosis factor-α blockers
  - Drugs with laxative properties and herbal or natural remedies for constipation
  - Sunitinib
  - Tyrosine kinase inhibitors that target EGFR (eg, erlotinib, gefinitib)
  - Live attenuated vaccines – also withhold use for at least 30 days after discontinuing study medications
  - Herbal and natural remedies which have immune-modulating effects (eg, ginseng, gingko biloba, ganoderma, astragalus, etc.)
- Do not donate blood while you are on this study. If you permanently stop taking the study drug (durvalumab), do not donate blood for at least 90 days after you stop taking these study drugs.
- **You should check with your doctor or pharmacist whenever you need to use an over-the-counter medicine or herbal supplement.**
  - Your regular prescriber should check a medical reference or call your study doctor before prescribing any new medicine for you. Your study doctor's name is _____ and he or she can be contacted at _____.

12.3 Cockcroft-Gault Formula

Males:

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

Females:

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

12.4 ECOG Performance Status

Grade	Description
0	Normal activity. Fully active, able to carry on all predisease performance without restriction
1	Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work)
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.
5	Dead.
Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.	

12.5 FACT-HN Quality of Life Assessment Tool

Version 4 is attached