December 1, 2021

PROTOCOL AMENDMENT # 4

AMENDMENT #4 INCORPORATES:

Administrative changes
X_ Scientific Changes
X_ Therapy Changes
_ Eligibility Changes

Rationale for Amendment: The primary reason for this amendment is update the dosing modification and toxicity management guidelines to an updated version. Specifically updating the guidance for dose modifications for biopsy-proven immune mediated myocarditis.

Scientific:

1. Appendix D, Section 11.4:
    a. Dosing modification and toxicity management guidelines replaced and updated with guidance October 28, 2021.
    b. AESI language for durvalumab updated in section 5.1.7.
2. Time and Events Table footnote 9 updated to include amylase and lipase analysis in serum chemistries.

The attached version dated December 1, 2021 incorporates the above revisions

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PROTOCOL AMENDMENT # 3

AMENDMENT #3 INCORPORATES:
X Administrative changes
_ Scientific Changes
_ Therapy Changes
_ Eligibility Changes

Rationale for Amendment: The primary reason for this amendment is to make editorial changes and add clarifications to the previous protocol amendment.

Administrative changes

1. Updated Section 3.1.1 to clarify that AJCC Cancer Staging Manual, 7th edition should be used in order to stage subjects for eligibility verification.
2. Updated Section 4.15 and Section 6.8.1 to state that subjects need to come in for initial follow up visit 8 to 12 weeks after treatment discontinuation and match timepoint presented in Time and Events table.
3. Updated footnote of 4 of Time and Events table to match the language in section 4.5.3 regarding requirements for post-operative chemoradiotherapy.
4. Updated Section 4.6.1 to clarify that treating physician may choose not to do dose adjustment based on clinical judgement.
5. Revised and updated Drug Information section to follow the template provided by UNC Investigational Drug Service.
6. Removed pediatric dose modification considerations from Appendix D as not applicable.
7. Updated sections 7.4.1.3, 9.3, 9.4 and 9.5 to reflect current UNC regulatory requirements.

Eligibility changes

1. Updated section 9.5.2 to state that eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials.
2. Revised exclusion criterion 3.2.5 for clarification to state for disease of the oropharynx and known HPV.

The attached version dated January 17, 2019 incorporates the above revisions

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PROTOCOL AMENDMENT # 2

AMENDMENT #2 INCORPORATES (Check all that apply):
X Editorial and Administrative changes
X Scientific Changes
X Therapy Changes
X Eligibility Changes

Rationale for Amendment: The primary reason for this amendment is to provide updated safety investigational drug information for durvalumab, as well to assure safety reporting is consistent with the UNC IRB policy.

Editorial changes

8. Edited Sections 4.2 and 4.4 to include post surgery induction 1-4 weeks

Scientific changes

1. Updated Section 5.1.4 based on durvalumab monotherapy pooled dataset.
2. Updated Section 7.3 on SAE reporting to be consistent with the UNC IRB policy.

Therapy changes

1. Updated Section 11.4 to include revised dose modifications and toxicity management for durvalumab.

Eligibility changes

3. Updated section 9.3 to state that eligibility single subject exceptions are not permitted for Lineberger Comprehensive Cancer Center Investigator Initiated Trials.

The attached version dated February 20, 2018 incorporates the above revisions

ATTACH TO THE FRONT OF EVERY COPY OF PROTOCOL

PROTOCOL AMENDMENT # 1

AMENDMENT #1 INCORPORATES:

X Editorial and Administrative changes
X Scientific Changes
Therapy Changes
X Eligibility Changes

Rationale for Amendment: The primary reason for this amendment is to provide investigational drug information for nab-paclitaxel for its use in head and neck cancer. In addition, editorial and scientific clarifications have been added to the text.

Editorial and Administrative changes

1. Removed co-investigator names from the front of the protocol
2. Minor editorial changes made to sections 1.1, 1.2.2, 1.2.4, 1.2.5, 2.2.3, and 2.2.4
3. Drug Information Section 5.3 Nab-paclitaxel section updated with appropriate language for investigational product to replace language appropriate for a commercial product including sections 5.3.1 Supplier, 5.3.3 Preparation and Administration. Special Handling instructions and the policy for unused nab-paclitaxel drug supply incorporated into the protocol. A cross reference to section 4.3.2 is provided in 5.3.3 which refers reader to section that describes induction chemotherapy dosing with nab-paclitaxel, carboplatin and durvalumab.
4. Section 5.2.3 for Carboplatin also updated with cross-reference to section 4.3.3
5. In Section 7.3.2.2: The address for expedited reporting to Celgene was updated, the definition of an overdose of nab-paclitaxel added and under pregnancy section for AE reporting requirements guidance provided on male subjects receiving nab-paclitaxel who impregnate a female partner is provided. Male subjects treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment with nab-paclitaxel.
6. Removed wording in section 4.3.2 to state that Nab-paclitaxel will be prepared according to institutional standards.
7. Added reference to section 4.3.3 to Drug information section 5.2.3. regarding carboplatin dosing during induction

Scientific changes

1. Updated sections 4.5.2 and 4.5.3 and 5.4.3 regarding appropriate dosing of cisplatin for medium (4.5.2) and high-risk (4.5.3) subjects during concurrent radiotherapy given after surgery per standard of care.

Eligibility changes

1. Revised exclusion criterion 3.2.20 to align with requirements for males regarding contraception requirements and sperm donation, etc. for nab-paclitaxel and durvalumab.

LINEBERGER COMPREHENSIVE CANCER CENTER
CLINICAL ONCOLOGY RESEARCH PROGRAM
UNIVERSITY OF NORTH CAROLINA AT CHAPEL HILL December 1, 2021

LCCC1621: Multimodality Therapy with Induction Carboplatin/nab-Paclitaxel/Durvalumab (MEDI4736) Followed by Surgical Resection and Risk-adapted Adjuvant Therapy for the Treatment of Locally-Advanced and Surgically Resectable Squamous Cell Carcinoma of the Head and Neck

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Sponsor: Lineberger Comprehensive Cancer Center
Funding Source: AstraZeneca
Version date/Version: December 1, 2021/ Version 2.1; Protocol Amendment 4

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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:_____

Version date/Version #: December 1, 2021/ Version 2.1, Protocol Amendment 4

LIST OF ABBREVIATIONS

5-FU	Fluorouracil
ACTH	Adrenocorticotropic hormone
AdEERS	Adverse Event Expedited Reporting System
AE	Adverse event
AJCC	American Joint Committee on Cancer
ALP	Alkaline phosphatase
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
AUC	Area under curve
CBC	Complete blood count
cc	Cubic centimeter
cCRR	Clinical complete response rate
CMP	Comprehensive metabolic panel
CPO	Clinical Protocol Office
CR	Complete response
CrCl	Creatinine clearance
cRR	Clinical response rate
CT	Computer tomography
CTV	Clinical Target Volume
DLT	Dose limiting toxicity
DSMB	Data and Safety Monitoring Board
DSMC	Data safety monitoring committee
ECG	Electrocardiography
ECHO	Echocardiography
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic case report form
Fcγ	Fragment crystallizable gamma receptor
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
fx	Fraction
GCP	Good clinical practice
GTV	Gross Tumor Volume
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human immunodeficiency virus
HPV	Human papillomavirus
ICH	International Conference on Harmonization
IDS	Investigational Drug Service
IgG	Immunoglobulin G
IGRT	Image guidance radiotherapy
IMRT	Intensity Modulated Radiotherapy Treatment
IP	Investigational product
irAE	Immune related adverse events
IRB	Institutional Review Board
IV	Intravenous
mAb	Monoclonal antibody
MRI	Magnetic resonance imaging
NCI	National Cancer Institute

NCI-CTCAE	National Cancer Institute – Common Terminology Criteria for Adverse Events
NSCLC	Non-small cell lung cancer
OHRE	Office of Human Research Ethics
ORR	Objective response rate
OS	Overall survival
pCRR	Pathologic complete response rate
PD	Pharmacodynamic or Progressive disease
PD-L1	Programmed cell death ligand 1
PET	Positron emission tomography
PFS	Progression free survival
PI	Principal investigator
PK	Pharmacokinetic(s)
PO	Oral(ly)
PR	Partial response
PRC	Protocol review committee
PRV	Planning risk volume
PTV	Planning target volume
Q2W	Every two weeks
Q3W	Every three weeks
QOL	Quality of life
QTc	Corrected QT Interval
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation therapy
SAE	Serious adverse event
SAR	Serious adverse reaction
SCCHN	Squamous cell cancer of the head and neck
SD	Stable disease
SOC	Standard of care
SqCC	Squamous cell carcinoma
SUSAR	Suspected Unexpected Serious Adverse Reaction
TSH	Thyroid-stimulating hormone
ULN	Upper limit of normal
UNC	University of North Carolina
UP	Unanticipated problem
WBC	White blood cell
WOCBP	Woman of childbearing potential

TABLE OF CONTENTS

1.0 BACKGROUND AND RATIONALE

1.1 Study Synopsis

This is a single-arm, non-randomized, phase II trial in previously untreated subjects with squamous cell carcinoma of the head and neck (SCCHN) that is locally advanced and amenable to surgical resection. Treatment will consist of 3 parts: neoadjuvant induction with weekly carboplatin and nab-paclitaxel in combination with every other week durvalumab (part 1) prior to surgery (part 2). Post-operative treatment (part 3) will vary depending on the risk category assigned to the subject following surgery as follows: durvalumab administered every 2 weeks for 3 cycles (low risk), ipsilateral radiation concurrent with weekly cisplatin followed by durvalumab once every 2 weeks for 3 cycles (medium risk), or standard of care adjuvant chemoradiotherapy for high risk followed by 3 cycles of durvalumab given every two weeks.

We plan to enroll a total of up to 39 untreated SCCHN subjects to ensure that 37 are evaluable. The primary objective of this study is to estimate the pathologic complete response rate (pCRR) after induction chemotherapy. Secondary objectives include estimating clinical response rate (cRR), clinical complete response rate (cCRR), overall survival (OS), progression-free survival (PFS), the percent of subjects who achieve a reduction in risk level post-induction chemotherapy with the use of pathologic evaluation (compared to risk level assigned based on physical examination and imaging prior to induction chemotherapy and surgery), and correlative studies.

1.2 Advances in Induction Chemotherapy

Chemotherapy initially found a role in the treatment of head and neck cancers as induction (neoadjuvant) therapy given prior to definitive radiation. Following this advance, the RTOG 91-11 trial compared sequential to concurrent therapy and showed a local-control advantage for concurrent therapy [1]. Concurrent therapy with chemotherapy and radiation therefore replaced induction chemotherapy followed by radiation as the new standard of care when chemotherapy and radiation are chosen for definitive therapy. More recently, multiple trials have explored the use of induction chemotherapy prior to definitive therapy. While early efforts focused on the three-drug regimen of cisplatin, 5-FU and docetaxel, these efforts have not improved outcomes. While some patients may have benefited, the toxicity of the regimen may counterbalance these benefits. Alternative approaches built on a platform of carboplatin, a taxane and a targeted therapy continue.

1.2.1 Docetaxel/Cisplatin/5FU (TPF) as Induction

The TAX323 study randomized patients with stage III/IV unresectable SCCHN to four cycles of either TPF (docetaxel 75mg/m^2, cisplatin 75mg/m^2 and 5FU 750mg/m^2 days 1-5) or PF (cisplatin 100mg/m^2 and 5FU 1000mg/m^2 days 1-5) administered every 3 weeks; both groups received subsequent radiation to 70Gy

[3]. The addition of docetaxel improved the post induction response rate from 47% to 59%, progression free survival (PFS) from 8 months to 11.2 months and median survival from 14.5 months to 18.8 months [3]. The TAX324 study randomized patients with stage III/IV unresectable disease or patients considered candidates for organ preservation to three cycles of TPF (docetaxel 75mg/m^2, cisplatin 100mg/m^2 and 5FU 1000mg/m^2 days 1-4 every 3 weeks) or PF (cisplatin 100mg/m^2 and 5FU 1000mg/m^2 days 1-5 every 3 weeks); both groups subsequently received chemoradiation to 70Gy concurrent with weekly carboplatin dosed to an AUC of 1.5. Patients were required to undergo neck dissection 6-12 weeks following chemoradiation for N2 disease with PR, any N3 disease or residual disease. For patients on the TPF arm, post induction response rates trended towards improvement (64% to 72%) [2] and median survival increased from 35 months to 71 months as compared to the PF arm [3].

Prior to these studies, induction chemotherapy was considered a controversial, but reasonable standard of care for inoperable patients or patients with advanced nodal status. Since presentation and publication of these trials, the popularity of induction chemotherapy has increased substantially, and docetaxel has received Food and Drug Administration (FDA) approval, in combination with cisplatin and fluorouracil, for induction treatment of patients with inoperable, locally advanced SCCHN.

Multiple recent clinical trials utilizing the TPF regimen have failed to improve outcomes as summarized in the Table 1.

Table 1. Clinical trials utilizing the TPF regimen

Regimen	Control Arm	Experimental Arm	Result
DeCIDE	Docetaxel/hydroxyurea/ 5FU/BID XRT	TPF x 2 then docetaxel/hyroxyurea/5FU/BID XRT	No difference in OS or DFS. More toxicity in TPF arm. Underpowered
Paradigm	Cisplatin x 2 concurrent with XRT	TPF x 3 then XRT with either docetaxel or carboplatin	No improvement in 3-year survival. Underpowered
GORTEC 2007-002	Carboplatin and 5FU concurrent with XRT	TPF x 3 then XRT with cetuximab	No improvement in PFS or OS.
Zhong et al. –oral cavity only	Radical surgery then adjuvant radiotherapy	TPF x 2 then radical surgery then adjuvant radiotherapy	No improvement in DFS or OS. Pts with ≤10% viable tumor cells had superior OS and disease control.

Table 2. Grade 3 or 4 Toxicities Associated with TPF Induction Chemotherapy for SCCHN

Grade 3/4 Toxicity	**TAX323[3] (% of patients)**	**TAX324[2,5] (% of patients)**
Neutropenia	76.9%	83%
Febrile neutropenia	5.2%	12%
Neutropenic infection	Not reported	12%
Leukopenia	41.6%	Not reported

Anemia	9.2%	12%
Thrombocytopenia	5.2%	4%
Stomatitis	4.6%	21%
Alopecia	11.6%	Not reported
Nausea	0.6%	14%
Esophagitis/Dysphagia/ Odynophagia	0.6%	13%
Vomiting	0.6%	8%
Anorexia	0.6%	12%
Diarrhea	2.9%	7%
Infection	6.9%	6%
Lethargy	2.9%	5%
Neurotoxicity	0.6%	Not reported
Local toxic effect	0.6%	Not reported

In addition to lack of definitive efficacy data (compared to chemoradiotherapy alone), TPF has a number of additional shortcomings. These include the requirement of a port for continuous infusion of 5FU, and, in many communities the need for inpatient hospitalization for therapy administration. Grade 3 and 4 toxicities from the TAX323 and TAX324 studies are summarized above, although the reported results do not begin to do justice to the degree of toxicity and sequelae often experienced in clinical practice. Further, the toxicity is not simply a matter of short-term suffering with potential long-term reward; in TAX324, 21% of patients did not proceed to potentially curative protocol-defined chemoradiation [4] because of toxicity during the induction phase of treatment. This high level of grade 3 and 4 toxicity with resultant failure to proceed to definitive therapy has led many institutions, including UNC, to seek alternative induction regimens. We hypothesize that regimens with less toxicity than TPF and greater efficacy could improve outcomes where TPF has failed.

1.2.2 Weekly regimens

Haraf et al. [5] treated a population consisting primarily (97%) of stage IV locally advanced patients with carboplatin AUC2 and paclitaxel 135mg/m^2 weekly for six cycles. This therapy was followed by twice daily radiation consisting of 1.5Gy daily in a split course. Treatment results from this phase II trial of 64 patients were promising with 100% complete response (CR) after total treatment, a 3-year overall survival (OS) of 70% and 3-year progression free survival (PFS) of 90% (all determined after the completion of radiation therapy).

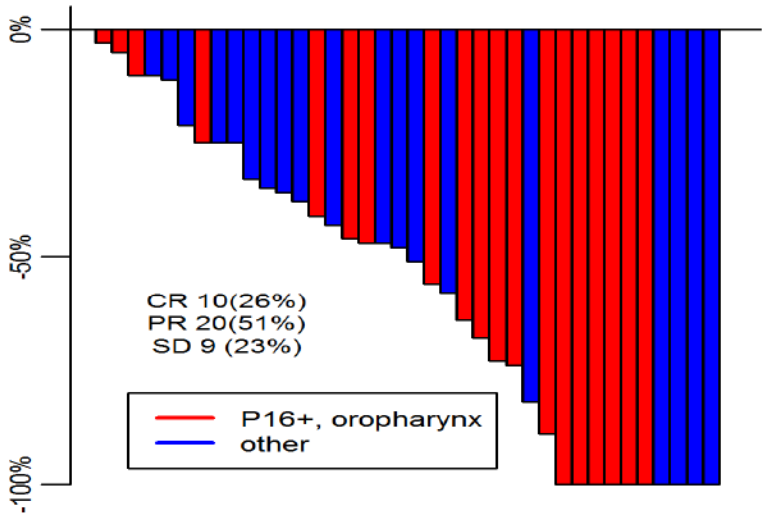
Because EGFR is overexpressed in most cancers of the epithelium, including SCCHN, Kies [6] and Wanebo [7] sought to improve upon the results seen with paclitaxel/ carboplatin with the addition of cetuximab. Kies and associates treated 47 patients with N2b or greater disease with carboplatin AUC2, paclitaxel 135 mg/m^2 and cetuximab 400 mg/m^2 loading followed by 250 mg/m^2 weekly for six weeks. Post induction therapy, patients received radiation therapy alone (n=23), chemoradiation (n=23), or surgery alone (n=1) depending on their stage and quality of response to induction. The overall response rate (CR + PR) at the end of radiation therapy (with or without chemotherapy) was 96% with a CR of 70%. The most common non-hematologic toxicity during induction therapy was

rash/folliculitis (grades 2 and 3 in 38% and 45% of patients, respectively), followed by fatigue (40% grade 2 and 2% grade 3), diarrhea (9% grade 2 and 9% grade 3) and sensory neuropathy (15% grade 2 and 2% grade 3). The most common grade 2 to 4 hematologic toxicity was neutropenia (grades 2, 3, and 4 in 23%, 19%, and 2% of patients, respectively). There were no instances of febrile neutropenia. Dose reductions were needed in one patient for cetuximab and in four and two patients for paclitaxel and carboplatin, respectively. Treatment delays of 7 days occurred in 60% of patients.

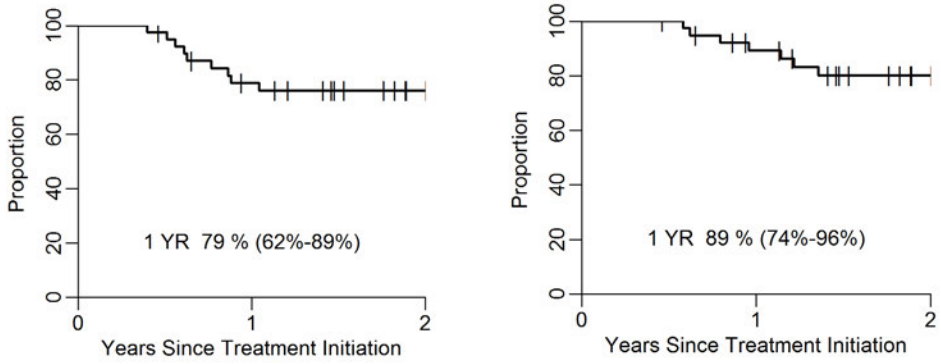
Wanebo et al, under the aegis of the ECOG, treated operable patients with stage III or IV disease with weekly carboplatin AUC2, paclitaxel 90mg/m^2 and cetuximab 400mg/m^2 loading followed by cetuximab 250mg/m^2 weekly for six weeks. During therapy, patients underwent tumor staging biopsies at the primary site until biopsy negativity. Forty of 67 evaluable patients had a clinical response to induction chemotherapy and 26 of 40 (65%) had a biopsy-proven CR. After 50 Gy radiation (concurrent with carboplatin AUC1, paclitaxel 30mg/m^2 and cetuximab 250 mg/m^2) all patients who had not yet had a negative biopsy were biopsied—all were negative. Together, the Kies and Wanebo reports provide very strong support for induction regimens that include a taxane, carboplatin, and cetuximab.

Based on promising results with nab-paclitaxel in SCCHN and SqCC lung, our group studied carboplatin AUC2, nab-paclitaxel 100mg/m^2 and cetuximab weekly for six weeks prior to standard of care chemoradiotherapy [8]. The population treated was very high risk both anatomically and biologically.

Response rate was 77% and was agnostic to HPV status:



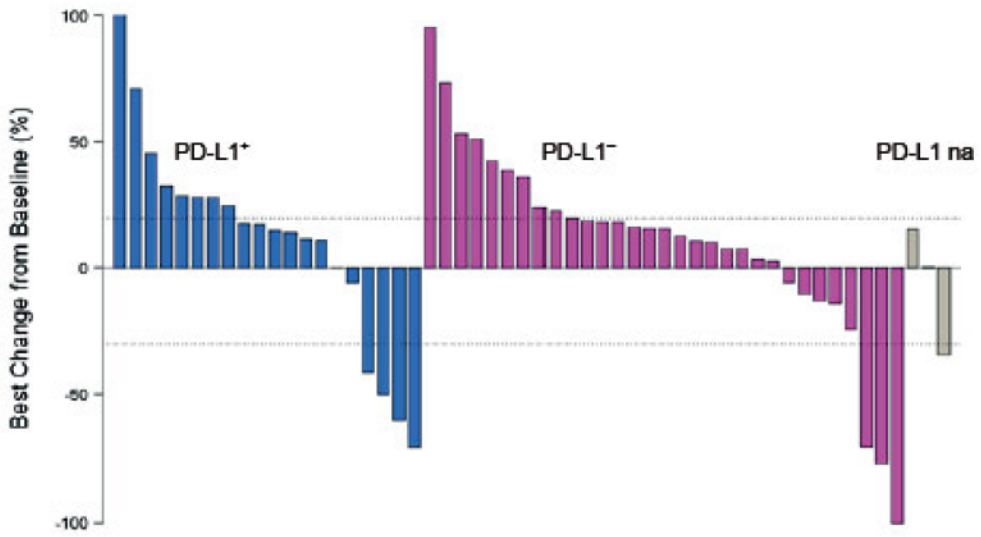
PFS and OS data are favorable, especially for this very high-risk population:



We also studied the combination of carboplatin AUC2, paclitaxel 135mg/m^2 and lapatinib daily for six weeks prior to transoral surgery (NCT01612351). In preliminary data on the first 36 patients (of 40 planned) pCRR was 33%. Only one patient has recurred or died; this patient had a response to induction chemotherapy and then declined study-mandate surgical resection and removed himself from the study. Other concurrent data have demonstrated an absence of activity of lapatinib in SCCHN [9], suggesting that these results simply demonstrated the high activity of weekly platinum and taxane. A more active targeted therapy, such as durvalumab, could further improve results.

1.2.3 Durvalumab

Durvalumab is being developed as a potential anticancer therapy for patients with advanced solid tumors. Durvalumab is a human monoclonal antibody (MAb) of the immunoglobulin G1 kappa (IgG1κ) subclass that inhibits binding of programmed cell death ligand 1 (PD-L1) (B7 homolog 1 [B7-H1], cluster of differentiation [CD]274) to programmed cell death 1 (PD-1; CD279) and CD80 (B7-1). Durvalumab is composed of 2 identical heavy chains and 2 identical light chains, with an overall molecular weight of approximately 149 kDa. Durvalumab contains a triple mutation in the constant domain of the immunoglobulin (Ig) G1 heavy chain that reduces binding to complement protein C1q and the fragment crystallizable gamma (Fcγ) receptors involved in triggering effector function.



A Phase I expansion study of durvalumab in metastatic/recurrent SCCHN showed a RR of 12% in heavily pretreated patients with good tolerability [10]. In NSCLC, PD1- and PDL1-targeting agents have been studied together with chemotherapy where they have demonstrated good preliminary efficacy and tolerability, including the specific combination with carboplatin and nab-paclitaxel [11].

Preclinical and Clinical experience with durvalumab is fully described in the current version of the durvalumab Investigator's Brochure (Edition 12). The safety of durvalumab monotherapy in ongoing clinical trials is briefly summarized in section 5.1.8.

Fixed Dosing

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

Similar findings have been reported by others [12-15]. Wang and colleagues investigated 12 monoclonal antibodies and found that fixed and body size-based dosing perform similarly, with fixed dosing being better for 7 of 12 antibodies [3]. In addition, they investigated 18 therapeutic proteins and peptides and showed

that fixed dosing performed better for 12 of 18 in terms of reducing the between-subject variability in pharmacokinetic/pharmacodynamics parameters [15].

A fixed dosing approach is preferred by the prescribing community due to ease of use and reduced dosing errors. Given expectation of similar PK exposure and variability, we considered it feasible to switch to fixed dosing regimens. Based on average body weight of 75 kg, a fixed dose of 750 mg Q2W durvalumab (equivalent to 10 mg/kg Q2W), is included in the current study. Fixed dosing of durvalumab is recommended only for subjects with > 30kg (66 pounds) body weight due to endotoxin exposure.

1.2.4 Summary of Adverse Events Reported in Clinical Trials of Durvalumab: CD-ON- MEDI4736-1108, ATLANTIC and PACIFIC

Safety data have been pooled for 3 durvalumab monotherapy studies (CDON-MEDI4736-1108, ATLANTIC and PACIFIC) for patients who received a durvalumab dose of 10 mg/kg Q2W; a total of 1889 patients are included in this validated pooled data set. Overall, AEs reported in ≥10% of patients were fatigue (31.7%), cough (23.1%), decreased appetite (21.4%), dyspnea (20.8%), nausea (20.2%), constipation (17.6%), diarrhea (17.4%), pyrexia (15.2%), back pain (13.8%), anemia (13.5%), vomiting (13.0%), pruritus (11.8%), arthralgia (11.6%), headache (11.0%), asthenia (10.8%), edema peripheral (10.5%) and rash (10.2%). AEs that were considered by the investigator as related to durvalumab in ≥5% of patients were fatigue (15.8%), diarrhea (8.1%), hypothyroidism (8.0%), nausea (7.2%), pruritus (6.9%), decreased appetite (6.4%) and rash (6.4%). New AEs of Grade 3 myositis (1 subject; <0.1%) and Grade 3 of intestinal perforation (3 subjects; 0.3%) in the combination of durvalumab with tremelimumab were reported.

A total of 853 patients (45.2%) reported AEs of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher: 796 patients (42.1%) had events of Grade 3, 126 patients (6.7%) had events of Grade 4 and 101 patients (5.3%) had Grade 5 (fatal) events. AEs of Grade 3 or higher considered related to durvalumab were reported in 201 patients (10.6%): 177 patients (9.4%) had events of Grade 3, 13 patients (0.7%) had events of Grade 4 and 11 patients (0.6%) had Grade 5 (fatal) events.

Grade 3 or 4 events occurring in ≥1% of patients were anaemia (5.5%); dyspnea (4.6%); hyponatraemia (3.6%); gamma-glutamyltransferase (GGT) increased (2.6%); pneumonia (2.5%); fatigue (2.4%); aspartate aminotransferase (AST) increased (2.1%); back pain (2.0%); abdominal pain (1.9%); sepsis (1.8%); hypertension (1.5%); dehydration (1.4%); decreased appetite and general physical health deterioration (1.3% each); alanine aminotransferase (ALT) increased, asthenia and hypokalaemia (1.2% each); blood alkaline phosphatase (ALP) increased, pleural effusion, pulmonary embolism, urinary tract infection and vomiting (1.1% each); and hyperglycemia and lung infection (1.0% each). Grade 3 or 4 events considered related to durvalumab occurring in ≥0.5% patients were fatigue (1.0%); AST increased (0.8%); GGT increased (0.7%); pneumonitis (0.6%); and ALT increased and diarrhea (0.5% each). The most common Grade 5 events were general physical health deterioration (15 patients [0.8%]), respiratory

failure (9 patients [0.5%]) and sepsis (7 patients [0.4%]); Grade 5 events of death, pneumonia and pneumonitis occurred in 5 patients each (0.3%) with the remainder of the Grade 5 events occurring in ≤3 patients for each event. The only Grade 5 event considered related to durvalumab occurring in ≥2 patients was pneumonitis (5 patients [0.3%]).

A total of 178 patients (9.4%) discontinued from study treatment due to an AE. The most common events leading to treatment discontinuation were pneumonitis (28 patients [1.5%]); pneumonia (10 patients [0.5%]); dyspnea and general physical health deterioration (9 patients each [0.5%]); and radiation pneumonitis (6 patients [0.3%]); all other discontinuation events occurred in ≤4 patients. A total of 108 patients (5.7%) had serious AEs (SAEs) that were considered by the investigator as related to durvalumab. The most common were: pneumonitis (25 patients [1.3%]); infusion related reaction (5 patients [0.3%]); colitis, diarrhea, fatigue, pneumonia and radiation pneumonitis (4 patients each [0.2%]); nervous system disorder (3 patients [0.2%]); abdominal pain, acute kidney injury, adrenal insufficiency, anemia, AST increased, autoimmune hepatitis, dehydration, dyspnea, herpes zoster, lung infection, nausea, pericardial effusion, thrombocytopenia and vomiting (2 patients each [0.1%]).

A total of 1063 patients (56.3%) experienced an AESI during the study. The most common grouped term AESI was diarrhea (329 patients [17.4%]; of whom 14 patients [0.7%] had events of Grade ≥3). Other common AESIs (grouped term) were dermatitis (299 patients [15.8%]; of whom 3 patients [0.2%] had events of Grade ≥3); rash (283 patients [15.0%]; of whom 11 patients [0.6%] had events of Grade ≥3); select hepatic events (227 patients [12.0%]; of whom 86 patients [4.6%] had events of Grade ≥3); hypothyroidism (206 patients [10.9%]; of whom 2 patients [0.1%] had events of Grade ≥3); hyperthyroidism (135 patients [7.1%]; of whom 1 patient [<0.1%] had events of Grade ≥3); select renal events (119 patients [6.3%]; of whom 23 patients [1.2%] had events of Grade ≥3); and pneumonitis (98 patients [5.2%]; of whom 20 patients [1.1%] had events of CTCAE Grade ≥3). There were 11 patients who had AESIs of CTCAE Grade 5 (fatal events); 5 patients had pneumonitis, 4 patients had hepatic events (autoimmune hepatitis, hepatic failure, hyperbilirubinemia and transaminases increased), 1 patient had acute kidney injury and 1 patient had immune thrombocytopenic purpura.

1.2.5 Limitations of adjuvant radiation therapy and chemoradiotherapy

In a pre-adjuvant therapy era, local and regional recurrence occurred in 30% of patients and distant recurrence in 25% [16]. Although adjuvant radiotherapy improves outcomes compared with radiotherapy alone, less than half of patients are disease free at five years. Two major studies attempted to improve outcomes for high-risk post-operative patients by adding cisplatin chemotherapy to adjuvant radiotherapy. RTOG 9501 [17, 18] 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 radiotherapy alone or radiotherapy plus three cycles of cisplatin at 100mg/m^2. A second study, EORTC 22931[19] 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. A combined analysis of these two trials [20] showed that benefit seemed restricted to patients with extracapsular extension or positive margins (statistically significant for this subgroup in EORTC with a strong trend in RTOG). Similar results/trends were seen in long term follow up of the RTOG study.

The RTOG study provided more detailed data on acute and chronic toxicity as outlined in the Table 3. The rate of acute G3-5 toxicity with radiotherapy alone was 34.4%; with the addition of cisplatin, this rose to 77.0%. In clinical practice long term otopathy, nephropathy and neuropathy are also commonly seen.

Adverse Effect	Radiotherapy			Combined Therapy		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
	number of patients (percent)					
Acute†						
Hematologic	1	0	0	61	17	0
Mucous membrane	35	2	0	55	7	0
Pharynx and esophagus	32	0	0	49	1	0
Nausea and vomiting	0	0	0	28	12	0
Upper gastrointestinal tract	6	0	0	25	7	0
Skin	20	1	0	14	0	0
Infection	1	0	0	12	0	1
Neurologic	0	0	0	9	1	0
Genitourinary tract	0	0	0	6	0	0
Anemia	0	0	0	6	0	0
Larynx	2	1	0	5	1	0
Renal	0	0	0	3	2	0
Salivary gland	2	0	0	3	1	0
Subcutaneous	0	0	0	2	0	0
Diarrhea	0	0	0	1	1	0
Hepatic	0	0	0	1	1	0
Respiratory tract	0	0	0	1	0	0
Bone	1	0	0	0	1	0
All others	1	3	0	25	6	2
Grade of most severe acute adverse effect	65	7	0	111	44	2
Late‡						
Pharynx and esophagus	12	1	0	15	0	0
Salivary gland	5	0	0	7	0	0
Larynx	3	1	0	5	0	1
Bone	1	1	0	1	5	0
Subcutaneous	6	1	0	3	0	0
Mucous membrane	3	2	0	1	3	0
Upper gastrointestinal tract	1	0	0	3	0	0
Hematologic	1	1	0	3	0	0
Joint	2	0	0	1	0	0
Neurologic	2	0	0	3	0	0
Renal	0	0	0	1	1	0
Skin	2	0	0	2	3	0
All others	5	2	0	4	1	1
Grade of most severe late adverse effect§	28	7	0	29	11	2
Any¶						
Grade of most severe adverse effect§	82 (39)	14 (7)	0	106 (51)	51 (25)	4 (2)

Table 3. Acute and chronic toxicity to chemoradiotherapy (RTOG 9501)

1.2.6 Safety of Durvalumab and Radiation

The LCCC1621 study does not concurrently administer durvalumab and radiation, but data on the safety of this combination are relevant to this study. A single center expansion cohort of the Phase I/2 trial of durvalumab enrolled 10 patients with solid tumors who also received either concurrent 3-dimensional radiotherapy (RT) (79%) or stereotactic RT (21%) [21]. Durvalumab (10mg/kg Q2W) was given with RT at a median biologically-effective dose of 28 Gy in a median number of 5 fractions over a median duration of 6 days. Five patients reported irradiation-related AEs and the most frequently reported event was grade 2 mucositis. There were no grade 3 or more RT-related AEs. There are currently over 20 planned, ongoing or completed clinical studies of durvalumab listed on the clinical trials.gov website that include administration of durvalumab alone or with tremelimumab in combination with radiotherapy or chemoradiotherapy in multiple solid tumor types. The PACIFIC/D4191C00001 study which is a randomized Phase III trial in subjects with locally advanced, unresectable Stage III NSCLC post concurrent chemoradiotherapy, has reported out safety data in a total of 115 subjects [22]. Subjects had received 1 to 26 doses of durvalumab (10mg/kg Q2W which is comparable to 750 mg Q2W proposed in LCCC1621) as reported in the current investigator's brochure for durvalumab. This study remains blinded. Treatment emergent AEs of special interest in this ongoing trial are provided below. Full data are not yet available but press release has indicated that the trial was positive for its primary endpoint of PFS.

Table 4. Treatment emergent AEs of special interest in the PACIFIC/D4191C00001 study

Specific Adverse Event of Interest Preferred Term (MedDRA V18.0)	Total (N = 115) n (%)	
	All Grades	≥ Grade 3
Hyperthyroidism	**2 (1.7)**	**0**
Hyperthyroidism	1 (0.9)	0
Thyroiditis	1 (0.9)	0
Nephritis/Acute Renal Failure	**2 (1.7)**	**0**
Acute kidney injury	1 (0.9)	0
Blood creatinine increased	1 (0.9)	0
Pancreatitis	**2 (1.7)**	**1 (0.9)**
Amylase increased	1 (0.9)	0
Lipase increased	1 (0.9)	1 (0.9)
Pancreatitis	1 (0.9)	0
Hypothyroidism	**1 (0.9)**	**0**
Hypothyroidism	1 (0.9)	0
Infusion Related/Hypersensitivity/Anaphylactic Reactions	**1 (0.9)**	**0**
Infusion related reaction	1 (0.9)	0
Select Hepatic Events	**1 (0.9)**	**0**
Gamma-glutamyltransferase increased	1 (0.9)	0

AESI = adverse event of special interest; MedDRA = Medical Dictionary for Regulatory Activities.

1.3 Study Rationale

Traditionally, induction chemotherapy in SCCHN has been studied prior to chemoradiotherapy. When radiation therapy is delivered definitively (up-front as the primary modality for cure) the radiation fields must be given widely to any areas considered at risk based on physical examination, imaging, and the natural patterns of disease spread. As CT imaging is limited in its ability to define the true extent of disease, patients receive wider fields than necessary, increasing long-term morbidity. This principal of uncertainty of the extent of disease on CT imaging is exacerbated by induction chemotherapy and because of this unreliability, the standard of care for radiation delivered after induction chemotherapy is to treat the pre-induction field, even if the tumor has shrunk dramatically [23].

The recently completed LCCC1125 study sought to not only improve cure rates, but to improve functional outcomes by avoiding radiation for patients with good response and by minimizing it to pathologically-proven involved fields for those who required it. In that study, most patients were able to avoid radiation and quality of life was preserved (data no published, submitted to ASCO 2017). LCCC1125 gave induction chemotherapy consisting of carboplatin, paclitaxel and lapatinib prior to surgical resection. In this study, surgical resection has not only allowed for extirpation of disease but has also provided clearer definition of the anatomic extent of disease. Long-term results are pending, but early results using this approach are favorable and we postulate that it will minimize radiation-induced morbidity, including xerostomia. Xerostomia occurs in all irradiated patients to some degree, regardless of radiation method (including intensity modulated radiation therapy (IMRT)). Xerostomia not only alters quality of life, but also can lead to dental compromise, and osteoradionecrosis. Knowing the true stage of a patient and burden of disease based on the gold standard of pathological review of surgical tissue allows one to offer the most appropriate adjuvant therapy and counseling on prognosis. Furthermore, the morbidity of an elective neck dissection is minimal, and people can return to normal activity within 3-5 days, with a restriction on lifting for 2 weeks.

With traditional surgery (external approaches) and traditional induction chemotherapy (TPF), options for further therapy are limited due to the toxic nature of the therapy. We have previously shown high RR to carboplatin, nab-paclitaxel and cetuximab. Based on data from the metastatic setting, we hypothesize that the combination with durvalumab will be more active.

In the metastatic setting, treatment with cetuximab resulted in a RR of 13%. In contrast, two PD1 inhibitors and the PDL1 inhibitor durvalumab have shown numerically superior RR, including some durable control. Treatment with pembrolizumab resulted in an 18% RR both in a study restricted to patients whose tumors were $PDL1^+$ [24] and in a study of unselected patients [25]. Nivolumab was recently compared to 2^{nd} line chemotherapy (methotrexate, docetaxel or

cetuximab) and showed both superior survival and superior quality of life; RR was 18% in unselected patients [26]. We hypothesize that beyond its superior single-agent activity, that antigen presentation from cytotoxic cell death with chemotherapy will synergize with immunotherapy and facilitate efficacy.

Thus, through the sequencing of induction chemotherapy, minimally invasive surgery and radiation in LCCC1125, we sought to not only enhance survival and cancer control benefit, but also simultaneously improve adjuvant therapy decisions to minimize morbidity. We propose to build on this approach in the current study LCCC1621 evaluating carboplatin, nab-paclitaxel and durvalumab induction therapy for locally-advanced and surgically resectable SCCHN.

1.4 Correlative Studies

The use of surgery for definitive therapy also allows for paired comparison of pre-treatment and post-treatment specimens. Subjects will be consented for collection of blood and tumor samples prior to and after induction therapy for immune correlative studies. During screening, archival tumor tissue will be obtained and optional fresh tumor biopsies will be requested and obtained from subjects who consent to this procedure. A pretreatment blood sample will be collected prior to initiating study treatment. Following induction therapy, tumor and blood samples will also be collected during the scheduled surgical resection for research purposes. Collection and processing of specimens will be described in the laboratory manual.

2.0 STUDY OBJECTIVES

2.1 Primary Objective

Estimate the pathologic complete response rate (pCRR) after induction chemotherapy with carboplatin, nab-paclitaxel, and durvalumab in previously untreated stage III and IV SCCHN amenable to surgical resection.

2.2 Secondary Objectives

2.2.1 Report the clinical complete response rate (cCRR) and clinical response rate (cRR) following induction chemotherapy

2.2.2 Estimate the percent of subjects who have a change in estimated risk level. Prior to induction, this will be assessed clinically (by imaging and physical exam). Post induction, this will be assessed by surgical pathology report.

2.2.3 Estimate the OS and PFS associated with 3-part therapy consisting of induction chemotherapy, surgery and risk-adapted use of chemoradiation.

2.2.4 Characterize the toxicity profile associated with both induction therapy and total 3-part therapy consisting of induction chemotherapy, surgery and risk-adapted use of chemoradiation.

2.3 Translational/Exploratory Objectives

2.3.1 [redacted]

2.4 Endpoints

2.4.1 Primary Endpoint

Pathologic complete response rate after neoadjuvant treatment with carboplatin, nab-paclitaxel, and durvalumab will be assessed via surgical pathology report. Pathologic complete response will require no viable cancer cells on the surgical pathology report after neoadjuvant treatment with carboplatin, nab-paclitaxel and durvalumab.

2.4.2 Secondary Endpoints

2.4.2.1 Risk level pre-induction will be based on physical examination and imaging and will be defined and documented in eCRFs prior to the initiation of induction therapy. Post-induction risk level will be determined based on pathologic evaluation of surgical specimen.

2.4.2.2 PFS will be defined as the time from D1 of study treatment until progression per RECIST 1.1 and overall survival will be defined as the time from D1 of study treatment until death from any cause.

2.4.2.3 Clinical complete response rate and clinical response rate (CR + PR) associated with 3-part therapy consisting of induction chemotherapy, surgery and risk-adapted use of chemoradiation will estimated using RECIST 1.1.

2.4.2.4 Safety associated with both induction alone and with 3-part therapy consisting of induction chemotherapy, surgery and risk-adapted use of chemoradiation will be assessed via the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE v4.03).

2.4.3 Translational/Exploratory Endpoints:

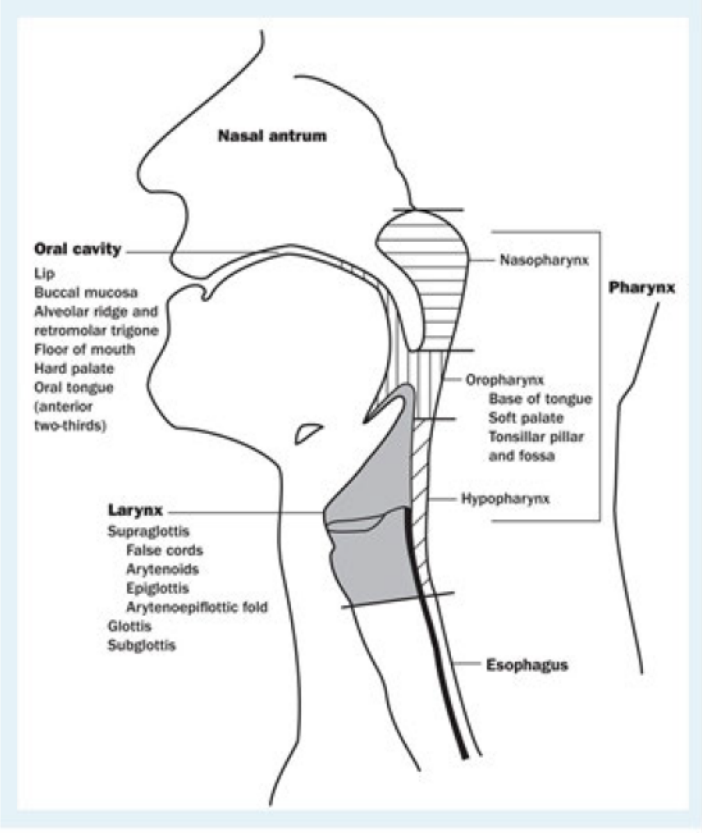
[redacted]

3.0 SUBJECT ELIGIBILITY

3.1 Inclusion Criteria

Subject must meet all of the following inclusion criteria to participate in this study:

3.1.1 Previously untreated, histologically proven, surgically resectable primary squamous cell carcinoma of the head and neck, stage III or IV (HPV positive or negative non-metastatic disease) according to the AJCC Cancer Staging Manual, 7th edition. SCCHN of unknown primary is excluded. SCCHN of the oral cavity is allowed*. Unambiguously squamous EBV-negative nasopharynx cancer will not be excluded nor will unambiguously squamous cancers of the skull base that are clearly surgically resectable and clearly squamous. Squamous skin cancer occurring in the head/neck region will not be eligible nor will EBV^{+} nasopharynx cancer (see figure below for anatomic subsites of head and neck cancer). (* Induction chemotherapy is not considered standard therapy for SCCHN of the oral cavity and participation on this trial will lead to a delay in time to definitive, potentially curative therapy, i.e. surgery).



Anatomic sites and subsites of the head and neck. The approximate distribution of head and neck cancer is oral cavity, 44%, larynx, 31%, and pharynx, 25%.

3.1.2 Eastern Cooperative Oncology Group (ECOG) performance status of ≤1 (see **Appendix A: ECOG Performance Status**).

3.1.3 Measurable disease as per RECIST1.1.

3.1.4 Age ≥18 years at time of study entry.

3.1.5 Adequate bone marrow function as demonstrated by:

- Absolute neutrophil count (ANC) ≥ 1,5 x 10^9/L
- Hgb ≥ 10 g/dL (use of transfusion to reach this threshold prior to study initiation is acceptable)
- Platelet count ≥ 100 x 10^9/L

3.1.6 Adequate hepatic and renal function as demonstrated by:

- Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN);
- Total serum bilirubin ≤1.5 ULN
- Creatinine clearance (CrCL) > 40mL/min as measured via Cockcroft-Gault

Males:

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

Females:

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

3.1.7 Negative serum β-hCG pregnancy test within 72 hours of day 1 of induction chemotherapy in women of child-bearing potential.

3.1.8 All males and females of childbearing potential must agree to use adequate contraception during the study. Adequate contraception is defined as any medically recommended method (or combination of methods) as per standard of care. Females of non-childbearing potential are those who are postmenopausal greater than 1 year or who have had a bilateral tubal ligation or hysterectomy or bilateral oophorectomy. See section 4.13 for list of acceptable methods of contraception.

3.1.9 Signed an institutional review board (IRB) approved informed consent and HIPAA authorization.

3.1.10 Subject is willing and able to comply with the protocol for the duration of the study including undergoing treatment and scheduled visits and examinations including follow up.

3.1.11 Subjects must agree to allow use of any pre-treatment tissue remaining after definitive diagnosis is made (i.e., archival and or fresh tissue) for research

purposes. In addition, subjects must consent to allow use of their residual post-operative tissue for research purposes.

3.2 Exclusion Criteria

Subjects who meet any of the following exclusion criteria will be ineligible to participate in this study:

3.2.1 Involvement in the planning and/or conduct of the study (applies to staff at the study site) or previous enrollment in the present study.

3.2.2 Any metastatic disease.

3.2.3 Known history of previous clinical diagnosis of tuberculosis.

3.2.4 History and/or confirmed pneumonitis.

3.2.5 Low-risk HPV^+ disease of the oropharynx, defined as meeting all of the following criteria:

- Subjects with known HPV^+ by FISH and/or p16
- smoking history $\leq$10 pack years
- Stage T1-2N0-2b, T3N0

3.2.6 Not considered eligible for any of the chemotherapy agents included in the induction regimen.

3.2.7 Current active hepatic or biliary disease (with exception of subjects with Gilbert's syndrome, asymptomatic gallstones, or stable chronic liver disease per investigator assessment).

3.2.8 Major surgery within 28 days prior to day 1 of study treatment from which the subject has not completely recovered.

3.2.9 Receiving any investigational agent currently or within 28 days or 5 half-lives of Day 1 of treatment on this study.

3.2.10 Active, serious infection, medical, or psychiatric condition that would represent an inappropriate risk to the subject or would likely compromise achievement of the primary study objective, including unstable angina, serious uncontrolled cardiac arrhythmia, uncontrolled infection, or myocardial infarction $\leq$ 6 months prior to study entry.

3.2.11 Active or prior documented autoimmune or inflammatory disorders (including inflammatory bowel disease [e.g., colitis, Crohn's disease], diverticulitis with the exception of a prior episode that has resolved or diverticulosis, celiac disease, irritable bowel disease, or other serious gastrointestinal chronic conditions associated with diarrhea; systemic lupus

erythematosus; Wegener's syndrome [granulomatosis with polyangiitis]; myasthenia gravis;; rheumatoid arthritis; hypophysitis, uveitis; etc.) within the past 2 years prior to the start of treatment. NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded

3.2.12 Known mean QT interval corrected for heart rate (QTc) ≥470 ms calculated from 3 electrocardiograms (ECGs) using Fredericia's Correction. (Note that ECG is not required for study entry and is not part of study procedures).

3.2.13 Other prior or concomitant malignancies with the exception of**:**

- Non-melanoma skin cancer
- In-situ malignancy
- Low-risk prostate cancer after curative therapy
- Other cancer for which the subject has been disease free for ≥ 5 years before the first dose of study drug and of low potential risk for recurrence.

3.2.14 Any concurrent chemotherapy, investigational treatment, biologic or hormonal therapy for cancer treatment. Concurrent use of hormonal therapy for non-cancer-related conditions (e.g. hormone replacement therapy) is acceptable.

3.2.15 Current or prior use of immunosuppressive medication within 14 days prior to the first dose of durvalumab. The following are exceptions to this criterion: intranasal, inhaled, topical or local steroid injections (eg. intra-articular injection); steroids as premedication for hypersensitivity reactions; systemic corticosteroid at physiologic doses not to exceed 10mg/day of prednisone or equivalent. [NOTE: If systemic corticosteroids are part of the treatment regimen for the indication under study, the systemic corticosteroid is permitted].

3.2.16 Known human immunodeficiency virus (HIV), hepatitis C virus (HCV) or evidence of active hepatitis B virus (HBV).

3.2.17 History of hypersensitivity to durvalumab or any excipient.

3.2.18 Receipt of live attenuated vaccination within 30 days prior the first dose of durvalumab [NOTE: If a vaccine is part of the treatment regimen for the indication under study, the vaccine is permitted].

3.2.19 Female subjects who are pregnant, breast-feeding or female subjects of reproductive potential who are not employing an effective method of birth control from starting dose of study medications (Cycle 1 Day 1), including dosing interruptions through 90 days after receipt of the last dose of durvalumab. Subjects must refrain from egg cell donation while taking durvalumab and for at least 90 days after the last dose of durvalumab.

3.2.20 Male subjects who are not employing an effective method of birth control from starting dose of study medications (Cycle 1 Day 1), including dosing interruptions through 6 months after receipt of study treatment. Male subjects should agree to refrain from sperm donation while taking study treatment and for at least 6 months after the last dose of nab-paclitaxel and at least 90 days after the last dose of durvalumab. Should a female partner of a male subject become pregnant or suspect she is pregnant while participating in the study, he should inform his treating physician and the female partner should call her physician immediately.

3.2.21 Any previous treatment with a PD1 or PD-L1 inhibitor, including durvalumab.

3.2.22 History of primary immunodeficiency.

3.2.23 History of organ transplant.

3.2.24 Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of subject safety or study results (e.g., uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent).

3.2.25 Subjects with known contraindications to radiotherapy including inherited syndromes associated with hypersensitivity to ionizing radiation (e.g., Ataxia Telangiectasia, Nijmegen Breakage Syndrome).

4.0 TREATMENT PLAN

4.1 Overview

The treatment plan for this study is comprised of three parts. Prior to surgery, subjects will be treated with induction chemotherapy (Part 1) comprised of weekly carboplatin and nab-paclitaxel for 6 weeks in combination with every other week durvalumab administered for 5 cycles (See schema in section 4.2).

Part 2 will consist of surgical resection. The results of pathology from this surgery will stratify subjects into one of three risk categories. Surgery will also allow investigators to pathologically define the extent of response to induction chemotherapy. After surgery, subjects will be assigned a treatment group based on their risk and treated with adjuvant therapy in Part 3.

Some subjects will be low risk at study entry, while others will become low risk as a consequence of the success of induction chemotherapy. Notably, this low risk group inherently includes subjects who have a complete response (CR) to induction chemotherapy. After surgery, subjects in the low risk category will be given durvalumab once every two weeks for 3 cycles as adjuvant therapy.

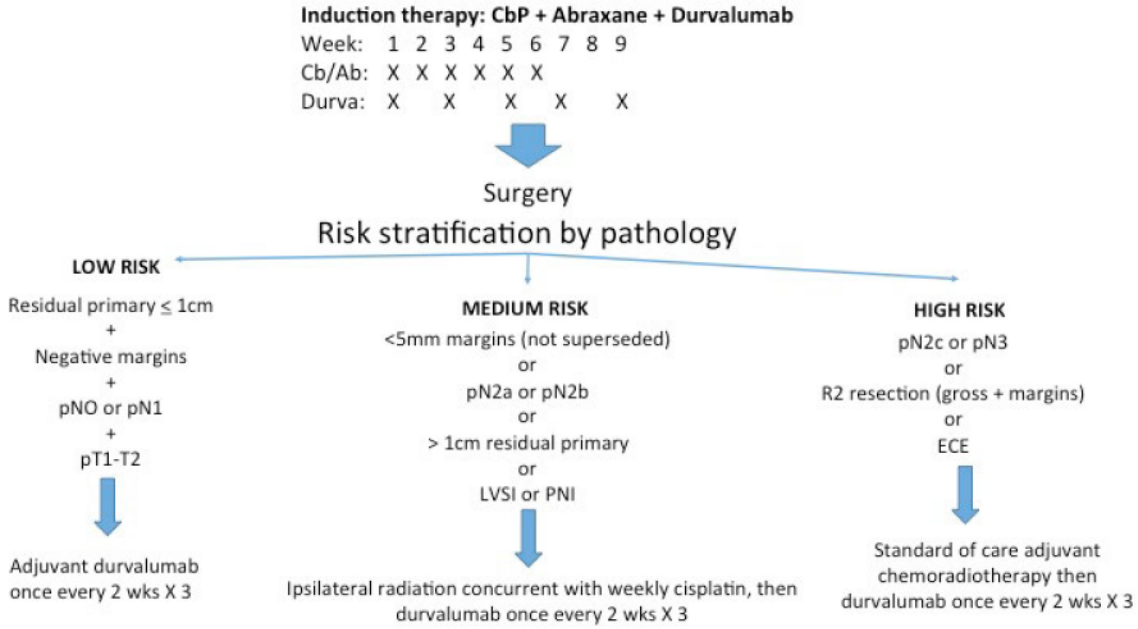
The medium risk subjects will require additional radiation to improve the cure rate following surgical resection. However, even here the morbidity of therapy may be decreased. First, the results of surgical resection will define the extent of the field of radiation. By having pathologic data regarding where there is residual disease, additional normal tissue may be spared. Second, as a consequence of the use of induction chemotherapy, high-dose cisplatin may be avoided. As such medium risk subjects will be treated concurrently with radiation and weekly cisplatin per standard of care (SOC) followed by durvalumab given once every two weeks for 3 cycles as adjuvant therapy.

The subject who remains high risk despite induction chemotherapy will require maximal therapy to elicit cure. Notably, these subjects are currently treated primarily with radiation concurrent with cisplatin. However, many ENT oncologists, both surgical and medical, argue that the addition of surgery might improve cure rates. Here such subjects would be treated with trimodality therapy (induction chemotherapy incorporating durvalumab then surgery then chemoradiotherapy). As such treatment is more intense than the current standard of care, we hope that this approach will improve the cure rate for these high-risk subjects. As such high-risk subjects will be treated concurrently with bilateral radiation and cisplatin every three weeks per SOC followed by durvalumab given once every two weeks for 3 cycles as adjuvant therapy. Again, the hypothesis for both increased efficacy without increased toxicity is derived from prior experience [27].

Operative delays and complications that may be related to induction therapy will also be documented. Specifically, we will document whether the induction

regimen resulted in blood chemistry imbalance, adverse reactions or varying degrees of pancytopenia, leading to a delay in surgical therapy. Adverse reactions could include dehydration, failure to thrive, nausea, poor nutritional intake, etc.

4.2 Schema



Study Population: Up to 39 treatment-naïve subjects with SCCHN may be enrolled to ensure 37 are evaluable. Risk level pre-induction will be based on physical examination and imaging and will be defined and documented in eCRFs prior to the initiation of induction therapy. Post-induction risk level will be determined based on pathologic evaluation of the surgical specimen.

This is a single-arm, nonrandomized phase II trial consisting of 3 parts. After informed consent and screening, pre-induction, risk levels will be assessed clinically, by a combination of physical exam and imaging. All subjects will then receive 6 weeks of induction chemotherapy in Part 1 comprised of weekly cycles of carboplatin and nab-paclitaxel X 6 cycles in combination with durvalumab administered once every two weeks for 5 cycles (D1 of weeks 1, 3, 5, 7, and 9).

Within a 1 to 4 week window post induction, tumor imaging will be followed by surgical resection (Part 2). After surgery, subjects will be stratified into one of 3 risk categories based on their disease pathology, assigned a treatment group based on their risk, and treated accordingly (Part 3) as outlined above. Low risk subjects with receive durvalumab once every two weeks x 3 cycles, while medium risk or high risks groups will receive concurrent chemoradiation therapy followed by durvalumab once every two weeks x 3 cycles. After completion of study therapy (which will vary by study arm) subjects will be evaluated every three months during follow up for progression over a period of 18 months. Each follow up visit will include physical examination, CT or MRI imaging of the neck. Chest imaging will be obtained (or not) as indicated by SOC. After the first 18 months,

subjects will be followed-up per SOC, with documentation in the electronic case report form (eCRF) limited to progression and survival noted at their SOC visits. If a subject should move away or otherwise be lost to in-person follow up but is amenable to telephone follow up, this will be permitted during the SOC follow up period.

4.3 Induction Chemotherapy

Induction chemotherapy will include weekly carboplatin dosed to an AUC2, weekly nab-paclitaxel 100 mg/m^2 administered for 6 weeks along with durvalumab (750 mg given once every 2 weeks for 5 cycles). Induction therapy will continue for a total of 9 weeks.

4.3.1 Premedications for Induction Chemotherapy

Premedication should include a 5HT-3 antagonist such as ondansetron 24mg PO (or 8mg IV). Steroids should be avoided as first-cycle primary prophylaxis against emesis, but dexamethasone 4mg PO or IV or equivalent may be added as needed. Aprepitant, fosaprepitant, compazine, and olanzapine are permitted.

4.3.2 Nab-Paclitaxel

Nab-paclitaxel 100 mg/m^2 will be diluted as per institutional standard and infused over 30 minutes. Actual body weight will be used for the calculation, and doses will be recalculated whenever body weight changes by ≥10%. Nab-paclitaxel must be administered prior to carboplatin.

4.3.3 Carboplatin

Carboplatin will be infused at an AUC of 2, with the dose calculated using the Calvert equation (total dose (mg) = 2 X (GFR +25). The dose will be re-calculated *prior to every cycle* in order to adjust for any potential change in renal function as assessed via serum creatinine (also checked each cycle). The subject's glomerular filtration rate (GFR) as creatinine clearance (CrCL) in mL/min will be calculated using the Cockcroft-Gault formula, with weight defined as actual body weight:

For males: Creatinine clearance (mL/min) = $\frac{(140 - \text{age}) \times \text{weight in kilograms}}{72 \times \text{serum creatinine in mg/dl}}$

For females: use same formula but multiply by 0.85 for creatinine clearance

A maximum GFR of 125 mL/min will be used. Therefore, the maximum dose of carboplatin possible in this study will be 300 mg. The carboplatin will be infused over 30 minutes. Carboplatin should be administered after Nab-paclitaxel.

4.3.4 Durvalumab

Durvalumab 750 mg will be administered every two weeks for 5 cycles on D1 of weeks 1, 3, 5, 7, and 9 of induction therapy in Part 1.

Durvalumab 750 mg will be administered every 2 weeks for 3 cycles either alone following surgical resection in low risk subjects or after surgery and following the completion of adjuvant chemoradiotherapy in subjects with medium or high-risk disease in Part 3.

4.4 Surgery

Surgical therapy will be at the discretion of the treating surgeon per standard of care. Surgery will be done at 1-4 weeks after the completion of induction therapy; an interval of > 50 days will be considered a dose limiting toxicity. The subject will undergo gross total resection of the pretreatment primary site cancer volume (as determined by a combination preoperative radiograph and either preoperative photo documentation or tattooing), including frozen section margins from the periphery and deep tissue planes. Reconstruction of the defect will be at the discretion of the surgeon. Primary site and neck surgery may be performed simultaneously or sequentially, but in the case of sequential surgery, both sites must be completed within 14 days from each other.

Bilateral neck dissections will be performed on all subjects at risk for contralateral metastasis per standard of care.

Specimens will be carefully oriented and anatomic location carefully annotated to allow for tailoring of radiation to the pathologically proven tumor area plus a margin.

4.5 Post-Operative Concomitant Chemoradiotherapy

4.5.1 Low Risk

Subjects in this category will receive durvalumab (750 mg) administered every two weeks for 3 cycles. The complexity or risk assessment in head/neck cancer is too great to ensure that all subjects deemed low risk by LCCC1621 criteria truly would not benefit from adjuvant radiotherapy. Therefore, to ensure optimal treatment of all subjects, in the case where a multidisciplinary tumor board recommends adjuvant radiotherapy or chemoradiotherapy for a subject meeting LCCC1621 criteria for low risk, this will be allowed and will not be considered a protocol deviation or violation. Of note, this should apply to either no subjects or to a very small number of subjects—routine exceptions for institutional or provider preference to routinely administer adjuvant therapy will not be allowed.

4.5.2 Medium risk

Subjects deemed medium risk as per surgical pathology will receive ipsilateral involved field radiation concurrent with weekly cisplatin 30 mg/m^2 weekly concurrent with radiation for up to 6 cycles. For the purposes of this study, "involved field radiation" will refer to areas demonstrated to harbor disease on pathology, and not elective areas. All subjects will be treated with IMRT. Radiation will commence once the subject has adequately healed from surgery; this will typically take place two to six weeks following surgery but will vary by subject. When surgical pathology results are sufficiently detailed to allow for

definite evaluation, the postinduction primary site and nodal gross tumor volumes (GTVs) should be used for radiation therapy (RT) planning.

Localization, Simulation, and Immobilization
Subjects must have an immobilization device for the head and neck (shoulders optional) (e.g., aquaplast mask) made prior to the treatment planning CT scan that is required for all subjects. The treatment planning CT scan can be performed with or without IV contrast (preferable). The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be maximum 3 mm.

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

Treatment Planning/Target Volumes

- CTV60: This volume will receive 2 Gy per day. CTV60 will include the primary tumor bed (based on operative findings and post-operative pathology) plus regions of pathologically involved lymphadenopathy. CTV60 may include the broader operative resection bed in the region of gross primary and nodal disease as well as the entire nodal regions in the involved neck at the discretion of the investigator for perceived higher-risk cancers.
- CTV54: This will include all other lesser risk regions without viable residual cancer in the pathology specimen but in the operative bed and 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 IMRT plan with the dose painted.
- 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: .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.

NOTE: Alternative regimens may be substituted for cisplatin in subjects who are not candidates for cisplatin at the discretion of the investigator. If carboplatin is used, a creatinine clearance cap of 125 mL/min must be used, as per standard of care. Regimens that may be used include:

- Weekly carboplatin at a dose of AUC of 1.5 [2].
- Weekly carboplatin at a dose of AUC of 1 combined with paclitaxel at a dose of 45mg/m^2 [28].
- Weekly cetuximab [29, 30], administered at a loading dose of 400 mg/m^2 followed by weekly therapy at a dose of 250 mg/m^2. The loading dose may be administered either the week preceding chemoradiotherapy or concurrent with the first week of therapy.
- Weekly cetuximab, administered at a loading dose of 400 mg/m^2 followed by weekly therapy at a dose of 250 mg/m^2. The loading dose may be administered either the week preceding chemoradiotherapy or concurrent with the first week of therapy. This will be administered with weekly docetaxel at 15 mg/m^2, starting concurrent with the first week of radiation therapy [31].

Radiation treatment breaks should be minimized as possible.

Once chemoradiotherapy is complete these subjects will receive durvalumab 750 mg every two weeks for 3 cycles.

4.5.3 High-risk

We do not anticipate any high-risk subjects. Based on existing data already described, we anticipate this regimen to be more effective than the LCCC1125 regimen and no subjects in that study were high risk. Nonetheless, in order to address optimal care of such a theoretical subject, therapy is discussed herein. Radiation will commence once the subject has adequately healed from surgery; this will typically take place two to six weeks following surgery but will vary by subject. All subjects will be treated with IMRT.

Localization, Simulation, and Immobilization

Subjects must have an immobilization device for the head and neck (shoulders optional) (e.g., aquaplast mask) made prior to the treatment planning CT scan that is required for all subjects. The treatment planning CT scan can be performed

with or without IV contrast (preferable) The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be maximum 3 mm.

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

Treatment Planning/Target Volumes

- 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) 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 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: .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.

Standard treatment in this arm will be defined as bolus cisplatin (100 mg/m^2 every 3 weeks for 3 cycles concurrent with radiation). For subjects not considered appropriate candidates for high dose bolus cisplatin (i.e., 100 mg/m^2 every 3 weeks for 3 cycles) in combination with radiotherapy, one of the choices below may be permitted. If carboplatin is used, a maximum of 125 mL/min must be used (see section 4.3.3), as per standard of care.

- Weekly cisplatin at a dose of 30-40 mg/m^2 [32].
- Weekly cisplatin at a dose of 20 mg/m^2 combined with paclitaxel at a dose of 30 mg/m^2 [33].
- Weekly carboplatin at a dose of AUC of 1.5 [2].
- Weekly carboplatin at a dose of AUC of 1 combined with paclitaxel at a dose of 45 mg/m^2 [28].
- Weekly cetuximab [29, 30], administered at a loading dose of 400 mg/m^2 followed by weekly therapy at a dose of 250 mg/m^2. The loading dose may be administered either the week preceding chemoradiotherapy or concurrent with the first week of therapy.
- Weekly cetuximab, administered at a loading dose of 400 mg/m^2 followed by weekly therapy at a dose of 250 mg/m^2. The loading dose may be administered either the week preceding chemoradiotherapy or concurrent with the first week of therapy. This will be administered with weekly docetaxel at 15 mg/m^2, starting concurrent with the first week of radiation therapy [31].

Other regimens may be optimal for the care of individual subjects. To ensure adherence to standard of care, other regimens will require the approval of the institutional (site) PI.

Once chemoradiotherapy is complete these subjects will receive durvalumab 750 mg every two weeks for 3 cycles.

4.6 Dosing Delays/Dose Modifications for Induction Chemotherapy

Any subject who receives any treatment on this protocol will be evaluable for toxicity. Each subject 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 Common Terminology Criteria for Adverse Events

(CTCAE), version 4.03. Dose adjustments should be made according to the system showing the greatest degree of toxicity.

A maximum of two reductions of each drug will be allowed per subject. If >2 dose reductions of nab-paclitaxel and carboplatin are required, protocol therapy is to be discontinued, response assessed, and the subject should proceed to optimal definitive therapy outside the clinical trial (as per standard of care). Once a subject's dose has been reduced, the dose reduction will be permanent—dose re-escalation will not be permitted.

For AEs that require dose reductions of nab-paclitaxel or carboplatin, please refer to the dose levels in the following table:

Dose Level	Nab-Paclitaxel (mg/m^2)	Carboplatin (AUC)
0 (starting dose)	100	2
-1	75	1.6
-2	50	1.2

Dose reductions for AEs related to Durvalumab are not allowed as noted in the table:

Dose Level	Durvalumab (mg)
0 (starting dose)	750
No dose reductions are allowed. Options are to withhold the dose or discontinue durvalumab. Guidelines for dosing and management of non-immune and immune-related AEs are provided in Appendix C and Appendix D. Guidelines for Infusion-related reactions are provided in Table 8 in section 5.1.6.1.	

4.6.1 Suggested Dose delays/Dose Modifications for Nab-Paclitaxel and Carboplatin During Induction

Both carboplatin and nab-paclitaxel are FDA approved chemotherapy agents which are routinely dose-adjusted by oncologists outside of protocol settings. Given the high level of clinical experience with these medications, clinicians can better individualize dose-reductions than rigid guidelines. Therefore, when dose adjustment is suggested per Table 5, the treating clinician shall decide whether to dose-reduce one or both agents. The magnitude of decrement shall follow the table above. The treating physician may also choose not to do any dose adjustment based on clinical judgement. Suggested dose delays and modifications for specific toxicities are provided in Table 5 below.

If hypersensitivity reactions to nab-paclitaxel occur, minor symptoms such as flushing, skin reactions, dyspnea, lower back pain, hypotension, or tachycardia may require temporary interruption of the infusion. However, severe reactions, such as hypotension requiring treatment, dyspnea requiring bronchodilators,

angioedema or generalized urticaria require immediate discontinuation of study drug administration and aggressive symptomatic therapy. Subjects who experience a severe hypersensitivity reaction to nab-paclitaxel should not be re-challenged. It is not recommended to administer nab-paclitaxel to subjects with prior hypersensitivity to a taxane.

Table 5. Suggested Dose Delays and Dose Modifications of Nab-paclitaxel and Carboplatin for Toxicity

	Toxicity on treatment days	**Dose Level for Subsequent Administration**	
If ANC <1, hold [2] carboplatin and nab-paclitaxel for that day. Do not make up missed doses. Resume per table when next dose is due if ANC ≥1	**Neutropenia[1]**	**Nab-paclitaxel**	**Carboplatin**
	Grade 2 w/o fever (ANC <1500/mm^3 to 1,000/mm^3	Maintain dose[4]; consider G-CSF	Maintain dose[4]; consider G-CSF
	Grade 3 w/o fever (ANC <1000/mm^3 to 500/mm^3	↓1 dose level; consider G-CSF	↓1 dose level; consider G-CSF
	Grade 4 neutropenia (ANC <500/mm^3 or Febrile neutropenia[3])	↓2 dose levels; consider G-CSF	↓2 dose levels; consider G-CSF
If platelets <75K, hold [2] carboplatin and nab-paclitaxel for that day. Do not make up missed doses. Resume per table when next dose is due if platelets ≥75K	**Thrombocytopenia**	**Nab-paclitaxel**	**Carboplatin**
	≤100 x 10^9/L	Maintain dose	Maintain dose
	50-75 x 10^9/L	↓1 dose level	↓1 dose level
	<50 x 10^9/L	↓2 dose levels	↓2 dose levels
If Hgb<8 g/dL, transfuse PRBCs. Once Hgb is ≥ 8, therapy may resume.	**Anemia**	**Nab-paclitaxel**	**Carboplatin**
	Grade ≥2 (Hgb <10)	Transfusion may be used as needed to maintain Hgb. If contraindicated or inadequate ↓1 dose level will be permitted but not required for Hgb<8	↓1 dose level will be permitted but not required for Hgb<8.
If ≥ grade 3, hold [2] nab-paclitaxel for that day. Do not make up missed doses. Resume per table when next dose is due if ≤grade 1	**Sensory neuropathy**	**Nab-paclitaxel**	**Carboplatin**
	Grade ≤2[5]	Maintain dose	Maintain dose
	Grade 3	↓1 dose level	↓1 dose level
	Grade 4	↓2 dose levels	↓2 dose levels

[1]G-CSF (filgrastim) may be used for ANC<1.5 at the investigator's discretion provided they are not substituted for a required dose reduction. See section 4.6.1.1 for instructions on dose and duration; peg-filgrastim (Neulasta®) is NOT permitted)
[2]Hold offending agent(s) as identified in table. If have to hold > 2 weeks, discontinue agent(s)
[3] Febrile neutropenia is typically treated with hospital admission and IV antibiotics, but low risk cases may be treated on an outpatient basis.
[4]In the event of early grade 2 neutropenia (after 1st or after 2nd cycle), the clinician will have discretion to dose-reduce 1 level of either or both drugs.
[5]Grade 2 neuropathy encompasses a wide range. Dose reduction 1 level for more severe grade 2 neuropathy is permitted at the discretion of the treating physician.

	Toxicity on treatment days	**Dose Level for Subsequent Administration**	
If bilirubin >2mg/dL, hold[a] treatment for that day. Do not make up missed doses. Resume per table when next dose is due if bilirubin <2mg/dL	**Hyperbilirubinemia**	**Nab-paclitaxel**	**Carboplatin**
	Grade ≤2	Maintain dose	Maintain dose
	Grade ≥3	↓1 dose level	↓1 dose level
If transaminases ≥3 x ULN hold[a] treatment for that day. Do not make up missed doses. Resume per table when next dose is due if transaminases < 3 x ULN	**Transaminase elevation**	**Nab-paclitaxel**	**Carboplatin**
	Grade ≤2	Maintain dose	Maintain dose
	Grade ≥3	↓1 dose level	↓1 dose level
If SCr >2 mg/dL, hold[a] treatment for that day. Do not make up missed doses. Resume per table when next dose is due if SCr<2 mg/dL	**Renal toxicity**	**Nab-paclitaxel**	**Carboplatin**
	Grade ≤2	Maintain dose	Maintain dose
	Grade ≥3	↓1 dose level	Maintain dose
Hold[a] dose of suspected offending agent(s) until toxicity resolves to ≤Grade 1, then resume treatment with dose adjusted per table.	**Other non-specified[4]**	**Nab-paclitaxel**	**Carboplatin**
	Grade ≥3	↓1 dose level	↓1 dose level
[a]Hold offending agent(s) as identified in table. If have to hold > 2 weeks, discontinue agent(s)			

4.6.1.1 Growth Factors

Use of erythropoietin stimulating agents (ESAs) will not be permitted during induction chemotherapy or during chemoradiotherapy. The use of prophylactic filgrastim (G-CSF) during induction chemotherapy may be considered. Peg-filgrastim (Neulasta®) is not permitted. The use of filgrastim will be permitted at the discretion of the treating physician in subjects with low blood counts that threaten treatment continuity. The use of filgrastim is strongly recommended for subjects who have had previous febrile neutropenia or have experienced treatment delays due to neutropenia. When G-CSF is used, administer G-CSF at 5 mcg/kg/day (rounded to the nearest vial size per investigator/institution's standard

of care). The number of days of GCSF is up to the discretion of the treating physician; however, the subject must start G-CSF at least 24 hours after the dose of chemotherapy and G-CSF must be held at least 48 hours prior to the next dose of induction chemotherapy. The dose of the G-CSF can be adjusted based on the investigator's discretion. ESAs, filgrastim (G-CSF) and peg-filgrastim will not be permitted during chemoradiotherapy.

4.6.2 Suggested Dose delays/Dose Modifications for Durvalumab During Induction

For adverse events (AEs) that are considered possibly due to administration of durvalumab, the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required).
- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care.
- All dose modifications should be documented with clear reasoning and documentation of the approach taken.

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

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune-related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

- Durvalumab dose modification recommendations and toxicity management guidelines for infusion-related reactions are provided in Table 8 located in section 5.1.6.1
- Durvalumab dose modification recommendations and toxicity management guidelines for non-immune-mediated reactions are detailed in Appendix C.
- Durvalumab dose modification recommendations and toxicity management guidelines for immune-mediated reactions are detailed in Appendix D.

In addition, management guidelines for adverse events of special interest (AESIs) for durvalumab are detailed in Section 7.4.2. All toxicities will be graded according to NCI CTCAE v4.03

4.7 Treatment with Adjuvant Durvalumab in Part 3

Subjects categorized as low risk following induction therapy and surgery will be treated with adjuvant durvalumab (750 mg) administered every 2 weeks for 3 cycles. The durvalumab treatment will commence once the subject has adequately healed from surgery; this will typically take place two to six weeks following surgery, but will vary by subject.

Subjects categorized as medium or high risk following induction therapy and surgery will be treated with adjuvant durvalumab (750 mg) administered every 2 weeks for 3 cycles after they have completed chemoradiotherapy. The durvalumab treatment will commence once the subject has adequately healed from surgery; this will typically take place two to six weeks following completion of chemoradiotherapy but will vary by subject.

4.8 Treatment Breaks for Radiation during Concomitant Chemoradiation therapy

Therapy interruptions will generally not be necessary and will be addressed per standard of care by the treating Radiation Oncologist.

Treatment breaks must be clearly indicated in the treatment record.

If radiation therapy is delayed, then chemotherapy should also be delayed to remain in synchronization with radiation per standard of care.

4.9 Dosing Delays/Dose Modifications for Chemotherapy during Concomitant Chemoradiotherapy (see Section 4.6)

Subjects may begin Part 3 chemoradiotherapy (medium and high-risk subjects, see Schema in section 4.2) provided they are still considered appropriate candidates for this therapy as per standard of care as determined by agreement between the surgical, medical and radiation oncologists. If the subject no longer meets the standard of care criteria for a particular agent (e.g. high dose cisplatin), then care may be optimized for the individual subject.

For durvalumab, please refer to the dose modifications/ supportive guidelines located in Appendices C and D of this protocol. For carboplatin (if this is substituted for cisplatin in medium risk subjects), the toxicities of carboplatin are well established and include myelosuppression, nausea and vomiting, peripheral neuropathy, and elevations in liver function tests. The toxicities are well documented and tolerable. Investigators will dose modify carboplatin during concomitant chemoradiotherapy as per standard of care.

For high-risk subjects, please refer to the dose modifications/ supportive guidelines located in Appendix C and Appendix D for durvalumab in this

protocol. For cisplatin the toxicities of cisplatin are well established, and include nausea and vomiting, risk of kidney failure, peripheral neuropathy, hearing loss and febrile neutropenia. The cisplatin dose of 100 mg/m^2 has been extensively studied in lung cancer and head and neck cancer, with and without radiotherapy. The toxicities, including the predictable increases of the radiotherapy local toxicities, are well documented and tolerable. Investigators will dose modify cisplatin during concomitant chemoradiotherapy as per standard of care.

4.10 Concomitant Medications/Treatments

Subjects will be instructed not to take any additional medications (including over-the-counter products) during the course of the study without prior consultation with the investigator. At each visit, the investigator will ask the subject about any new medications he/she is or has taken after the start of the study drug.

Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care (including antibiotics, nutritional support, growth factor support (see section 4.6.1.1 above), metabolic disorder corrections, optimal symptom control, and pain management).

4.11 Prohibited Medications

The following medications are considered exclusionary during the study:

- The use of any other investigational agent(s) or other anti-cancer agents other than those outlined in the protocol is prohibited for subjects while on study.

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

- Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, radiation, nausea, etc).

- Live attenuated vaccines within 30 days of durvalumab dosing (ie, 30 days prior to the first dose, during treatment with durvalumab and for 30 days post discontinuation of durvalumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted. [NOTE: If a vaccine is part of

the treatment regimen for the indication under study, the vaccine is permitted].

- Herbal and natural remedies should be avoided during the study.

4.12 Medications to be used with Caution

Investigators, at their discretion, may administer concomitant medications from the categories below (see Appendix B: Subject Handout regarding Drug Interactions) to subjects enrolled in LCCC1621. Subjects receiving such medications must be carefully monitored for potentiation of toxicity due to any individual concomitant medication and may require dose modifications.

Use caution when concomitantly administering nab-paclitaxel with inhibitors (e.g. ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritanovir, saquinavir, indinavir, and nelfinavir) or inducers (e.g. rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine) of either CYP2C8 or CYP3A4. A complete list is available at http://medicine.iupui.edu/clinpharm/ddis/main-table

The renal effects of nephrotoxic compounds may be potentiated by carboplatin. Cisplatin produces cumulative nephrotoxicity which is potentiated by aminoglycoside antibiotics. The serum creatinine, blood urea nitrogen (BUN), creatinine clearance, and magnesium, sodium, potassium, and calcium levels should be measured prior to initiating therapy and prior to each subsequent course. Drugs that can induce nephrotoxicity should be avoided or used with caution in combination with cisplatin. A list of drugs that cause nephrotoxicity can be found in Naughton CA, et al., Am Fam Physician, 2008;78(6):743-750 [34].

Peripheral blood counts should be monitored weekly. Liver function should be monitored periodically. Neurologic exams should be performed on a regular basis.

Plasma levels of anticonvulsant agents may become sub-therapeutic during cisplatin therapy. In a randomized trial in advanced ovarian cancer, response duration was adversely affected when pyridoxine was used in combination with altretamine (hexamethylmelamine) and cisplatin.

4.13 Contraception

The following restrictions apply while the subject is receiving study treatment and for the specified times before and after:

1. Female subjects of childbearing potential who are sexually active with a non-sterilized male partner must use at least one highly effective method of contraception (Table 6) from the time of screening and must agree to continue using such precautions for 90 days after the last dose of investigational product. Male partners of a female subject 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 trial and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Female subjects should refrain from breastfeeding throughout this period.

2. Non-sterilized male subjects who are sexually active with a female partner of childbearing potential must use male condom plus spermicide from screening through 6 months after the last dose of investigational product. Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice; however, occasional abstinence, the rhythm method, and the withdrawal method are not acceptable methods of contraception. Male subjects should refrain from sperm donation throughout this period. Female partners of a male subject must use a highly effective method of contraception throughout this period.

3. 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 (defined as 12 months with no menses without an alternative medical cause).

4. Highly effective methods of contraception are described in Table 6. A highly effective method of contraception is defined as one that results in a low failure rate (i.e. less than 1% per year) when used consistently and correctly. Note that 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).

Table 6. Highly Effective[a] Methods of Contraception

Barrier/Intrauterine Methods	Hormonal Methods
• Copper T intrauterine device • Levonorgesterel-releasing intrauterine system (eg, Mirena®)[b]	• "Implants": Etonogestrel-releasing implants: e.g. Implanon® or Norplan® • "Intravaginal Devices": 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® • "Minipill[c]": Progesterone based oral contraceptive pill using desogestrel e.g. Cerazette®
[a] Highly effective (i.e. failure rate of <1% per year) [b] This is also considered a hormonal method [c] Cerazette® is currently the only highly effective progesterone based pill	

Blood donation

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

4.14 Duration of Therapy

In the absence of treatment delays due to adverse events, induction therapy will continue for a period of 9 weeks concluding with the final dose of durvalumab administered on D1 of week 9 of induction therapy, followed by surgery. The addition of post-operative chemoradiation will depend on the risk category, with a duration varying from 0 to approximately 7 weeks (or per standard of care) followed by durvalumab administered every 2 weeks for 3 cycles (6 weeks) unless the following occurs that would lead to permanent discontinuation from the study medication:

- Withdrawal of consent or lost to follow up
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event(s) or adverse event that in the opinion of the investigator or sponsor, contraindicates further dosing
- Subject decides to withdraw from the study, or
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.
- Non-compliance by the subject to protocol mandated procedures in a manner that compromises data integrity or subject safety
- Pregnancy
- Grade ≥3 infusion reaction
- Initiation of alternative anticancer therapy not allowed by this protocol

- Removal from study by investigator determination that subject is no longer benefitting from study therapy

4.15 Duration of Follow Up

Subjects will be followed in clinic 8-12 weeks after treatment discontinuation, with subsequent follow-up visits every 3 months thereafter per standard of care (SOC). SOC typically includes physical exam of neck and primary site and/or imaging of these areas every 3 months for at least 2 years with documentation in the case report form (CRF) limited to progression and survival noted at their SOC MD visits for at least 5 years. Subjects removed from study treatment for unacceptable AEs will be followed until resolution or stabilization of the AE.

4.16 Removal of Subjects from Protocol Therapy

Subjects will be removed from study when any of the criteria listed in Section 4.14 apply. Notify the Principal Investigator and document the reason for study removal and the date the subject was removed on the electronic case report form (eCRF). The subject should be followed up per protocol.

5.0 DRUG INFORMATION

5.1 Durvalumab

5.1.1 Supplier/How Supplied

Durvalumab will be supplied by AstraZeneca in single-use vials. Each vial will be supplied to the investigator as a liquid solution containing 500 mg (nominal) of durvalumab at a concentration of 50 mg/mL and will also include 26 mM histidine/histidine hydrochloride, 275 mM trehalose dihydrate, and 0.02% (weight/volume) polysorbate 80; it has a pH of 6.0. The nominal fill volume is 10 mL.

The investigator or designee is responsible for taking an inventory of each shipment of durvalumab received and comparing it with the corresponding packing list. The investigator or designee will verify the accuracy of the information and confirm shipment receipt or note lost or damaged shipment.

5.1.2 Preparation of Infusion Solution

The dose of durvalumab for administration must be prepared by trained personnel under aseptic conditions. Vials must be used for specific subjects and must not be shared between subjects.

1. 2 vials are needed to achieve 750 mg dose (500 mg/vial, 50 mL).
2. Inspect visually for any particulate matter and discoloration prior to dose preparation.
3. Durvalumab vials may be gently inverted for mixing but must not be shaken
4. 15 mL durvalumab (750 mg durvalumab) will be added to IV infusion bags of normal saline (0.9% [w/v] sodium chloride injection, 250 mL size or 5% (w/v) dextrose, 250 mL size, followed by mixing by gentle inversion to ensure homogeneity of the solution. Final in-bag concentration should be within 1 – 20 mg/mL. Saline bags must be latex-free and can be made of polypropylene, polyethylene, polyolefin copolymers, or polyvinyl chloride.
5. Following preparation of the dose, the entire contents of the IV bag must be administered.
6. Flush the IV line with a volume of 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 the institutional policy to ensure the full dose is administered. If the line was not flushed, this must be documented.

5.1.3 Storage and Handling

At the study site, all durvalumab received will be stored according to the storage conditions described on the packaging label. Investigational product must be stored at controlled temperature and a temperature log must be maintained at the site. In case of a temperature excursion, such an excursion must be documented on the temperature excursion log and the site must notify AstraZeneca immediately. In addition, all IPs must be stored in a secured/locked area to prevent unauthorized access. If a site is participating in more than one AstraZeneca study, clearly separate/ identify supplies from other studies.

Sites should follow standard and local aseptic procedures and instructions for all activities. All dispensing activities should be documented according to local procedures.

Durvalumab must be used within the individually assigned expiry date on the product label.

5.1.4 Stability

Total in-use storage time from needle puncture of the durvalumab vial to start of administration must not exceed 4 hours at room temperature or 24 hours at 2°C to 8°C (36°F to 46°F) as shown in Table 5. If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration. Durvalumab does not contain preservatives, therefore, any unused portion must be discarded.

The shelf lives stated in this document are based on chemical and physical stability. Assignment of microbial shelf life is the responsibility of the clinical site and must be aligned with local procedures for managing microbial risk as long as the times specified in Table 5 are not exceeded.

Table 7. In-use stability of drug – Durvalumab

		Storage Temperature	Duration
Durvalumab for IV infusion	Vial contains 500 mg/vial	2°C - 8°C (36°F - 46°F)	Within the individually assigned expiration date on the label
	Prepared IV Bag (needle puncture of vial to start of administration)	Room Temperature	≤ 4 hours
		2°C - 8°C (36°F - 46°F)	≤ 24 hours
	Prepared IV Bag (maximum	Room Temperature	≤ 8 hours

	time for IV bag infusion, including interruptions)		

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

5.1.5 Method of Administration

Site personnel will review the dosing information with the subject (or legally authorized representative) on scheduled clinic visit days. Site personnel will perform an IP administration compliance check and record this information in the subject's source documentation. Administration of all IP will be recorded including dispensing, dosing, and any changes in dosage administration such as interruption or reduction in dosing due to an adverse event (AE).

Subjects will receive durvalumab, 750 mg every 2 weeks (1 cycle = 2 weeks) by IV infusion over approximately 1 hour (± 5 minutes).

- Durvalumab will be given on D1 of Weeks ,1, 3, 5, 7 and 9 as a component of induction therapy

- Durvalumab will be given every 2 weeks X 3 as adjuvant therapy after surgical resection.

  - Low risk subjects will receive durvalumab alone
  - Medium and high-risk subjects will receive this regimen after adjuvant chemoradiotherapy is complete

Following preparation of durvalumab, the entire contents of the IV bag should be administered at room temperature by controlled infusion via an infusion pump into a peripheral or central vein over approximately 60 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter. Subjects will be monitored during and after the infusion at the times specified in the Study Protocol. Infusions of durvalumab may be interrupted, slowed, or discontinued in order to address toxicity. If there are interruptions during infusion, the total allowed time from the start of infusion until the end of infusion should not exceed 8 hours at room temperature as shown in the Table 5.

An allergic reaction following dose administration may occur. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment. The study site must also have the ability to admit subjects to an intensive care unit if necessary.

5.1.6 Drug Accountability

The investigator is responsible for keeping accurate records of the clinical supplies received from AstraZeneca or designee, the amount dispensed to the subjects and the amount remaining at the conclusion of the trial.

Final accountability may be conducted prior to the close-out visit once all subjects are no longer using IP. The investigator will ensure that a final report of drug accountability to the unit dose level, (vial for durvalumab) is prepared and placed in both the investigator study file and the central clinical study file.

Upon completion or termination of the study, all unused and/or partially used investigational product will be destroyed at the site per UNC IDS drug destruction policy (or other site institutional policy as applicable). 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.

5.1.6.1 Monitoring of dose administration for infusion-related reactions

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

- In the event of a Grade ≤2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion.
- For subjects with a Grade ≤2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator.
- If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued.
- The standard infusion time is one hour, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature (otherwise requires new infusion preparation).

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

subjects to an intensive care unit if necessary. See Table 6 below for management guidelines for infusion-related reactions.

Table 8. Guideline for Management of Infusion-related Reactions (Durvalumab)

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor subjects for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, or skin rashes) and anaphylaxis (eg, 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 (eg, IM epinephrine, followed by IV diphenhydramine and ranitidine, and IV glucocorticoid).

5.1.7 Adverse Events Associated with Durvalumab

For adverse events (AEs) that are considered possibly due to administration of durvalumab, the following dose adjustment guidance may be applied:

- Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required)

- If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of durvalumab along with appropriate continuing supportive care

- All dose modifications should be documented with clear reasoning and documentation of the approach taken

AESIs observed with durvalumab include:

- Diarrhea / Colitis and intestinal perforation
- Pneumonitis / ILD
- hepatitis / transaminase increases
- Endocrinopathies (i.e. events of hypophysitis/hypopituitarism, thyroiditis, adrenal insufficiency, hyper- and hypothyroidism 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 etiology include, but are not limited to:

- Pericarditis
- Neuromuscular toxicities (such as Guillain-Barre syndrome and myasthenia gravis)
- Sarcoidosis
- Uveitis
- Other events involving the eye and skin
- Hematological events
- Rheumatological events
- Vasculitis
- Non-infectious meningitis
- Non-infectious encephalitis.

It is possible that events with an inflammatory or immune mediated mechanism could occur in nearly all organs.

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 Appendix C: Dose Modifications/Toxicity Management for Durvalumab (Non-immune-mediated) and Appendix D: Dose Modifications/Toxicity Management for Durvalumab (Immune-related). 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.

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

Based on the mechanism of action of durvalumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related. Following the first dose of durvalumab, subsequent administration of durvalumab can be modified based on toxicities observed.

Dose modification recommendations and toxicity management guidelines for infusion-related reactions are provided in section 5.1.6.1 above in Table 8.

Dose modification recommendations and toxicity management guidelines for non-immune-mediated reactions are detailed in Appendix C.

Dose modification recommendations and toxicity management guidelines for immune-mediated reactions are detailed in Appendix D.

5.2 Carboplatin

5.2.1 Supplier

Commercial supplies of carboplatin will be used for this study and billed to subjects and/or their insurance company. See the package insert for complete prescribing information available at following link:
http://www.sagentpharma.com/wp-content/uploads/2014/11/Carboplatin_PI.pdf

5.2.2 Storage, Handling and Disposal

Carboplatin should be stored, handled and disposed per institutional guidelines.

5.2.3 Preparation

Carboplatin should be prepared per institutional guidelines and as outlined in section 4.3.3.

5.2.4 Adverse Events Associated with Carboplatin

Incidence rates of adverse events associated with carboplatin are provided in the product's prescribing information. Some of the adverse events expected with carboplatin treatment are listed below.

Hematologic: Myelosuppression is the major dose-limiting toxicity. Thrombocytopenia, neutropenia, leukopenia, and anemia are common, but typically resolve by Day 28 when carboplatin is given as a single agent.

Allergic reactions: Hypersensitivity to carboplatin has been reported in 2% of patients receiving the drug. Symptoms include rash, urticaria, erythema, pruritus, and rarely anaphylaxis with bronchospasm and hypotension. The reactions can be successfully managed with standard epinephrine, corticosteroid, and antihistamine therapy.

Neurologic: Peripheral neuropathies have been observed in 4% of patients receiving carboplatin with mild paresthesia being the most common.

Gastrointestinal: Nausea and vomiting are the most common gastrointestinal events; both usually resolve within 24 hours and respond to antiemetics. Other gastrointestinal events include diarrhea, weight loss, constipation, and gastrointestinal pain.

Hepatic toxicity: Elevated alkaline phosphatase, total bilirubin, and AST have been observed.

Other: Pain and asthenia are the most common miscellaneous adverse events. Alopecia has been reported in 3% of the patients taking carboplatin.

5.3 Nab-Paclitaxel

5.3.1 Drug supply

Nab-paclitaxel will be supplied by Celgene Corporation and labeled appropriately as investigational material for this study. Labels will bear Celgene's name and address, the protocol number LCCC1621, product name, dosage form and strength, medication identification/kit number, lot number, expiry date, dosing instructions, storage conditions, the quantity of IP contained, and required caution statements and/or regulatory statements as applicable. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with Nab-paclitaxel upon identification and screening of a potential trial subject.

Each single-use vial contains 100 mg of paclitaxel and approximately 900 mg of human albumin. Each milliliter (mL) of reconstituted suspension contains 5 mg paclitaxel.

5.3.2 Preparation of Infusion Solution

Please see local prescribing information for nab-paclitaxel (100 mg/m^2) for detailed instructions on the reconstitution and administration.

5.3.3 Special Handling Instructions

Nab-Paclitaxel is a cytotoxic anticancer drug and, as with other potentially toxic paclitaxel compounds, caution should be exercised in handling nab-paclitaxel.

The use of gloves is recommended. If nab-paclitaxel (lyophilized cake or reconstituted suspension) contacts the skin, wash the skin immediately and thoroughly with soap and water. Following topical exposure to nab-paclitaxel, events may include tingling, burning and redness. If nab-paclitaxel contacts mucous membranes, the membranes should be flushed thoroughly with water.

5.3.4 Storage and Handling

At the study site, all nab-paclitaxel received will be stored according to the storage conditions described on the packaging label. Investigational product must be stored at controlled temperature and a temperature log must be maintained at the site. In case of a temperature excursion, such an excursion must be documented on the temperature excursion log and the site must notify Celgene immediately. In addition, all IPs must be stored in a secured/locked area to prevent unauthorized access. If a site is participating in more than one Celgene study, clearly separate/ identify supplies from other studies.

5.3.5 Method of Administration

Nab-paclitaxel is injected into a vein via intravenous (I.V.) infusion over 30 minutes. The use of an in-line filter is not recommended. Following administration, the intravenous line should be flushed with sodium chloride 9 mg/ml (0.9%) solution for injection to ensure complete administration of the complete dose, according to local practice.

5.3.6 Drug Ordering and Accountability

Upon identification of a potential subject, sites must order nab-paclitaxel. The site should order nab-paclitaxel through the Endpoint (IDOS) online drug ordering system. Allow 5 working days for drug shipment and note there are no drug shipments on Fridays and holidays.

The Investigator or designee is responsible for taking an inventory of each shipment of study drug received and comparing it with the accompanying study drug accountability form. The Investigator will verify the accuracy of the information on the form, sign and date it, retain a copy in the study file, and return a copy to Celgene or its representative.

5.3.7 Return and Retention of Study Drug

Celgene will instruct the Investigator on the return or destruction of unused study drug. If any study drug is lost or damaged, its disposition should be documented

in the source documents. Study drug supplies will be retained at the clinical site pending instructions for disposition by Celgene.

5.3.8 Adverse Events Associated with Nab-paclitaxel

The most common toxicities associated with nab- paclitaxel for metastatic breast cancer (≥ 20%) include alopecia, neutropenia, sensory neuropathy, abnormal ECG, fatigue/asthenia, myalgia/arthralgia, AST elevation, alkaline elevation, anemia, nausea, infections, and diarrhea.

The most common AEs (≥ 20%) for nab-paclitaxel in NSCLC are anemia, neutropenia, thrombocytopenia, alopecia, peripheral neuropathy, nausea, and fatigue.

The most common toxicities (≥ 20%) of nab-paclitaxel in adenocarcinoma of the pancreas are neutropenia, fatigue, peripheral neuropathy, nausea, alopecia, peripheral edema, diarrhea, pyrexia, vomiting, decreased appetite, rash and dehydration.

5.4 Cisplatin

5.4.1 Supplier

Cisplatin is commercially available and approved by the US Food and Drug Administration (FDA) for the treatment of advanced bladder, ovarian and testicular cancer. It has been widely studied in a variety of solid tumor types. Commercial supplies of cisplatin will be used for this study and billed to subjects and/or their insurance company. See package insert for complete prescribing information available at the following link:
http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/018057s083lbl.pdf

5.4.2 Storage, Handling and Disposal

Cisplatin should be stored, handled and disposed per institutional guidelines.

5.4.3 Preparation

Cisplatin should be prepared per institutional guidelines. As stated in section 4.5.2, post-operative radiation and concomitant weekly cisplatin (30 mg/m^2) may be administered to medium-risk subjects for up to 6 cycles.

As stated in section 4.5.3 post-operative radiation and concomitant high dose bolus cisplatin (100 mg/m^2) may be administered to high-risk subjects every 3 weeks for up to 3 cycles.

5.4.4 Adverse Events Associated with Cisplatin

The toxicities of cisplatin are well established, and include nausea and vomiting, risk of kidney failure, peripheral neuropathy, hearing loss and febrile neutropenia. The cisplatin dose of 100mg/m^2 has been extensively studied in lung cancer and head and neck cancer, with and without radiotherapy. The toxicities, including

the predictable increase of the radiotherapy local toxicities, are well documented and tolerable.

6.0 EVALUATIONS AND ASSESSMENTS

6.1 Time and Events Table

Procedure	Screening[1]	D1 Weekly visits (1-6)[2a]	D1 Week 7	D1 Week 9	1-4 weeks post induction[3]	Surgical resection[4]	SOC Adjuvant TXT Day 1 (+/-1 day) of each chemoradiotherapy cycle (or every three weeks for weekly regimens)[4]	Adjuvant Durvalumab Q2 weeks x 3	Treatment Discontinuation[5]	Follow-up[6]
Informed Consent	X									
Medical History	X[7]	X[7]	X		X		X[7]	X	X	X
Physical Exam	X[8]	X	X		X		X	X	X	X
ECOG Performance status	X	X	X		X		X	X	X	X
Weight	X	X	X		X		X	X	X	X
CBC with differential	X	X		X			X		X	
Serum chemistries[9]	X	X	X	X			X[8]	X	X	
Calculated CrCl[11]	X	X					X[11]	X		
TSH		X[15]		X				X[16]		
Serum pregnancy test	X[12]									
Tumor evaluation[13]	X				X				X	X
Blood draw for correlatives[18]		X[19]			X				X	
Archived or fresh tissue	X[1,14]					X[14]				
Toxicity assessment	X	X	Monitor throughout study at each clinic visit						X[17]	X[17]
Carboplatin		X[2b]								
Nab-paclitaxel		X[2b]								
Durvalumab (pulse and BP)[2d]		X[2b,d]	X	X				X[2c,d]		
Radiation							X[4]			
Cisplatin							X[4,]			
Concomitant Meds	X	X	X	X	X		X	X		
Risk stratification						X[4]				
Ensure subject has operative appointment			X							
QOL (FACT-HN)[20]	X				X				X	
Survival assessment										X

Key to Time and Events Table Footnotes

1. Unless otherwise noted, screening evaluations to take place within 2 weeks prior to day 1 of study treatment. For D1 of week 1, if screening (baseline) evaluations were performed within 7 days of D1 of treatment, these do not need to be repeated.

2. **A**) Day 1 (+/-) 1 day; paclitaxel and carboplatin administered weekly for 6 weeks, concomitant with durvalumab (See 2B). Laboratory evaluations on day 1 of cycle 1 need be repeated only if >7 days have elapsed between screening laboratory tests and day 1.

2. **B)** Nab-Paclitaxel (100 mg/m^2), carboplatin (AUC2) administered weekly for 6 weeks + Durvalumab (750 mg) administered every 2 weeks X 5 (i.e., week 1, week 3, week 5, week 7, week 9).

2. **C)** Adjuvant Durvalumab (750 mg) administered every 2 weeks X 3 (i.e., week 1, week 3, week 5)

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

3. This clinic visit should take place 1-4 weeks after subject completes induction treatment or ceases therapy for other reasons (including early discontinuation). Surgery may follow immediately after.

4. Surgical resection should occur 1-4 weeks following completion of induction therapy. Subjects deemed low risk will receive 3 cycles of durvalumab at a dose of 750 mg administered every two weeks after surgery (see exceptions noted for involved field radiation in section 4.5.1). Those in the medium risk group will receive radiation as per standard of care with concurrent weekly cisplatin chemotherapy (see section 4.5.2 for alternative options); cycles will be defined as every 3 weeks. Subjects in the high-risk group will receive post-operative radiation and concomitant high dose bolus cisplatin 100 mg/m^2 every 3 weeks for up to 3 cycles (see section 4.5.3 for possible exceptions to this regimen in high-risk group). Some clinicians may choose to see some subjects weekly during weekly chemoradiation regimens. This will be left to clinician discretion. Following chemoradiotherapy, subjects in the medium and high-risk groups will receive 3 cycles of durvalumab (750mg) administered every two weeks. Visits will be documented for study purposes only at the every three weeks visits per the T and E table.

5. This visit should take place when subject stops treatment due to documented radiographic or clinical disease progression, unmanageable toxicity, or when study treatment is complete. In the case of subjects who reach this milestone due to completion of study therapy, this visit should occur 8-12 weeks following the conclusion of adjuvant durvalumab. Subjects who experience a grade 4 toxicity or SAE will be contacted every 2 weeks until the event is resolved, determined to be irreversible by the investigator, or until the subject begins an alternate form of treatment.

6. The first follow up, described as "treatment discontinuation above," contains study-mandated follow up including imaging. Subsequent follow-up visits will take place per standard of care (SOC). SOC typically includes physical exam of neck and primary site and/or imaging of these areas every 3 months for at least 2 years with documentation in the electronic case report form (eCRF) limited to progression and survival noted at their SOC MD visits for at least 5 years.

7. Complete medical history at baseline to include demographics, HPV status and smoking history.

8. Physical examination to include height at baseline only, and complete examination of head and neck.

9. Serum chemistries to include sodium, potassium, chloride, CO_2, BUN, creatinine, glucose, calcium, albumin, total protein, total bilirubin, AST, ALT, amylase, lipase and alkaline phosphatase.

10. Liver function tests to include total bilirubin, alkaline phosphatase, AST, ALT.

11. Using Cockroft & Gault formula (see section 4.3.3). This should be calculated prior to each dose of carboplatin

12. To be done within 72 hours prior to day 1 of treatment in women of childbearing potential.

13. The same method of evaluation should be used throughout study and may include CT or MRI of the neck, and chest imaging (X-ray or CT scan at discretion of physician). CT of the neck should have IV contrast unless contraindicated (allergy or adverse reaction or renal issues). Screening radiologic evaluation may take place within 4 weeks of treatment initiation. If PET/CT or PET/MRI was used for baseline imaging, it is acceptable to obtain CT or MRI (respectively) alone for follow up imaging. See section 6.2.2 for frequency to tumor evaluation during follow up (i.e., every 3 months).

14. At screening archival tumor tissue should be obtained. Collect a fresh biopsy from subjects who agree to this procedure via consent. Collect tissue during surgery for correlative studies.

15. Weeks 1, 5 and 9. Thyroid panel includes TSH, T_3 and free T_4. If consistent with institutional standard of care, it is acceptable to obtain TSH alone and only obtain T_3 and free T_4 if clinically useful.

16. Before 1st and 3rd cycle only.

17. Subjects who have an ongoing Grade 4 toxicity at the time of discontinuation from treatment will continue to be followed until the event is resolved or deemed irreversible by the investigator.

18. Blood draw - 3x 8mLs whole blood in ACD tubes will be to evaluate for clonally restricted circulating B and T cells.

19. Cycle 1, day 1 only. Collect specimen prior to treatment.

20. Functional Assessment of Cancer Therapy-Head and Neck, Version 4.

6.2 Follow-up Assessments

Subjects who withdraw consent from study drug treatment should enter the follow up period (unless consent to follow-up is specifically withdrawn). After study drug treatment ends, subsequent anti-cancer medications taken by the subject should be documented in the eCRF if this information is available during follow-up.

6.2.1 Initial Follow-up Visit

Following completion of all treatment, the first follow-up visit will occur at 8 to 12 weeks after treatment discontinuation. This visit will include:

Physical examination (including weight), and symptom directed medical history
ECOG Performance Status (see Appendix A)
Laboratory evaluations:

- CBC with differential
- Serum chemistries (sodium, potassium, chloride, bicarbonate, BUN, serum creatinine, glucose, calcium, magnesium, albumin)
- Liver function tests
- TSH

Toxicity Assessment: As per NCI CTCAE v4.03. Subjects who experienced a grade 4 or SAE during the treatment phase will be contacted every 2 weeks until the event is resolved or deemed irreversible by the investigator.
Quality of life: FACT-HN

6.2.2 Subsequent Follow-up through 5 years

Subsequent follow-up visits will take place per standard of care (SOC). SOC typically includes physical exam of neck and primary site and/or imaging of these areas every 3 months for at least 2 years with documentation in the electronic case report form (eCRF) limited to progression and survival noted at their SOC MD visits for at least 5 years.

6.3 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 after definitive diagnosis is made (i.e., archival and or fresh tissue) for research purposes. In addition, subjects will be required to allow use of their residual operative tissue for research purposes.

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 1621 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 subject'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 subject's participation in the clinical study may also be included. This information may be important for understanding how the subject'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 stored for at least 5 years for this study and up to 15 years, if consent was obtained from the subject to use tissue for other research purposes (e.g., TPF consent form was signed by the subject).
  - The investigator agrees to abide by policies and procedures of the TPF facility and will sign a letter of research agreement for ethical and appropriate conduct of their research that utilizes specimens obtained from the TPF facility.

Compliance Statement

Biospecimen collection for this study will be conducted in full accordance to 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 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.

6.4 Assessment of Safety

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

Any subject who receives treatment on this protocol will be evaluable for toxicity. Each subject 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 CTCAE v 4.03.

6.4.1 Durvalumab Safety

The safety profile of durvalumab is consistent with the pharmacology of the target and other agents in the immune checkpoint inhibitor class. No tumor types appeared to be associated with unique AEs. Immune-related AEs (irAEs), which are important risks of immune checkpoint inhibitors, have been observed with durvalumab and include colitis, pneumonitis, hepatitis/hepatotoxicity, neuropathy/neuromuscular toxicity, endocrinopathy, dermatitis, and nephritis. In addition, pancreatitis is an important potential risk particularly with durvalumab and tremelimumab combination therapy; This study considers only Durvalumab and not Tremelimumab. These events are manageable by available/established treatment guidelines as described in the study protocol.

6.4.2 Assessment of Safety Parameters

Assessment of Severity

For both AEs and SAEs, the Investigator must assess the severity / intensity of the event.

The severity/intensity of AEs will be graded based upon the subject's symptoms according to the current active minor version of the Common Terminology Criteria for Adverse Events (CTCAE, Version 4.03); http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40

AEs that are not defined in the CTCAE should be evaluated for severity/intensity according to the following scale:

- Grade 1 = Mild – transient or mild discomfort; no limitation in activity; no medical intervention/therapy required
- Grade 2 = Moderate – mild to moderate limitation in activity, some assistance may be needed; no or minimal medical intervention/therapy required
- Grade 3 = Severe – marked limitation in activity, some assistance usually required; medical intervention/therapy required, hospitalization is possible
- Grade 4 = Life-threatening – extreme limitation in activity, significant assistance required; significant medical intervention/therapy required, hospitalization or hospice care probable
- Grade 5 = Death - the event results in death

The term "severe" is often used to describe the intensity of a specific event (as in mild, moderate or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This criterion is not the same as "serious" which is based on subject/event outcome or action criteria associated with events that pose a threat to a subject's life or functioning.

Seriousness, not severity, serves as a guide for defining regulatory obligations.

Causality

The Investigator must determine the relationship between the administration of IP and the occurrence of an AE/SAE as Not Suspected or Suspected as defined below:

Not suspected: A causal relationship of the adverse event to IP administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event.

Suspected: There is a **reasonable possibility** that the administration of IP caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the IP and the adverse event.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

If an event is assessed as suspected of being related to a comparator, ancillary or additional IP that has not been manufactured or provided by Celgene, please provide the name of the manufacturer when reporting the event.

Duration

For both AEs and SAEs, the Investigator will provide a record of the start and stop dates of the event.

Action Taken

The Investigator will report the action taken with IP as a result of an AE or SAE, as applicable (e.g., discontinuation, interruption of IP, as appropriate) and report if concomitant and/or additional treatments were given for the event.

Outcome

The Investigator will report the outcome of the event for both AEs and SAEs. All SAEs that have not resolved upon discontinuation of the subject's participation in the study must be followed until recovered (returned to baseline), recovered with sequelae, or death (due to the SAE).

6.4.3 Adverse Event Reporting

Adverse Event intensity and/or severity will be graded using CTCAE Version 4.03 for toxicity and adverse event reporting. A copy of the CTCAE Version 4.03 can be downloaded from CTEP (http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm#ctc_40). All appropriate treatment areas should have access to a copy of the CTCAE Version 4.03. All adverse clinical experiences, whether observed by the investigator or reported by the subject, must be recorded, with details about the duration and intensity of each episode, the action taken with respect to the test drug, and the event's outcome, including lab abnormalities. The investigator must

evaluate each adverse experience for its relationship to the test drug and for its seriousness.

The investigator must appraise all abnormal laboratory results for their clinical significance. If any abnormal laboratory result is considered clinically significant, the investigator must provide details about the action taken with respect to the test drug and about the event's outcome or lab abnormality.

Monitoring, recording and reporting adverse events

An AE is any noxious, unintended, or untoward medical occurrence that may appear or worsen in a subject during the course of a study. It may be a new intercurrent illness, a worsening concomitant illness, an injury, or any concomitant impairment of the subject's health, including laboratory test values, regardless of etiology. Any worsening (i.e., any clinically significant adverse change in the frequency or intensity of a pre-existing condition) should be considered an AE. A diagnosis or syndrome should be recorded rather than the individual signs or symptoms of the diagnosis or syndrome.

Abuse, withdrawal, sensitivity or toxicity to an investigational product should be reported as an AE. An overdose, accidental or intentional, whether or not it is associated with an AE, should be reported. Any sequela of an accidental or intentional overdose of an investigational product should be reported as an AE. If the sequela of an overdose is an SAE, then the sequela must be reported on an SAE report form and as an AE.

All subjects will be monitored for AEs during the study. Assessments may include monitoring of any or all of the following parameters: the subject's clinical symptoms, laboratory, pathological, radiological or surgical findings, physical examination findings, or findings from other tests and/or procedures.
All AEs will be recorded by the Investigator from the time the subject signs informed consent until 90 days after the last dose of IP and those SAEs made known to the investigator at any time thereafter that are suspected of being related to IP. AEs and serious adverse events (SAEs) will be recorded in the subject's source documents. All SAEs must be reported to Celgene Drug Safety within 24 hours of the Investigator's knowledge of the event by facsimile, or other appropriate method, using the SAE Report Form, or approved equivalent form.

6.5 Assessment of Efficacy

The primary endpoint of pathologic complete response rate (pCRR) will be defined as per RECIST1.1. [35] An intent-to-treat approach will be followed in all data summaries using all available data in the analyses. Each subject enrolled will be in the primary ITT analysis set. Consequently, no special adjustments to the data are intended for dealing with missing values or subjects who withdraw prior to completing study. In the case of no tumor assessment, the subject will count as a non-responder if failure to acquire tumor assessment was even possibly related to study procedures (for example, discontinuation due to toxicity); in the case that failure to acquire tumor assessment is clearly not due to study

procedures (for example, subject choice unrelated to toxicity or failure of efficacy) then such a subject will be excluded from the analysis.

6.5.1 Tumor Measurement

Tumor lesions will be evaluated via CT scan of the neck and chest imaging (X-ray or CT scan at discretion of physician). Measurable disease will be defined as the presence of at least one measurable lesion that can be accurately measured in at least one dimension with the longest diameter a minimum size of:

- ≥10 mm by CT scan (CT scan slice thickness no greater than 5 mm)
- 10 mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable)
- 20 mm by chest X-ray

For malignant lymph nodes to be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

All other lesions, including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥10 to <15 mm short axis) as well as truly non-measurable lesions, will be considered non-measurable. Lesions considered truly non-measurable include: leptomeningeal disease; ascites; pleural/pericardial effusion; inflammatory breast disease; lymphangitic involvement of skin or lung; abdominal masses/abdominal organomegaly identified by physical exam that is not measurable by reproducible imaging techniques.

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment. The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam. Clinical lesions will only be considered measurable when they are superficial and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesions is recommended.

6.5.2 Baseline Documentation of Target and Non-Target Lesions

All measurable lesions up to a maximum of 5 lesions total (and a maximum of 2 lesions per organ) representative of all involved organs should be identified as target lesions and will be recorded and measured at baseline.

Target lesions should be selected on the basis of their size (lesions with the longer diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements.

A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize the objective tumor response of the measurable dimension of the disease.

All other lesions (or sites of disease) including pathological lymph nodes should be identified as non-target lesions and should also be recorded at baseline. Measurements are not required and these lesions should be followed as "present" or "absent", or in rare cases "unequivocal progression".

6.5.3 Evaluation of Target Lesions

Complete response (CR) – Disappearance of all target lesions. Any pathological lymph node (LN) target or not must have decreased in short axis to <10 mm.

Pathologic complete response (pCR) – The absence of any residual cancer cells within the resected surgical specimen

Partial response (PR) – At least a 30% decrease in the sum of the LD of the target lesions taking as reference the baseline sum LD.

Progressive Disease (PD) – At least a 20% increase in the sum of the LD of the target lesions taking as reference the smallest sum LD recorded since the treatment started including baseline if that is the smallest on study. In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. The appearance of one or more new lesions also constitutes PD.

Stable disease (SD) – Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD taking as references the smallest sum LD since the treatment started. In the case of SD, measurements must have met the SD criteria at least once after study entry at a minimum interval of 8 weeks from initiation of treatment.

6.5.4 Evaluation of Non-Target Lesions

Complete response (CR) – Disappearance of all non-target lesions. All LN must be non-pathological in size (<10 mm short axis).

Non-complete response (non-CR)/non-progression (non-PD) – Persistence of one or more non-target lesion(s) or/and maintenance of tumor marker level above the normal limits.

Progressive disease (PD) – Appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

6.5.5 Evaluation of Best Overall Response

The best overall response is defined as the best response achieved across all time points prior to progression (for example, a subject who has SD at first assessment, PR at second assessment, and PD on last assessment has a best overall response of PR).

7.0 ADVERSE EVENTS

7.1 Definitions

7.1.1 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 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.

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

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.

7.1.2 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

7.1.3 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.

7.1.4 Serious AE or SAR

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 subject and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.
- Pregnancies will also be reported promptly to Astrazeneca/MedImmune and Celgene in a similar manner to SAEs

*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.

Important medical events are defined as those occurrences that may not be immediately life threatening or result in death, hospitalization, or disability, but may jeopardize the subject or require medical or surgical intervention to prevent one of the other outcomes listed above. Medical and scientific judgment should be exercised in deciding whether such an AE should be considered serious. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalizations; or development of drug dependency or drug

abuse. Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation.

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

Events not considered to be SAEs are hospitalizations for:

- A standard procedure for protocol therapy administration. However, hospitalization or prolonged hospitalization for a complication of therapy administration will be reported as an SAE.
- Routine treatment or monitoring of the studied indication not associated with any deterioration in condition.
- The administration of blood or platelet transfusion as routine treatment of studied Indication. However, hospitalization or prolonged hospitalization for a complication of such transfusion remains a reportable SAE.
- A procedure for protocol/disease-related investigations (e.g., surgery, scans, endoscopy, sampling for laboratory tests, bone marrow sampling). However, hospitalization or prolonged hospitalization for a complication of such procedures remains a reportable SAE.
- Hospitalization or prolongation of hospitalization for technical, practical, or social reasons, in absence of an AE.
- A procedure that is planned (i.e., planned prior to starting of treatment on study); must be documented in the source document and the CRF. Hospitalization or prolonged hospitalization for a complication remains a reportable SAE.
- An elective treatment of or an elective procedure for a pre-existing condition unrelated to the studied indication.
- Emergency outpatient treatment or observation that does not result in admission, unless fulfilling other seriousness criteria above.

If an AE is considered serious, both the AE page/screen of the CRF and the SAE Report Form must be completed. For each SAE, the Investigator will provide information on severity, start and stop dates, relationship to IP, action taken regarding IP, and outcome.
In addition, the following variables will be collected for SAEs as applicable:

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- Criteria for AE to be considered serious
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death

- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)

7.2 Documentation of non-serious AEs or SARs

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

The following variables will be collected for each AE:

- AE (verbatim)
- The date and time when the AE started and stopped
- Changes in NCI CTCAE grade and the maximum CTC grade attained
- Whether the AE is serious or not
- Investigator causality rating against durvalumab and/or comparator/combination drug
- Action taken with regard to durvalumab /comparator/combination agent
- Outcome

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

- Date AE met criteria for serious AE
- Date Investigator became aware of serious AE
- AE is serious due to the following i.e., specify criteria
- Date of hospitalization
- Date of discharge
- Probable cause of death
- Date of death
- Autopsy performed
- Description of AE
- Causality assessment in relation to Study procedure(s)
- Causality assessment in relation to Additional Study Drug

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

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

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

For non-serious AEs or SARs, documentation must begin from day 1 of study treatment and continue through the 90-day follow-up period for durvalumab or 28 days after other study treatment is discontinued.

Collected information should be recorded in the electronic case report forms (eCRF) for that subject. 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.

7.3 SAEs or Serious SARs

7.3.1 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 30 days after study treatment discontinuation.

7.3.2 Documentation and Notification

SAEs or Serious SARs must be recorded in the SAE console within OnCore® for that subject within 24 hours of learning of its occurrence. Additionally, the NCCN Project Manager must also be notified via email of all SAEs within 24 hours of learning of its occurrence.

7.4 Adverse Event Reporting

7.4.1 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.

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 28 days of the subject's last dose of study should be recorded as SAEs. The subject is to be discontinued immediately from the study.

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 UNC Study Coordinator. 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.

7.4.1.1 AstraZeneca Reporting Requirements:

All SAEs will be reported, whether or not considered causally related to the investigational product, or to the study procedure(s). The reporting period for SAEs is the period immediately following the time that written informed consent is obtained through 90 days after the last dose of durvalumab (or at least 5 half-lives of other study medications) or until the initiation of alternative anticancer therapy. The investigator and/or Sponsor are responsible for informing the Ethics Committee and/or the Regulatory Authority of the SAE as per local requirements.

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

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

- "Notification from an Investigator Sponsored Study"
- The investigator IND number assigned by the FDA
- The investigator's name and address
- The trial name/title and AstraZeneca ISS reference number (ESR-16-12068)

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

7.4.1.2 Expedited Reporting by Investigator to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a SAE form or MedWatch 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile within 24 hours. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s). Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation of the SAE report to Celgene should be attached to the SAE and retained with the subject records.

Drug Safety Contact Information:

Celgene Corporation
Global Drug Safety and Risk Management
556 Morris Avenue, Building S12
Summit, New Jersey 07901
Fax: (908) 673-9115
E-mail: drugsafety@celgene.com
Telephone: 1-908-673-9667
Toll Free: 1-800-640-7854

7.4.1.3 FDA Expedited Reporting requirements under 21CFR312.32 for studies conducted under an IND

A sponsor must report any suspected adverse reaction that is both serious and unexpected to the FDA. The sponsor must report an adverse event as a suspected adverse reaction only if there is evidence to suggest a causal relationship between the drug and the adverse event, such as:

- A single occurrence of an event that is uncommon and known to be strongly associated with drug exposure (e.g., angioedema, hepatic injury, Stevens-Johnson Syndrome);

- One or more occurrences of an event that is not commonly associated with drug exposure, but is otherwise uncommon in the population exposed to the drug (e.g. tendon rupture);
- An aggregate analysis of specific events observed in a clinical trial (such as known consequences of underlying disease or condition under investigation or other events that commonly occur in the study population independent of drug therapy) that indicates those events occur more frequently in the drug treatment group than in a concurrent or historical control group.

The sponsor must submit each IND safety report on FDA Form 3500A. Each notification to FDA must bear prominent identification of its contents, i.e., "IND Safety Report," and must be transmitted to the review division that has the responsibility for review of the IND.
If the sponsor deems that an event is both a serious 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 faxed to the UNC Multicenter Project Manager at 919-966-4300 (or emailed at CPOMultiCenter@med.unc.edu) along with supporting documentation defining the event and causality. The UNC 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).

Once the sponsor determines an event is a serious SAR AND unexpected, the MedWatch 3500A form will be submitted to the FDA. If the event is serious, unexpected and considered to be possibly-, probably- or definitely-related to the study treatment, the UNC Multicenter Project Manager will inform the Regulatory Associate at UNC who will be responsible for submitting the SAR via serial submission to the IND. The MedWatch form should also be sent to the Regulatory Associate and the IND Specialist within 48 hours of the sponsor being aware of the event. The Regulatory Associate with the aid of the IND Specialist will submit the IND Safety Report via IND serial submission to the FDA review division. All IND safety reports must be submitted on Form 3500A and be accompanied by Form 1571. The FDA must be notified or any unexpected or life-threatening suspected adverse reactions as soon as possible, but no later than 7 calendar days of learning of the event. If the event is serious, but not life-threatening, FDA must be notified as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

The UNC Multicenter Project Manager will also be responsible for informing each Affiliate site of all serious and unexpected SARs reported to the FDA via fax as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

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.

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

Any overdose of a study subject with durvalumab, with or without associated AEs/SAEs, is required to be reported within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety or designee using the designated Safety e-mailbox (see Section 7.4.1.1 for contact information). If the overdose results in an AE, the AE must also be recorded as an AE. Overdose does not automatically make an AE serious, but if the consequences of the overdose are serious, for example death or hospitalization, the event is serious and must be recorded and reported as an SAE. There is currently no specific treatment in the event of an overdose of durvalumab.

An overdose of nab-paclitaxel is defined, on a per dose basis, as the following amount over the protocol-specified dose of nab-paclitaxel assigned to a given subject, regardless of any associated adverse events or sequelae.

- IV 10% over the protocol-specified dose

On a schedule or frequency basis, an overdose is defined as anything more frequent than the protocol required schedule or frequency.

On an infusion rate basis, an overdose is defined as any rate faster than the protocol-specified rate. For nab-paclitaxel, an infusion completed in less than 25 minutes may increase Cmax by approximately 20%, therefore a nab-paclitaxel infusion completed in less than 25 minutes will meet the infusion rate criterion for an overdose.

Complete data about drug administration, including any overdose, regardless of whether the overdose was accidental or intentional, should be reported in the case report form.

The investigator will use clinical judgment to treat any overdose.

Hepatic Function Abnormality

Hepatic function abnormality in a study subject, with or without associated clinical manifestations, is required to be reported as "hepatic function abnormal" within 24 hours of knowledge of the event to the sponsor and AstraZeneca/MedImmune Patient Safety using the designated Safety e-mailbox provided in section 7.4.1.1, unless a definitive underlying diagnosis for the abnormality (e.g., cholelithiasis or bile duct obstruction) that is unrelated to the study medications has been confirmed.

- If the definitive underlying diagnosis for the abnormality has been established and is unrelated to investigational product, the decision to continue dosing of the study subject will be based on the clinical judgment of the investigator.

- If no definitive underlying diagnosis for the abnormality is established, dosing of the study subject must be interrupted immediately. Follow-up investigations and inquiries must be initiated by the investigational site without delay.

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

Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the study medications under study may have interfered with the effectiveness of a contraceptive medication. 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 durvalumab or other study medications, or within at least 90 days of the subject's last dose of durvalumab, are considered immediately reportable events. Study medications are to be discontinued immediately. The pregnancy, suspected pregnancy, or positive pregnancy test must be reported to AstraZeneca/Celgene Drug Safety immediately by facsimile, or other appropriate method, using the Pregnancy Initial Report Form, or approved equivalent form 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 female subject may be referred to an obstetrician-gynecologist (not necessarily one with reproductive toxicity experience) or another appropriate healthcare professional for further evaluation and counseling. The same timelines apply when outcome information is available.

The Investigator will follow the female subject until completion of the pregnancy and must notify AstraZeneca/Celgene Drug Safety immediately about the outcome of the pregnancy (either normal or abnormal outcome) using the Pregnancy Follow-up Report Form, or approved equivalent form. 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 to AstraZeneca/Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form. 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 subject was discontinued from the study.
All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to the study medications should also be reported to AstraZeneca/Celgene Drug Safety immediately by facsimile, or other appropriate method, within 24 hours of the Investigator's knowledge of the event using the SAE Report Form, or approved equivalent form.

Male Subjects
Durvalumab: Male subjects should refrain from fathering a child or donating sperm during the study and for 90 days after the last dose of durvalumab monotherapy.
If a female partner of a male subject taking study medications becomes pregnant, the male subject taking the study medications should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately.

Nab-paclitaxel: If a female partner of a male subject receiving nab-paclitaxel becomes pregnant, the male subject on nab-paclitaxel should notify the Investigator, and the pregnant female partner should be advised to call their healthcare provider immediately. Male subjects treated with nab-paclitaxel are advised not to father a child during and up to 6 months after treatment with nab-paclitaxel.

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

Where a report of pregnancy is received, prior to obtaining information about the pregnancy, the Investigator must obtain the consent of the subject'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.

7.4.2 Definition of Adverse Events of Special Interest (AESI)

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

AESIs for durvalumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with durvalumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate etiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

If the Investigator has any questions in regards to an adverse event (AE) being an irAE, the Investigator should promptly contact the Study Physician.

AESIs observed with durvalumab include:

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

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

7.4.2.1 Pneumonitis

Adverse events of pneumonitis are of interest for AstraZeneca/MedImmune, as pneumonitis has been reported with anti-PD-1 MAbs [36]. Initial work-up should include high-resolution CT scan, ruling out infection, and pulse oximetry. Pulmonary consultation is highly recommended.

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

7.4.2.2 Hypersensitivity Reactions

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

Guidelines for management of subjects with hypersensitivity (including anaphylactic reaction) and infusion-related reactions are outlined in Section 5.1.2.2.

7.4.2.3 Hepatic function abnormalities (hepatotoxicity)

Increased transaminases have been reported during treatment with anti-PD-L1/anti-PD-1 antibodies [37]. Inflammatory hepatitis has been reported in 3% to 9% of subjects treated with anti-CTLA-4 monoclonal antibodies (e.g., ipilimumab). The clinical manifestations of ipilimumab-treated subjects included general weakness, fatigue, nausea and/or mild fever and increased liver function tests such as AST, ALT, alkaline phosphatase, and/or total bilirubin.

Hepatic function abnormality is defined as any increase in ALT or AST to greater than 3 × ULN and concurrent increase in total bilirubin to be greater than 2 × ULN. Concurrent findings are those that derive from a single blood draw or from separate blood draws taken within 8 days of each other. Follow-up investigations and inquiries will be initiated promptly by the investigational site to determine whether the findings are reproducible and/or whether there is objective evidence that clearly supports causation by a disease (e.g., cholelithiasis and bile duct obstruction with distended gallbladder) or an agent other than the investigational product. Guidelines for management of subjects with hepatic function abnormality are outlined in Section 4.6.2 .

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

Criteria for Hy's Law (FDA Guidance 2009)

- The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (non-hepatotoxic) control drug or placebo

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

7.4.2.4 Gastrointestinal disorders

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

7.4.2.5 Endocrine disorders

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

7.4.2.6 Pancreatic disorders

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

7.4.2.7 Neurotoxicity

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

7.4.2.8 Nephritis

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

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

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

7.4.3 Disease-Related Events and/or Disease-Related Outcomes Not Qualifying as SAEs:

An event which is part of the natural course of the disease under study (i.e., disease progression) does not need to be reported as an SAE. Progression of the subject's neoplasia will be recorded in the clinical assessments in the CRF. Death due to progressive disease is to be recorded on the 'Record of Death' CRF page and not as an SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between study treatment or protocol design/procedures and the disease progression, then this must be reported as an SAE. Any new primary cancer must be reported as an SAE.

7.5 Data and Safety Monitoring Plan

The Principal Investigator will provide continuous monitoring of subject safety in this trial with periodic reporting to the Data and Safety Monitoring Committee (DSMC).

Meetings/teleconferences will be held at a frequency dependent on study accrual, and in consultation with the study Biostatistician. These meetings will include the investigators as well as protocol nurses, clinical research associates, regulatory associates, data managers, biostatisticians, 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, data collection, etc."

The team will produce summaries or minutes of these meetings. These 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 subjects 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.

8.0 STATISTICAL CONSIDERATIONS

8.1 Study Design/Study Endpoints

This is a single-arm non-randomized phase II trial in previously untreated subjects with SCCHN. Treatment will consist of 3 parts: neoadjuvant induction with weekly carboplatin, nab-paclitaxel for six weeks in combination with every other week durvalumab for five doses (9 weeks) (Part 1) prior to standard of care surgery (Part 2). Post-operative treatment (Part 3) will vary depending on the risk category assigned to the subject during surgery.

The primary objective of this study is to estimate the pathologic complete response rate after induction chemotherapy.

8.2 Sample Size and Accrual

Based on preliminary data from LCCC 1125, which had lower risk subsites (the subjects mostly had oropharynx cancer due to the requirement for transoral resectability) and used lapatanib instead of durvalumab, we have set the null hypothesis pathologic complete response rate (pCRR) at 30%. This null hypothesis will be tested against a one-sided alternative. A one sample binomial test with a 0.050 one-sided significance level will have 80% power to detect the difference between the null hypothesis proportion of 0.3 and the alternative proportion of 0.5 when the sample size is 37. If 17/37 or more have a pCR, we will reject the null hypothesis. Of note, we allow for a total of up to 2 unevaluable subjects, thus the total n of up to 39 subjects. This sample size was calculated using SWOGStat online calculator.

Sequential boundaries will be used to suspend the trial if excessive toxicity is seen. If the study reaches a stopping boundary, it may be terminated by the PI, or submitted to the Data and Safety Monitoring Committee with a description of the failures to date and a rationale for why the study should be continued. A dose-limiting toxicity (DLT) is defined as any grade 4 adverse event attributed to induction therapy or any delay to surgery greater than 50 days following the last dose of induction therapy. The accrual will be halted if the number of DLTs is equal to or exceeds bn out of n subjects with full toxicity follow-up (see table below). This is a Pocock type stopping boundary [38] that assumes that a DLT rate of 0.15 is acceptable. If the true DLT rate is equal to 0.15, the probability of crossing the boundary is 0.05 [39]. Stopping rule for DLT. The trial is stopped if there are

Number of Subjects, n	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
Boundary, b_n	-	-	3	3	4	4	4	5	5	5	6	6	6	6	7	7	7	7	8	8
Number of Subjects, n	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40
Boundary, b_n	8	8	8	9	9	9	9	10	10	10	10	10	11	11	11	11	12	12	12	12

8.3 Data Analysis Plans

For the primary objective of estimating pathologic complete response rate to the induction regimen, the percent of subjects who have a pathologic complete response (no viable cancer cells) on surgical pathology will be reported with an exact 95% confidence interval and compared to the null using a binomial test.

Before beginning any protocol treatment, the subjects will be assigned a risk group based on their baseline characteristics (as though they were starting in Part 3). The percent of subjects whose risk level is successfully improved by induction chemotherapy (comparing initial estimate of risk with surgical pathology) will be reported.

The following will also be reported:

After subjects have completed Part 1:
- Report the AEs during induction therapy
- Report the percentage of subjects predicted to be assigned to each risk group in Part 3
- Report/ describe the percentage of subjects who drop out of study protocol after Part 1, including whether they proceed to another definitive treatment
- Report the clinical response rate and clinical complete response rates.

After subjects have completed Part 2:
- Report the risk groups that the subjects are assigned to after surgery (low, med, high)
- Evaluate the percentage of subjects whose risk level is higher or lower than that assigned before Part 1
- Evaluate the efficacy of radiography in assessing post-induction stage

After subjects have completed Part 3:
- Report PFS and OS overall and separately for each risk group
- Within each group and overall, report PFS and OS for HPV positive and negative subjects
- Conduct biomarker assessment

All percentages will be reported with exact 95% confidence intervals. A kappa statistic will be used to see how well the predicted risk group agrees with the actual assigned risk group for Part 3. Time to event analyses will be done using the Kaplan Meier method and median times will be reported with 95% confidence intervals.

9.0 STUDY MANAGEMENT

9.1 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 subject 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 subject and the investigator is assured that the subject understands the implications of participating in the study, the subject will be asked to give consent to participate in the study by signing an IRB-approved consent form.

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

9.2 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
- CAP and CLIA Laboratory certification numbers and institution lab normal values
- Executed clinical research contract

9.3 Registration Procedures

All subjects must be registered with the LCCC CPO Multicenter Office at the University of North Carolina before enrollment to study. To register a subject,

call the Multicenter office at 919-966-7359 Monday-Friday 8:30 am – 5:00 pm EST. Scan and email the UNC Project Manager (CPOMultiCenter@med.unc.edu; preferred) or fax (919-966-4300) the registration form, signed informed consents, signed eligibility form and all source documents to confirm eligibility. Eligibility may be confirmed by the UNC Study Coordinator for subjects treated at UNC. When sending registration request with eligibility documentation, please allow 24 hours for source to be reviewed.

9.4 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 affiliate 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.

9.5 Adherence to the Protocol

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

9.5.1 Emergency Modifications

UNC and Affiliate 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 Affiliate 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:

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

9.5.2 Single 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.

9.5.3 Other Protocol DeviationsViolations

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:

<u>For Institutions Relying on UNC's IRB</u>:
Protocol Deviations: UNC or Affiliate personnel will record the deviation in OnCore®, and report to any sponsor or data and safety monitoring committee in accordance with their policies. Deviations should be summarized and reported to the IRB at the time of continuing review.

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 UNC Multicenter Project Manager within 5 days. UNC-CH will determine if the violation affects the safety of the subject and integrity of the data. Once your institution's IRB response is received, please forward to the Multicenter Regulatory Associate.

Unanticipated Problems:
Affiliate Sites:
Any events that meet the criteria for "Unanticipated Problems (UPs)" as defined by UNC's IRB must also be reported to the UNC Multicenter Projec Manager. The UNC Multicenter Regulatory Associate will report the event 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.

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

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 subject, 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 UNC IRB approved amendment to their institution's IRB for approval. For multi-center studies, any affiliate site must submit their informed consent revisions to the Multicenter Regulatory Associate prior to submission to their IRB.

9.6 Record Retention

Study documentation includes all eCRFs, data correction forms or queries, source documents, Sponsor-Investigator correspondence, monitoring logs/letters, and regulatory documents (e.g., protocol and amendments, IRB correspondence and approval, signed subject 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.

9.7 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 subjects. 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.

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11.0 APPENDICES

11.1 Appendix A: ECOG Performance Status

Score	Definition
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light hours work, office work
2	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 or chair more than 50% of waking hours
4	Totally confined to bed or chair – cannot carry on any self-care.
5	Dead

11.2 Appendix B: Subject Handout regarding Drug Interactions

- Drugs such as nab-paclitaxel that you will be given are processed by a certain enzyme in the liver called CYP3A4 or CYP2C8. Drugs that increase the activity of this enzyme are called "inducers", and drugs that decrease the activity of this enzyme are called "inhibitors". Nab-paclitaxel must be used very carefully with other medicines that are **inducers** or **inhibitors** of CYP3A4 or CYP2C8.
- You and healthcare providers who prescribe drugs for you must be careful about adding or removing any drug in this category
- Before you start the study, your study doctor will work with your regular prescriber to switch the following medications if you are taking them: inhibitors such as ketoconazole and other imidazole antifungals, erythromycin, fluoxetine, gemfibrozil, cimetidine, ritanovir, saquinavir, indinavir, and nelfinavir or inducers such as rifampicin, carbamazepine, phenytoin, efavirenz, and nevirapine**. You should also avoid grapefruit juice while you are on this study.**
- Your regular prescribers should look at this web site: http://medicine.iupui.edu/clinpharm/ddis/table.asp to see if any medicine they want to prescribe is on a list of drugs to avoid (that is, any strong inhibitor of the liver enzyme CYP3A4. Your study doctor may also have a list of medications for you to show your regular prescribers instead of, or in addition to, this website.
- If you drink grapefruit juice or eat grapefruit, you should avoid these until the study is over.
- Other medicines such as aminoglycoside antibiotics should not be prescribed or given with your 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 _____.

11.3 Appendix C: Dose Modifications/Toxicity Management for Durvalumab (Non-immune-mediated)

Non-immune-mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (ie, 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.

11.4 Appendix D: Dose Modifications/Toxicity Management for Durvalumab (Immune-related)

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy – 28 October 2021

General Considerations

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 v4.03. 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** after last dose of study drug/study regimen • Recurrence of a previously experienced Grade 3 treatment-related AE following resumption of dosing **Grade 1** No dose modification **Grade 2** Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. If toxicity worsens, then treat as Grade 3 or Grade 4. Study drug/study regimen can be resumed once event stabilizes to Grade ≤1 after completion of steroid taper. Subjects with endocrinopathies who may require prolonged or continued steroid replacement can be retreated with study drug/study regimen on the following conditions: 1. The event stabilizes and is controlled. 2. The subject is clinically stable as per Investigator or treating physician's clinical 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. **Grade 4** Permanently discontinue study drug/study regimen. Note: For Grade ≥3 asymptomatic amylase or lipase levels, hold study drug/study regimen, and if complete work up shows no evidence of pancreatitis, study drug/study regimen may be continued or resumed. 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).	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, subjects 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., myo-carditis, 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 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

Dosing Modification and Toxicity Management Guidelines (TMGs) for Durvalumab Monotherapy, Durvalumab in Combination with other Products, or Tremelimumab Monotherapy – 28 October 2021

General Considerations

Dose Modifications	Toxicity Management
	benefit-risk analysis for that subject.

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.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
Pneumonitis/Interstitial Lung Disease (ILD)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to – rule out any alternative etiology (e.g. – infection, progressive disease) – – Monitor patients for signs and symptoms of – pneumonitis or ILD (new onset or worsening – shortness of breath or cough). Evaluate – patients with imaging and pulmonary – function tests, including other diagnostic – procedures as described below. – – Suspected pneumonitis should be confirmed – with radiographic imaging and other – infectious and disease-related aetiologies – excluded, and managed as described below. – – Initial work-up may include clinical – evaluation, monitoring of oxygenation via – pulse oximetry (resting and exertion), – laboratory work-up, and high- resolution – computed tomography (CT) scan. – – Consider Pulmonary and Infectious Diseases – consults.
	Grade 1	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** – 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.
	Grade 2	Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • 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** – Monitor symptoms daily and consider hospitalization. – Obtain Pulmonary and Infectious Diseases Consults; consider discussing with Clinical Study Lead, as needed. - Promptly start systemic steroids (e.g., prednisone 1 to 2 mg/kg/day PO or IV equivalent). – Reimage as clinically indicated, consider chest CT with contrast and repeat in 3-4 weeks. – If no improvement within 2 to 3 days, additional workup should be considered and prompt treatment with IV methylprednisolone 2 to 4 mg/kg/day started. – If no improvement within 2 to 3 days despite IV methylprednisolone at 2 to 4 mg/kg/day,

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			promptly start immunosuppressive therapy. such as tumor necrosis factor (TNF) inhibitors (e.g., infliximab at 5 mg/kg IV once, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Consider, as necessary, discussing with Clinical Study Lead.
	Grade 3 or 4	Permanently discontinue study drug/study regimen.	**For Grade 3 or 4** – Promptly initiate empiric IV methylprednisolone 1 to 4 mg/kg/day or equivalent. – Obtain Pulmonary and Infectious disease consult; consider, as necessary, discussing with study physician. – Hospitalize the subject. – Supportive care (e.g., oxygen). – If no improvement within 2 days, additional workup should be considered and prompt treatment with additional immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). Caution: rule out sepsis and refer to infliximab label for general guidance before using infliximab.
Diarrhea/Colitis	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade:** – 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. – 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 AN INTESTINAL PERFORATION IS SUSPECTED, CONSULT A SURGEON EXPERIENCED IN ABDOMINAL SURGERY IMMEDIATELY WITHOUT ANY DELAY.** – **PERMANENTLY DISCONTINUE STUDY DRUG FOR ANY GRADE OF**

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			INTESTINAL PERFORATION. – 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 events, including intestinal perforation. – Use analgesics carefully; they can mask symptoms of perforation and peritonitis.
	Grade 1	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, and other supportive care measures. – If symptoms persist, consider checking lactoferrin; if positive, treat as Grade 2.
	Grade 2	Hold study drug/study regimen until resolution to Grade ≤1 • If toxicity improves to Grade ≤1, then study drug/study regimen can be resumed after completion of steroid taper (<10mg prednisone, or equivalent).	**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 2 to 3 days or worsens despite prednisone at 1 to 2 mg/kg/day PO or IV equivalent, consult a gastrointerstinal (GI) specialist for consideration of further workup, such as imaging and/or colonoscopy, to confirm colitis and rule out perforation. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg IV methylprednisolone, promptly start immunosuppressives such as infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. **Caution:** it is important 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.** – Consider, as necessary, discussing with Clinical Study Lead if no resolution to Grade – ≤1 in 3 to 4 days.
	Grade 3 or 4	**Grade 3** - For patients treated with durvalumab monotherapy, hold study drug/study regimen until	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		resolution to Grade ≤1; study drug/study regimen can be resumed after completion of steroid taper (<10 mg prednisone per day, or equivalent). - For patients treated with durvalumab in combination with other products (not tremelimumab), decision to be made at the discretion of the study investigator, in discussion with AstraZeneca Clinical Study Lead. - For patients treated with durvalumab in combination with tremelimumab or tremelimumab monotherapy, Permanently discontinue study drug for 1) Grade 3 diarrhea colitis or 2) Any grade of intestinal perforation in any patient treated with immune checkpoint inhibitor (ICI). **Grade 4** Permanently discontinue study drug/study regimen.	– Monitor stool frequency and volume and maintain hydration. – Urgent GI consult and imaging and/or colonoscopy as appropriate. – If still no improvement within 2 days continue steroids and promptly add further immunosuppressants. (e.g., infliximab at 5mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practive guidelines). **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.
Hepatitis (elevated liver function tests (LFTs)) **Infliximab should not be used for management of immune-related hepatitis.**	**Any Grade (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)**	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications). – Monitor and evaluate LFTs: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), and total bilirubin (T. bili.).
	Grade 1	• No dose modifications. • If it worsens, then treat as Grade 2 event.	**For Grade 1:** – Continue LFT monitoring per protocol.
PLEASE SEE shaded area immediately below	**Grade 2**	• Hold study drug/study regimen dose until Grade 2 resolution to Grade ≤1. • If toxicity worsens, then treat as Grade 3 or Grade 4. • If toxicity improves to Grade ≤1 or baseline and	**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 discussing with Clinical Study Lead, as needed.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
this section to find guidance for management of "Hepatitis (elevated LFTS)" in hepatocellular carcinoma (HCC) patients		there were no elevations in bilirubin, resume study drug/study regimen after coplation of steroid taper (<10mg prednisone or equivalent). • 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 ALP) and in the absence of any alternative cause.	– If event is persistent (>2 to 3 days) or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.
	Grade 3 or 4	**For Grade 3:** • Hold study drug/study regimen For elevations in transaminases ≤8 × ULN (and no elevations in bilirubin), or elevations in bilirubin ≤5 × ULN until resolution to Grade <1 or baseline. Resume study drug/study regimen if elevations downgrade to Grade ≤1 or baseline after completion of steroid taper (<10 mg prednisone, or equivalent). • If in combination with tremelimumab, do not restart tremelimumab. Permanently discontinue study drug/study regimen for ansaminases >8 × ULN or any elevations bilirubin >5 × ULN **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Promptly initiate empiric IV methylprednisolone at 1 to 2 mg/kg/day or equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, promptly start treatment with an additional immunosuppressive therapy (i.e., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss with Clinical Study Lead if mycophenolate is not available. **Infliximab should NOT be used.** – Perform hepatology consult, abdominal workup, and imaging as appropriate.
Hepatitis	**Any Elevations of**	**General Guidance**	**For Any Elevation Described:**

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
(elevated LFTs) **THIS shaded area is guidance *only* for management of "Hepatitis (elevated LFTs)" in HCC patients** **Infliximab should not be used for management of immune-related hepatitis.** **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**	**AST, ALT, or T. Bili as Described Below**		– Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., viral hepatitis, disease progression, concomitant medications, worsening of liver cirrhosis [e.g., portal vein thrombosis]). – Monitor and evaluate liver function test: AST, ALT, ALP, and T. Bili. – For hepatitis B (HBV) + patients: evaluate quantitative HBV viral load, quantitative Hepatitis B surface antigen (HBsAg), or Hepatitis B envelope antigen (HBeAg). – For hepatitis C (HCV) + patients: evaluate quantitative HCV viral load. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HBV medications if HBV viral load is >2000 IU/ml. – Consider consulting Hepatology or Infectious Diseases specialists regarding changing or starting antiviral HCV medications if HCV viral load has increased by ≥2-fold. – For HCV+ with Hepatitis B core antibody (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 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	• Hold study drug/study regimen dose until	– Regular and frequent checking of LFTs (e.g., every 1 to 3 days) until elevations of these are improving or resolved.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	at baseline **Isolated AST or ALT >2.0×baseline and ≤12.5×ULN, if elevated >ULN at baseline**	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 (<10 mg prednisone, or equivalent). • Permanently discontinue study drug/study regimen for any case meeting Hy's law criteria, in the absence of any alternative cause.[b]	Recommend consult hepatologist; consider abdominal ultrasound, including Doppler assessment of liver perfusion. – Consider, as necessary, discussing with Clinical Study Lead. – If event is persistent (>2 to 3 days) or worsens, and investigator suspects toxicity to be an imAE, start prednisone 1 to 2 mg/kg/day PO or IV equivalent. – If still no improvement within 2 to 3 days despite 1 to 2 mg/kg/day of prednisone PO or IV equivalent, consider additional workup. If still no improvement within 2 to 3 days despite 2mg/kg/day of IV methylprednisolone, consider additional abdominal workup (including liver biopsy) and imaging (i.e., liver ultrasound), and consider starting additional immunosuppressants. (e.g., mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with hepatology consult or relevant practice guidelines). Discuss Clinical Study Lead 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 and after completion of steroid taper (<10 mg prednisone, or equivalent). • Permanently discontinue study drug/study regimen if the elevations do not downgrade to AST or ALT ≤5.0×ULN within 14 days	– 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 discussing with Clinical Study Lead, as needed. – If investigator suspects toxicity to be immune-mediated, promptly initiate empiric IV methylpred mg/kg/day or equivalent. –If no improvement within 2 to 3 days despite 1 to 2 mg/kg/day methylprednisolone IV or equivalent, obtain liver biopsy (if it has not been done already) and promptly start treatment with an additional immunosuppressant. (e.g.,, mycophenolate mofetil 0.5 – 1 g every 12 hours then taper in consultation with a hepatologist or relevant practice guidelines). Discuss with Stucy Clinical Lead if mycophenolate is not available. **Infliximab should NOT be used.**
	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			

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
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** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections, recent IV contrast, medications, fluid status). – Consult a 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, decreased urine output, or proteinuria). – Consider using steroids in the absence of a clear alternative etiology even for low-grade events (Grade 2), in order to prevent potential progression to higher grade events.
	Grade 1	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.
	Grade 2	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 beyond 3 to 5 days or worsens, promptly start prednisone 1 to 2 mg/kg/day PO or IV equivalent.

Specific Immune-Mediated Reactions

Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			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, consider additional workup. should be considered and prompt treatment wit 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. – 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, considered additional workup and prompt treatment with immunosuppressant in consultation with a nephrologist.
Rash or Dermatitis (Including Pemphigold)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for definition of severity/grade depending on type of skin rash)	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology. – Monitor for signs and symptoms of dermatitis (rash and pruritus). – **HOLD STUDY DRUG IF STEVENS-JOHNSON SYNDROME (SJS), TOXIC EPIDERMAL NECROLYSIS (TEN), OR OTHER SEVERE CUTANEOUS ADVERSE REACTION (SCAR) IS SUSPECTED.** – **PERMANENTLY DISCONTINUE STUDY DRUG IF SJS, TEN, OR SCAR IS CONFIRMED.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy (e.g., emollient, lotion, or institutional standard).
	Grade 2	For persistent (>1 week) Grade 2 events, hold scheduled study drug/study regimen until resolution to Grade ≤1 or baseline. • If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion	**For Grade 2:** – Obtain dermatology consult. – Consider symptomatic treatment, including oral antipruritics (e.g., diphenhydramine or hydroxyzine) and topical therapy. – Consider moderate-strength topical steroid. – If no improvement of rash/skin lesions occurs within 3 days or is worsening despite

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Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		of steroid taper (< 10mg prednisone, or equivalent).	– symptomatic treatment and/or use of moderate strength topical steroid, consider discussing with Clinical Study Lead, as needed, and promptly start systemic steroids such as prednisone 1 to 2 mg/kg/day PO or IV equivalent. – Consider skin biopsy if the event persists for >1 week or recurs.
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen until resolution to Grade ≤1 or baseline. If toxicity improves to Grade ≤1 or baseline, then resume drug/study regimen after completion of steroid taper (<10 mg prednisone, or equivalent). **For Grade 4:** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consult dermatology. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – Consider hospitalization. – Monitor extent of rash [Rule of Nines]. – Consider skin biopsy (preferably more than 1) as clinically feasible. Consider, as necessary, discussing with Clinical Study Lead.
Endocrinopathy (e.g., hyperthyroidism, hypothyroidism, Type 1 diabetes mellitus, hypophysitis, hypopituitarism, and adrenal insufficiency)	**Any Grade** (Depending on the type of endocrinopathy, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression including brain metastases, or infections). – Consider consulting an endocrinologist for endocrine events. – Consider discussing with Clinical Study Lead, as needed. – Monitor patients for signs and symptoms of endocrinopathies. (Non-specific symptoms include headache, fatigue, behaviour changes, mental status changes, photophobia, visual field cuts, vertigo, abdominal pain, unusual bowel habits, dipsia, polyuria, hypotension, and weakness.) – Depending on the suspected endocrinopathy, monitor and evaluate thyroid function tests: thyroid stimulating hormone (TSH), free T3 and free T4 and other relevant endocrine and related labs (e.g., blood glucose and ketone levels, hemoglobin A1c (HgA1c)).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. – Investigators should ask subjects with endocrinopathies who may require prolonged or continued hormonal replacement, to consult their

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Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			primary care physicians or endocrinologists about further monitoring and treatment after completion of the study.
	Grade 1	No dose modifications.	**For Grade 1** – Monitor subject 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 T_4; 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 T_4 at subsequent cycles as clinically indicated and consider consultation of an endocrinologist.
	Grade 2, 3, or 4	For Grade 2-4 endocrinopathy <u>other than hypothyroidism and Type 1 diabetes mellitus</u>, consider holding study drug/study regimen dose until subject is clinically stable. Study drug/study regimen can be resumed once patient stabilizes and after completion of steroid taper (<10mg prednisone or equivalent). Patients with endocrinopathies who may require prolonged or continued steroid replacement (e.g., adrenal insufficiency) can be retreated with study drug/study if the patient is clinically stable as per investigator or treating physician's clinical judgement.	**For Grade 2, 3, or 4** – Consult endocrinologist to guide evaluation of endocrine function and, as indicated by suspected endocrinopathy and as clinically indicated, consider pituitary scan. – For all subjects with abnormal endocrine work up, except those with isolated hypothyroidism or T1DM, 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. – Isolated hypothyroidism may be treated with replacement therapy, without study drug/study regimen interruption, and without corticosteroids. – Isolated T1DM may be treated with appropriate diabetic therapy, and without corticosteroids. **Only hold study drug/study regimen in setting of hyperglycemia when diagnostic workup is positive for diabetic ketoacidosis.** – For subjects with normal endocrine workup (laboratory assessment or MRI scans), repeat laboratory assessments/MRI as clinically indicated.
Neurotoxicity	**Any Grade**	**General Guidance**	**For Any Grade:**

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Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
(to include but not limited to non-infectious meningitis, non-infectious encephalitis, and autonomic neuropathy, excluding Myasthenia Gravis and Guillain-Barre)	(Depending on the type of neurotoxicity, refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)		– Patients should be evaluated to rule out any alternative etiology (e.g., disease progression, infections, metabolic syndromes, or medications). – Monitor subject for general symptoms (headache, nausea, vertigo, behavior change, or weakness). – Consider appropriate diagnostic testing (e.g., electromyogram and nerve conduction investigations). – Perform symptomatic treatment with neurological consult as appropriate.
	Grade 1	No dose modifications.	**For Grade 1:** – See "Any Grade" recommendations above.
	Grade 2	For acute motor neuropathies or neurotoxicity, hold study drug/study regimen dose until resolution to Grade ≤1. For sensory neuropathy/neuropathic pain, consider holding study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 2 imAE does not resolve to Grade ≤	**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 2 to 3 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 or other immunosuppressant depending on the specific imAE).
	Grade 3 or 4	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4:** – Consider, as necessary, discussing with Clinical Study Lead. – Obtain neurology consult. – Consider hospitalization. – Promptly initiate empiric IV methylprednisolone 1 to 2 mg/kg/day or equivalent. – If no improvement within 2 to 3 days despite IV corticosteroids, consider additional workup and promptly treat with additional immunosuppressants (e.g., IV IG or other immunosuppressant depending on the specific imAE).
Peripheral neuromotor syndromes (such as Guillain-Barre and myasthenia gravis)	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade:** – The prompt diagnosis of immune-mediated peripheral neuromotor syndromes is important, since certain subjects may unpredictably experience acute decompensations that can result in

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Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			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. – The patient 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 subjects with underlying cancer, due to the multiple potential confounding effects of cancer (and its treatments) throughout the neuraxis. Given the importance of prompt and accurate diagnosis, it is essential to have a low threshold to obtain a neurological consult. – Neurophysiologic diagnostic testing (e.g., electromyogram and nerve conduction investigations, and "repetitive stimulation" if myasthenia is suspected) are routinely indicated upon suspicion of such conditions and may be best facilitated by means of a neurology consultation. – **It is important to consider that the use of steroids as the primary treatment of Guillain-Barre is not typically considered effective. Patients requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.**
	Grade 1	No dose modifications.	**For Grade 1:** – Consider, as necessary, discussing with the study physician. – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above. – Consult a neurologist.
	Grade 2	Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if it does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory insufficiency or autonomic instability.	**For Grade 2:** – Consult a neurologist. – Consider discussing with the Clinical Study Lead, as needed. – Care should be taken to monitor subjects for sentinel symptoms of a potential decompensation as described above. – Sensory neuropathy/neuropathic pain may be managed by appropriate medications (e.g., gabapentin or duloxetine).

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Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			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 subject. 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. o Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants). *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	**For Grade 3 or 4** Permanently discontinue study drug/study regimen.	**For Grade 3 or 4 (severe or life-threatening events):** – Consider, as necessary, discussing with Clincal Study Lead, as needed. – Recommend hospitalization. – Monitor symptoms and obtain neurological 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 Subjects unable to tolerate steroids

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Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			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. o Avoid medications that can worsen myasthenia gravis (e.g. some antibiotics, beta blockers, calcium channel blockers, muscle relaxants). *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 Subjects requiring treatment should be started with IV IG and followed by plasmapheresis if not responsive to IV IG.
Myocarditis	**Any Grade** **(Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)**	**General Guidance** Discontinue drug permanently if biopsy-proven immune-mediated myocarditis.	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections) – The prompt diagnosis of immune-mediated myocarditis is important, particularly in patients with baseline cardiopulmonary disease and reduced cardiac function. – Consider discussing with the Clinical Study Lead, as needed. – 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). Consult a cardiologist early, to promptly assess whether and when to complete a cardiac biopsy, including any other diagnostic procedures. Initial work-up should include clinical evaluation, B-type natriuretic peptide (BNP), cardiac enzymes, electrocardiogram (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.

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Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
	Grade 2, 3 or 4	If Grade 2-4, 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 2 to 3 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 IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines. **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab. Infliximab is contraindicated for patients who have heart failure.**
Myositis/Polymyositis ("Poly/myositis")	**Any Grade** (Refer to NCI CTCAE applicable version in study protocol for defining the CTCAE grade/severity)	**General Guidance**	**For Any Grade:** – Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, other medications, or infections). – 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 Clinical Study Lead. – Initial work-up should include clinical evaluation, creatine kinase, aldolase, lactate dehydrogenase (LDH), blood urea nitrogen (BUN)/creatinine, erythrocyte sedimentation rate or C-reactive protein (CRP) 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,

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Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
			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.
	Grade 1	- 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	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 2 to 3 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 2 to 3 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.**
	Grade 3 or 4	**For Grade 3:** Hold study drug/study regimen dose until resolution to Grade ≤1. Permanently discontinue study drug/study regimen if Grade 3 imAE does not resolve to Grade ≤1 within 30 days or if there are signs of respiratory	**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 Clinical Study Lead. – Promptly start IV methylprednisolone 2 to 4 mg/kg/day systemic steroids along with

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Adverse Events	Severity Grade of the Event	Dose Modifications	Toxicity Management
		insufficiency. **For Grade 4:** - Permanently discontinue study drug/study regimen.	receiving input from Neurology consultant. – If after start of IV methylprednisolone at 2 to 4 mg/kg/day there is no improvement within 2 to 3 days, consider start of immunosuppressive therapy such as TNF inhibitors (e.g., infliximab at 5 mg/kg IV, may be repeated at 2 and 6 weeks after initial dose at the discretion of the treating provider or relevant practice guidelines). **Caution: It is important to rule out sepsis and refer to infliximab label for general guidance before using infliximab.** – Consider whether subject may require IV IG, plasmapheresis.

Infusion-Related Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	General Guidance	**For Any Grade:** – Manage per institutional standard at the discretion of investigator. – Monitor subjects for signs and symptoms of infusion-related reactions (e.g., fever and/or shaking chills, flushing and/or itching, alterations in heart rate and blood pressure, dyspnea or chest discomfort, 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.

Non–Immune-Mediated Reactions

Severity Grade of the Event (NCI CTCAE version 4.03)	Dose Modifications	Toxicity Management
Any Grade	Note: Dose modifications are not required for AEs not deemed to be related to study treatment (i.e., events due to underlying disease) or for laboratory abnormalities not deemed to be clinically significant.	Treat accordingly, as per institutional standard.
Grade 1	No dose modifications.	Treat accordingly, as per institutional standard.
Grade 2	Hold study drug/study regimen until resolution to ≤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.