A phase II trial of carboplatin, paclitaxel, and nivolumab induction therapy followed by response-stratified locoregional therapy for patients with locally advanced, HPV-negative head and neck cancer. The DEPEND Trial.

DEPEND – **D**e-**E**scalation Therapy for Human **P**apillomavirus **N**egative **D**isease

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This study is being conducted by institutional members of the Personalized Cancer Care Consortium (PCCC), as well as additional sites.

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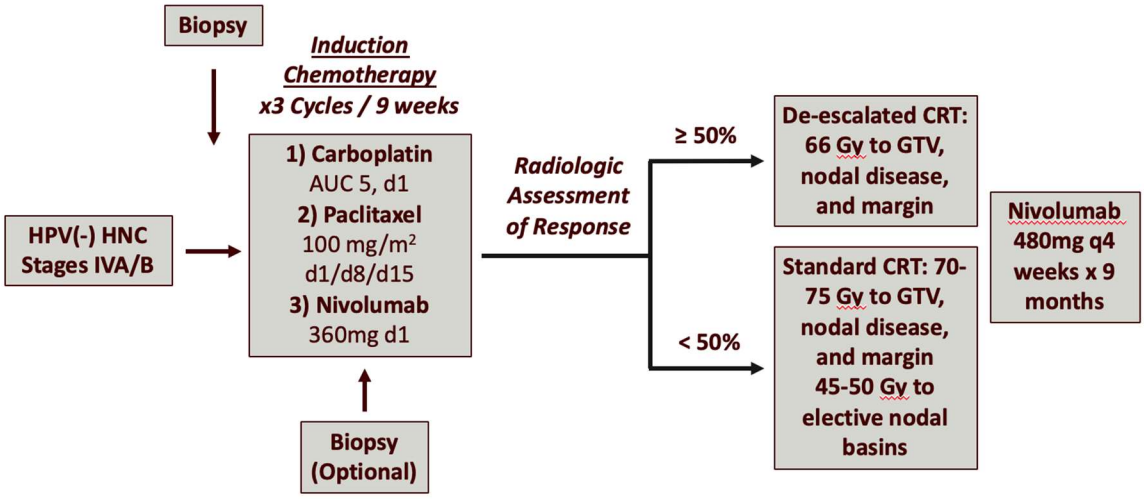
1 PROTOCOL SCHEMA

1.1 Trial Schema



2 OBJECTIVES

2.1 Primary Objective

- To intensify induction chemotherapy with the addition of an immune checkpoint inhibitor aimed at increasing the proportion of patients achieving a deep tumor response in order to subsequently allow risk-adapted definitive chemoradiotherapy in advanced stage HPV negative head and neck squamous cell cancer patients.
    - Endpoint: The proportion of patients who achieve a deep response rate (50% or greater response per RECIST v1.1 criteria) after induction chemoimmunotherapy

2.2 Secondary Objectives

- Assess survival outcomes in all patients receiving induction chemoimmunotherapy and compare survival between radiation arms.
    - Endpoints
        - Progression free survival at 24 months after completing chemoradiation
        - Overall survival at 24 months after completing chemoradiation
- Assess disease control in all patients receiving induction chemoimmunotherapy and compare disease control between radiation arms.
    - Endpoints

- Locoregional control at 24 months after completing chemoradiation
- Distant control at 24 months after completing chemoradiation

2.3 Exploratory Objectives

- Assess long-term/late toxicities including enteral tube dependence in all patients receiving induction chemoimmunotherapy.
  - Endpoints
    - Acute and late toxicity as assessed by CTCAE v5.0 measured during treatment and at 1 month, 3 months, and 1-year post-chemoradiation
    - Enteral tube dependency at 3 months and 1-year post-chemoradiation
- Assess acute and long-term toxicity in patients who received risk-adapted chemoradiotherapy after deep response to induction chemoimmunotherapy.
  - Endpoints
    - Acute and late toxicity as assessed by CTCAE v5.0 measured during treatment and at 1 month, 3 months, and 1-year post-chemoradiation
    - Enteral tube dependency at 3 months and 1-year post-chemoradiation
- Evaluate quality of life in patients who receive dose-reduced chemoradiotherapy after a deep response to induction therapy.
- Interrogate and understand the immune micro-environment at baseline and 2-3 weeks into induction therapy with extensive immunohistological and serum biomarkers.

3 BACKGROUND AND RATIONALE

3.1 Locally Advanced Head and Neck Cancer

Approximately 50,000 new cases of head and neck cancer are diagnosed annually in the United States.[1] The majority (90-95%) of these cases are squamous cell carcinomas of the head and neck and approximately two-thirds are locoregionally advanced cancers (AJCC stage III-IV). Despite advances over the past two decades, these patients still experience significant morbidity and mortality.

Historically, locoregionally advanced tumors were treated with surgery, radiation therapy, or both. Locoregional failure rates were approximately 30% at 2 years and locoregional failures accounted for nearly 60% of failures. Survival at 5 years was reported to be only 40%. Approximately 20% of patients developed metastatic disease and nearly one-fifth of these patients died of distant metastases without evidence of locoregional recurrence.[2-4]

3.2 Chemoradiotherapy

Given the discouraging outcomes with surgery and radiation, investigators became increasingly interested in the incorporation of chemotherapy for the treatment of locally advanced HNSCC. The feasibility of a non-surgical, organ preservation approach with concomitant chemoradiation was first established by the landmark Veterans Affairs Laryngeal Cancer Study.[5] Since then, several randomized trials and meta-analyses have demonstrated improved disease-free and/or overall survival with concomitant chemoradiotherapy and confirmed its role as standard therapy for patients with locoregionally advanced unresectable disease.[6-11] The positive effects of disease-free and overall survival seem to be predominantly mediated through improved locoregional control, thus affecting the traditionally predominant pattern of failure for this disease.

Concurrent chemoradiotherapy attempts to capitalize on both the radiosensitizing properties of chemotherapy at sites of known disease targeted by radiation in addition to delivering agents that function systemically to treat occult metastatic disease. However, sensitizing effects are not tumor specific and exert both locoregional effects on adjacent normal tissues within the radiation field as well as systemic effects, particularly on the bone marrow and peripheral nervous system. Concurrent chemoradiotherapy trials have consistently reported an increased incidence of acute grade 3 and 4 toxic effects, with mucositis, dermatitis, and cytopenias being the most prominent.[12] The rise creates concern about chronic toxic effects, including consequential late effects, which evolve from persistent severe acute toxic effects.

Optimizing the therapeutic ratio of treatment benefit to toxicity has thus become a focus of recent investigation. Advances in the delivery of conformal radiation, including the development of intensity modulated radiation therapy (IMRT), have allowed significant improvements in sparing normal tissue structures. This is best exemplified by the reduction in rates of xerostomia with sparing of the parotid glands.[13] However, other treatment-related morbidities such as dysphagia are still problematic. Rates of feeding tube dependence at 1 year in the 3D-confromal era have been reported to be approximately 25%.[14] This is particularly significant given recent data that quality of life among patients with HNSCC treated with radiotherapy is substantially affected by swallowing dysfunction and the need for enteral nutrition support.[15] In the IMRT-era, efforts have been focused on decreasing the dose of radiation to dysphagia-related structures, particularly the pharyngeal constrictors, which are prone to structure formation with doses $\geq$ 50 Gy.[16] Single-institution reports of treatment of oropharyngeal cancer in the IMRT-era demonstrated long-term feeding tube dependence rates of approximately 5-10%.[17]

3.3 CRT Platforms: Concurrent Cisplatin-Radiation or TFHX

Chemoradiotherapy with concurrent bolus cisplatin (100 mg/m^2 delivered q3 weeks) and conventionally fractionated radiotherapy remains the commonly accepted standard of care for the treatment of locally advanced HNSCC. The randomized Head and Neck Intergroup

trial and RTOG 91-11 demonstrated improved locoregional control and prolonged survival with concomitant chemoradiotherapy with every-3-weeks cisplatin in unresectable locally advance HNSCC.[18,19]

At the University of Chicago, we have investigated multiple intensive concomitant chemoradiotherapy regimens. We initially studied the interaction of 5-FU, hydroxyurea, and radiotherapy (FHX).[20,21] Both chemotherapy agents have shown systemic activity and have been shown to act as radiation enhancers in vitro and in vivo.[22,23] Cytotoxic activity is synergistic as hydroxyurea modulates the activity of 5-FU by depleting cellular pools of deoxyuridine monophosphate (dUMP) and facilitating the binding of the 5-FU metabolite, 5-FdUMP, to its target enzyme thymidylate synthase.[24] Paclitaxel was subsequently added to the FHX regimen (TFHX) and the radiation scheme changed to twice daily to further intensify the treatment.[25-28]

The TFHX regimen was demonstrated to be a highly active and tolerable concomitant chemotherapy and hyperfractionated radiation regimen: overall survival and locoregional control rates at 3 years were 60% and 86%, respectively.[27,29] Since surgery was used primarily as a salvage procedure, excellent organ preservation was also achieved. Acute toxicities were severe in a majority of patients but were considered tolerable overall. Mucositis (84% grade 3+), "in-field" dermatitis (38% grade 3+), leukopenia (34% grade 3+), and anemia (22% required transfusion) were the most common side effects. At 1-year post-treatment, 61% of patients had severe xerostomia and 47% had compromised swallowing; the rate of feeding tube dependence was 20%.

In an attempt to decrease the toxicity of concomitant chemoradiation, we conducted prospective investigations into reducing the radiation dose in sequential cohorts to areas at risk for microscopic disease.[30,31] The cohort receiving 75 Gy to gross disease (high risk), 54 Gy to intermediate-risk volumes, and 39 Gy to low-risk volumes experienced the best therapeutic ratio. Again, high locoregional and distant control rates were seen, though the rate of dermatitis (45%) was significantly lower.

With improved locoregional control, the systemic control of micrometastatic disease emerged as an important goal that was not achieved optimally with the chemotherapy doses applied during concomitant chemoradiotherapy. Indeed, approximately 20% of patients were noted to recur distantly, despite the addition of cytotoxic chemotherapy to radiation therapy as part of the TFHX regimen.

3.4 Induction Chemotherapy

On the basis of the aforementioned studies, induction chemotherapy was investigated as a method of successfully eradicating micrometastatic disease. At the University of Chicago, carboplatin and paclitaxel were initially chosen as an induction chemotherapy regimen because they are typically well-tolerated with low rates of mucositis. The first report of

this regimen demonstrated both high locoregional control and improved distant control.[32] Systemic disease progression was noted in 7% of patients; this translated into improved 3-year progression-free and overall survival rates of 80% and 77%, respectively.

Currently, the triplet combination of a taxane (docetaxel or paclitaxel), cisplatin, and 5-FU (TPF) is considered one standard induction regimen (if induction therapy is considered). This is largely based on the results of a meta-analysis demonstrating a 5% increase in survival for cohorts using a cisplatin/5-FU combination and published phase III trials demonstrating the superiority of induction docetaxel, cisplatin, and 5-FU over cisplatin and 5-FU when followed by radiotherapy or chemoradiotherapy.[10,33-35]

Controversy still exists regarding the overall survival benefit of adding induction TPF to chemoradiotherapy. Recent studies demonstrating no additional survival benefit are limited by methodological deficiencies.[36-38] Additionally, recent data demonstrate that TPF and carboplatin/paclitaxel seem to have equivalent activity while the latter platform is associated with decreased toxicity.[39] Two studies evaluating carboplatin/paclitaxel induction demonstrated 82% and 87% response rates compared to our DeCIDE trial 64% response to TPF.[31,32,36]

3.5 Response-Adapted Volume De-Escalation (RAVD)

It has been shown that patients with favorable response to induction therapy have superior prognosis and are less likely to experience locoregional failure after definitive chemoradiation.[30] Strategies to decrease the late toxicity associated with chemoradiation have focused on radiotherapy dose reduction and constraints for organs at risk. It has also been shown that the majority of locoregional failures after CRT are “in-field” and occur within the highest-risk radiation treatment volume.[40]

Conventional head and neck radiation elective nodal volumes are based on historic surgical data regarding the risk of occult lymph node involvement. Several series have investigated decreasing elective nodal radiation coverage. For patients with limited tonsillar cancer, elimination of contralateral elective neck radiation has shown to be feasible.[41] Additionally, it has recently been shown that elimination of elective radiation to the retropharyngeal and high level II lymph nodes in the contralateral uninvolved neck is feasible and results in decreased toxicity.[42] In our RAVD trial, we utilized radically reduced radiation volumes entirely omitting elective nodal coverage in good responders to induction and significantly decreasing coverage in non-responders.[43]

3.6 Nivolumab/Anti-PD-1

Nivolumab is a fully humanized, IgG4 (kappa) isotype monoclonal antibody that binds the programmed death receptor-1 (PD-1). PD-1 is a transmembrane protein primarily found expressed on activated immune cells. In its usual function, the binding of PD-1 to its

ligand PD-L1 and PD-L2 inhibits T-cell proliferation and activation. Upregulation of PD-1 ligands can occur in tumors and is thought to serve as a means of immune evasion by the tumor.[44] Nivolumab blocks the interaction of the PD-1 T-cell receptor with its ligands, potentially enabling the reactivation of immunosurveillance and cancer eradication.

Nivolumab is currently approved for head and neck cancer based on the results of the CheckMate 141 study.[45] In this phase III randomized trial, eligibility criteria included recurrent/metastatic HNSCC of the oral cavity, pharynx, or larynx with progression on or within 6 months of the last dose of platinum-based therapy (irrespective of number of prior lines of therapy or PD-L1 status). Patients were randomized to receive nivolumab (3 mg/kg IV q 2 weeks) versus investigator's choice of therapy. Median overall survival was 7.5 months for nivolumab versus 5.1 months for investigator's choice therapy (HR 0.70, p = 0.01). The 1-year overall survival rate was 36.0% for nivolumab versus 16.6% for investigator's choice. The objective response rate with nivolumab was 13.3% (2.5% complete, 10.8% partial). Overall, nivolumab was well-tolerated with 3.8% of patients not continuing treatment due to study drug toxicity and 13.1% of patients experiencing any treatment-related grade 3-4 adverse event. The most common grade 3-4 treatment related adverse events were fatigue (2.1%), anemia (1.3%), and asthenia (0.4%).

3.7 Study Rationale

At the University of Chicago, we have demonstrated the ability to de-escalate therapy for patients with HPV-positive oropharyngeal HNSCC. Patients with response to induction chemotherapy received modified radiation doses based off the depth of response. In doing so, we demonstrated reduced toxicities and excellent outcomes while delivering nearly one-third lower total dose of radiation therapy.[46] To build on this promising data, our follow up trial added nivolumab to the induction regimen with the intention of improving deep response rates allowing more patients to receive de-escalated therapy.

While a majority of oropharyngeal cancers are HPV-related, the remainder of head and neck cancers are typically not. Much of the historical data in HPV negative disease has investigated how to safely perform treatment intensification since about 30% of these patients will have recurrence. In order to accomplish this goal, many trials have tested the role of altered fractionation including hyperfractionation and accelerated fractionation.[47,48] While these trials have formed a strong foundation for the current standard of care for HPV negative HNSCC, treatment-related toxicity is a potential drawback to such aggressive management. As discussed earlier, we have studied the use of induction therapy to stratify patients who may be better or worse candidates for smaller radiation fields as one approach to de-escalated therapy. Patients with a response to induction did not require elective nodal coverage which was associated with similar oncologic outcomes and an improved toxicity profile.[43]

Increasing the response rate to induction therapy is an important endpoint in order to increase the proportion of patients who qualify for de-intensified locoregional therapy and extend this concept from HPV+ disease to carcinogen-induced head and neck cancer. With the addition of nivolumab to the induction chemotherapy regimen, we hope to increase this response rate as demonstrated in squamous cell lung cancer.[49] Chemotherapy leads to tumor lysis and release of tumor antigens, which may prime the immune system for checkpoint inhibitors.

Given the above, we hypothesize that the addition of a checkpoint inhibitor to induction chemotherapy will increase the response rate to induction therapy, and therefore increase the proportion of patients who may qualify for de-escalated locoregional therapy.

In this study, we propose adding nivolumab to induction carboplatin and paclitaxel to increase deep response rate and hence, de-intensify definitive chemoradiation for patients with non-metastatic, locally advanced HPV negative HNSCC. The ability to obtain deep responses with induction chemotherapy may be particularly meaningful for such patients and holds immediate potential to translate into more effective and less toxic definitive locoregional therapy. In particular, de-escalation of locoregional radiation therapy may be associated with improved quality of life, decreased enteral tube dependence, and improved swallowing function.

As an institution, we have had great success treating HPV negative head and neck cancer, but despite a high cure rate, many patients suffer from debilitating long-term side effects 5-10 years after completing therapy. The therapy approach proposed in this trial has already generated encouraging results in HPV positive disease, extending this treatment paradigm to HPV negative disease represents a natural progression for advancement of oncological care.

4 PATIENT SELECTION

4.1 Eligibility Criteria

1) Patients must have pathologically confirmed locally advanced, non-metastatic, HPV-negative head and neck squamous cell carcinoma of the oral cavity, oropharynx, hypopharynx, nasopharynx, larynx, or sinuses.
2) Stage IV disease with the exception of nasopharyngeal T3N2 (stage III) based of AJCC staging 8th edition.
3) If a primary oropharyngeal squamous cell carcinoma is diagnosed, HPV must be ruled out by immunohistochemistry.
4) Availability of ≥10 unstained 5 micron slides (to be provided to HTRC at the University of Chicago). Patients who cannot fulfill this requirement will need to undergo a new biopsy prior to enrollment on study.

5) Patients must be at least 18 years of age.
6) Measurable disease (either primary site and/or nodal disease) by RECIST 1.1 criteria.
7) No previous radiation or chemotherapy for a head and neck cancer.
8) No complete surgical resection for a head and neck cancer within 8 weeks of enrollment (although lymph node biopsy including excision of an individual node with presence of residual nodal disease, or surgical biopsy/excision of the tumor with residual measurable disease is acceptable.) No surgical procedures or biopsies will occur after baseline scans are performed and measurable lesions are identified.
9) ECOG performance status 0-1
10) Normal Organ Function
    a. Leukocytes $\geq 3000/mm^3$
    b. Platelets $\geq 100{,}000/mm^3$
    c. Absolute neutrophil count $\geq 1{,}500$
    d. Hemoglobin ≥ 9.0 gm/dL
    e. AST and ALT ≤ 2.5x upper limit of normal
    f. Alkaline phosphatase ≤ 2.5x upper limit of normal
    g. Albumin > 2.9 gm/dL
    h. Total bilirubin ≤ 1.5 mg/dL
    i. Creatinine clearance > 45 mL/min, normal within 2 weeks prior to start of treatment (Of note, the standard Cockcroft and Gault formula must be used to calculate CrCl for enrollment or dosing)
11) Patients must sign a study-specific informed consent form prior to study entry. Patients should have the ability to understand and the willingness to sign a written informed consent document.
12) Women of childbearing potential must have a negative serum or urine pregnancy test (minimum sensitivity 25 IU/L or equivalent units of HCG) within 24 hours prior to the start of study drug
13) Women must not be breastfeeding
14) Women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 months after completing chemoradiation or receiving the last dose of consolidative nivolumab, whichever occurs latest.
15) Men who are sexually active with women of childbearing potential must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 7 months after completing chemoradiation or receiving the last dose of consolidative nivolumab, whichever occurs latest.

4.2 Exclusion Criteria

1) Unequivocal demonstration of distant metastatic disease (M1 disease).
2) Unidentifiable primary site.

3) Intercurrent medical illnesses which would impair patient tolerance to therapy or limit survival. This includes but is not limited to ongoing or active infection, immunodeficiency, symptomatic congestive heart failure, pulmonary dysfunction, cardiomyopathy, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance. Patients with clinically stable and/or chronically managed medical illnesses that are not symptomatic and/or are not expected to impact treatment on protocol are still eligible (conditions to be reviewed by the PI to confirm eligibility).
4) Prior surgical therapy other than incisional/excisional biopsy or organ-sparing procedures such as debulking of airway-compromising tumors. Residual measurable tumor is required for enrollment as discussed above.
5) Patients receiving other investigational agents.
6) Diagnosis of immunodeficiency or is receiving systemic steroid therapy in excess of physiologic dose or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment.
7) Known history of active tuberculosis (Bacillus Tuberculosis infection).
8) Hypersensitivity to nivolumab or any other drug used in this protocol.
9) Prior systemic anti-cancer treatment within the last 8 weeks.
10) Has a known additional malignancy that is progressing or requires active treatment. Exceptions include basal cell carcinoma of the skin or squamous cell carcinoma of the skin that has undergone potentially curative therapy or in situ cervical cancer or any tumors that are not likely to influence life expectancy in the subsequent 3 years without active treatment.
11) Has active autoimmune disease that has required systemic therapy in the past year (i.e. with steroids or immunosuppressive drugs). Replacement therapy e.g. levothyroxine, insulin, or physiologic corticosteroid doses for adrenal or pituitary insufficiency, etc. are not considered a form of systemic treatment.
12) Has known history of, or any evidence of active, non-infectious pneumonitis.
13) Has a history of HIV.
14) Has known active Hepatitis B or hepatitis C. If eradicated, patient is eligible.
15) Has received a live vaccine within 28 days of planned start of study therapy.

4.3 Pregnancy Prevention

Investigators shall counsel women of child-bearing potential (WOCBP) and male patients who are sexually active with WOCBP on the importance of pregnancy prevention and the implications of an unexpected pregnancy. Investigators shall advise WOCBP and male patients who are sexually active with WOCBP on the use of highly effective methods of contraception. Highly effective methods of contraception have a failure rate of <1% when used consistently and correctly.

At a minimum, patients must agree to the use of one method of highly effective contraception as listed below. In addition, male patients are expected to use a condom as noted in the list below.

Highly effective methods of contraception include:

- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs)
- Non-hormonal IUDs
- Bilateral tubal ligation
- Vasectomized partner
- Complete abstinence which is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs.

WOCBP must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the patient chooses to forego complete abstinence. Patients are encouraged to use two methods of contraception, with one method being highly effective and the other being either highly effective or less effective as listed below.

Less effective methods of contraception include:

- Diaphragm with spermicide
- Male condoms and spermicide
- Male condom without spermicide
- Female condom – A male and female condom must not be used together

Unacceptable methods of contraception include:

- Vaginal sponge
- Progestin only pills
- Cervical cap with spermicide
- Periodic abstinence (calendar, sympthothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method

5 REGISTRATION PROCEDURES

5.1 General Guidelines

Prior to registration and any study-specific evaluations being performed, all patients must have given written informed consent for the study and must have completed the pre-

treatment evaluations. Patients must meet all of the eligibility requirements listed in Section 4. Eligible patients will be entered on study centrally by the University of Chicago study coordinator. All sites should email PhaseIICRA@medicine.bsd.uchicago.edu to verify availability of a slot.

5.2 Registration Process

When a potential patient has been identified, notify the CRC via email at phaseIIcra@medicine.bsd.uchicago.edu to ensure a reservation on the study. Reservations for potential subjects will only be held for subjects who have signed consent for that particular study.

When registering a subject, the following must occur:

- Confirm that the institution has a current IRB approval letter for the correct version of protocol/consent and has an annual update on file, if appropriate.
- Submit all required materials (Eligibility Checklist, Source documentation, & signed consent form) to confirm eligibility and required pre-study procedures to the CRC a minimum of 48 hours prior to the subject's scheduled therapy start date.
- Source documentation includes copies of all original documents that support each inclusion/exclusion criteria. The eligibility checklist does not serve as source documentation but rather as a checklist that original source documentation exists for each criterion.
- Communicate with the CRC to ensure all necessary supporting source documents are received and the potential subject is eligible to start treatment on schedule. If there are questions about eligibility, the CRA will discuss it with the PI. PI may clarify, but not overturn, eligibility criteria.
- Affiliate sites must confirm registration of subjects by obtaining a subject study ID number from the CRC via phone, fax or email.
- If a subject does not start on the scheduled day 1 treatment date, promptly inform the CRC as the delay in start may deem the subject ineligible and/or require further or repeat testing to ensure eligibility.
- The date the patient is randomized if randomization is involved or receives treatment for the first time will be considered the patient's "OnStudy Date." The patient's subject ID will be assigned and a confirmation of registration will be issued by the CRC on this date. Subjects that sign consent and do not go "OnStudy" will be recorded in the database with the date they signed consent and the reason for not going "OnStudy" (e.g., Ineligible, Screen Failure or Withdrawn Consent).

6 TREATMENT PLAN

6.1 General Considerations

Induction chemoimmunotherapy will be administered on an outpatient basis. Chemoradiotherapy may be administered on an inpatient basis (using the TFHX regimen) or outpatient basis (with cisplatin). Patients receiving consolidative nivolumab will receive this on an outpatient basis. All patients will be evaluated by surgical, medical, and radiation oncologists prior to trial entry to determine optimal local treatment. Patients will start induction chemoimmunotherapy within 2 weeks of signing consent. Three cycles of carboplatin, paclitaxel, and nivolumab induction chemoimmunotherapy will be followed by response-adjusted locoregional control. In no case should the three cycles of induction chemotherapy be given over a period exceeding 12 weeks. As we have had extensive experience with this regimen in our HPV-positive de-escalation trials, we do not anticipate significant delays in chemoradiation.

Patients in the de-escalated cohort will undergo de-escalated chemoradiation with a total of 66 Gy to the gross tumor volume, nodal disease, and margins. Patients in the standard arm will receive chemoradiation to a total of 70-75 Gy to the gross tumor volume, nodal disease, and margin in addition to 45-50 Gy to elective nodal basins. Patients will have a pre-induction chemotherapy CT simulation performed. Chemoradiation should be initiated within 10 days of the last dose of paclitaxel during the induction regimen, and no later than 14 days. Chemoradiation should be initiated no later than 13 weeks after the first dose of induction therapy (12 weeks, as above, plus 1 week to recover from any potential toxicity). Discontinuation of this trial will occur if excessive toxicity leads to delays in definitive chemoradiation. Delays will be defined as starting chemoradiation >13 weeks after receiving the first dose of induction therapy or >14 days after completing the last dose of induction therapy. Excessive toxicity leading to delays to definitive treatment with concurrent chemoradiation will be based on continuous assessment after the fifth patient has been enrolled. If >30% of patients experience a delay in definitive chemoradiation, the trial will be halted (as an example, a table has been provided for the first 10 patients below). Consolidative nivolumab will be offered to all patients for 9 months on an outpatient basis.

Number of Patients Starting Induction Therapy	Number of Patients Experiencing Delay to Definitive CRT	Further Enrollment
5	2	Halt
6	2	Halt
7	3	Halt
8	3	Halt
9	4	Halt

10	4	Halt

6.2 Pre-treatment evaluation

Patient must have completed the following within 4 weeks of starting therapy unless noted (also see study calendar in section 10 for additional details):

- Inclusion and exclusion criteria reviewed.
- Physical examination including examination by a head and neck surgeon
- Pan-endoscopy with biopsy, tumor mapping, and documentation (if clinically indicated per assessment at the multidisciplinary tumor board)
- Biopsy proven squamous cell carcinoma.
- Baseline diagnostic CT or MRI scan of the head and neck.
- CT chest that includes entire disease extent within 1 month before initiating therapy. CT chest only required if PET/CT not performed.
- Multidisciplinary team recommendation to proceed with induction therapy.
- PET/CT is recommended but not required prior to start of induction chemoimmunotherapy.
- One week prior to chemoimmunotherapy - CBC with differential and platelet count, and complete metabolic profile.
- Ultrasound or CT imaging of the liver if chemistries (SGOT, SGPT, and bilirubin) are above upper limit of normal.
- Additional studies (bone scan, barium swallow, etc.) to exclude distant metastases or second primaries as clinically indicated.
- Complete dental evaluation before or during induction therapy, unless not clinically indicated and waiver approved by PI. If indicated, this must be completed prior to starting chemoradiation.
- Speech and swallowing consultation before or during induction therapy. This must be completed prior to starting chemoradiation.
- Blood draws for basic labs and study labs including cell free DNA
- Refer to section 10 for a complete list of required baseline evaluations.

6.3 Study Evaluations

Patients will have the following exams and tests throughout the study as specified time points (please see study chart in section 10):

- Physical examination
- Performance status evaluation
- CBC with differential and platelet count
- Complete metabolic panel
- Study blood draws including cell free DNA
- Toxicity and quality of life evaluations

- Optional second biopsy of original biopsy site around cycle 2, day 8 of induction therapy
- Repeat imaging of the head and neck (CT or MRI; generally the same modality as pre-treatment imaging) on or within 10 days of cycle 3 day 15 for stratification of locoregional therapy.
- Recommended PET/CT between the completion of induction therapy and the beginning of definitive chemoradiation.
- Follow up imaging of head and neck (CT or MRI) with re-staging PET/CT at 12 weeks post-chemoradiation.
- Option for neck dissection and organ-preserving surgery at the primary site after 3 cycles of induction chemoimmunotherapy will be allowed if it allows for a reduction in radiotherapy field size.

6.4 Induction Chemotherapy Details and Guidelines

Induction chemotherapy will be administered on an outpatient basis. Expected adverse events (AEs) and appropriate dose modifications for these agents are described in section 7. No other investigational agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

Carboplatin, paclitaxel, and nivolumab combination will be administered for three cycles of three weeks duration each. Dose delays and dose modifications should take place as outlined in section 7. In no case should the three cycles of induction chemotherapy be given over a period exceeding twelve weeks.

- Nivolumab: 360 mg flat dose on day 1; every 21 days (3 doses)
- Paclitaxel: 100 mg/m^2 on days 1, 8, and 15 (9 doses total)
- Carboplatin: AUC 5 on day 1 (3 doses total). A baseline creatinine level should be drawn within 1 week prior to starting chemotherapy.
- Anti-emetics: Pre-treatment with a 5 HT-3 antagonist prior to chemotherapy on day 1 is recommended. The use of additional anti-emetics and the prevention of delayed emesis are left to the discretion of the treating investigator. Dexamethasone/steroids as anti-emetic therapy should be avoided, and only should be given after discussion with the study PI.
- Hydration: Hydration is left to the discretion of the treating physician.
- For each cycle: Filgrastim can be given on days 16, 17, and 18 if clinically indicated. This can also be increased or decreased as clinically indicated.

6.5 Definitive Chemoradiation Details and Guidelines

6.5.1 Response Stratified Grouping

Response and extent of response will be assessed during treatment week 9 (during cycle 3), and depending on extent of response:

- If <50% reduction decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters according to RECIST v1.1:
    - Standard chemoradiotherapy with paclitaxel, 5-FU, hydroxyurea and hyperfractionated, accelerated radiotherapy to 75 Gy encompassing GTV of primary and nodal disease as well as elective prophylactic nodal irradiation. OR
    - Standard chemoradiotherapy with cisplatin and radiotherapy to 70 Gy encompassing GTV of primary and nodal disease as well as elective prophylactic nodal irradiation
- If ≥ 50% reduction decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters according to RECIST v1.1:
    - De-escalated chemoradiotherapy with paclitaxel, 5-FU, hydroxyurea and hyperfractionated, accelerated radiotherapy to 66 Gy encompassing GTV of primary and nodal disease without elective prophylactic nodal irradiation. OR
    - De-escalated chemoradiotherapy with cisplatin and radiotherapy to 66 Gy encompassing GTV of primary and nodal disease without elective prophylactic nodal irradiation.
- Any patient who has progressive disease will receive CRT to 75 Gy on the TFHX platform (5 cycles).

Expected adverse events and appropriate dose modifications for carboplatin, paclitaxel, nivolumab, and radiation are described in section 7.1 and 7.2.

6.5.2 Concurrent Cisplatin-Radiation

Cisplatin will be given on an every-3-weeks basis at a dose of 100 mg/m^2 IV over 3-4 hours day 1 (or 2), 22 (or 23), and day 43 (or 44). Mannitol should be given to decrease risk of toxicity if clinically appropriate. Radiation therapy is administered once daily at 2 Gy per fraction.

6.5.3 TFHX Regimen

Patients received de-escalated or standard CRT will receive chemoradiation for 4.5-5 cycles (8.5-9 weeks) and chemotherapy should be administered during all weeks of radiotherapy except during the last week of radiation for patients receiving de-escalated CRT.

<u>Day 0</u>
PM: Start hydroxyurea at 500 mg PO q12 hours x 6 days (11 doses). The first daily dose of hydroxyurea on days 1-5 is given 2 hours prior to the first fraction of daily radiotherapy.
6:00 PM: Start continuous infusion of 5-FU at 600 mg/m^2/day x 5 days (120 hours).

Days 1-5
Dexamethasone 20 mg PO (IV) in morning day 1, 1 hour prior to paclitaxel
Famotidine 20 mg PO (IV) in morning day 1, 1 hour prior to paclitaxel
Diphenhydramine 50 mg PO (IV) in morning day 1, 30 minutes prior to paclitaxel

Start paclitaxel 100 mg/m^2 after first RT fraction on day 1 of each cycle with exception for the last half cycle for patients receiving de-escalated CRT. Paclitaxel should be administered in 250 mL 0.95 NaCl over 60 minutes.

Radiation therapy is administered twice daily at 1.5 Gy per fraction.

Days 6-13
No chemoradiotherapy. Patients should be seen once on an outpatient basis during these non-treatment days to monitor for toxicity.

For each cycle
Administer 5 micrograms/kg subcutaneously (SQ) of G-CSF (filgrastim) daily, beginning on day 6 through 12 at a minimum of 24 hours after completion of 5-FU in patients who develop grade 3 neutropenia or who have grade 2+ neutropenia on Day 0 of any cycle. In these patients, G-CSF should be utilized in all subsequent cycles. G-CSF can be utilized prophylactically from the start of chemoradiotherapy in all cycles at the discretion of the treating physician.

Chemoradiotherapy cycles are repeated every 14 days until the completion of radiotherapy. If patients are on the de-escalated cohort, the final half cycle of TFHX will be completed without chemotherapy.

6.5.4 Radiation Therapy Guidelines

1. When indicated, all patients will have a complete dental evaluation prior to the start of radiation therapy, ideally prior to the start of chemotherapy.

2. Treatment approaches will use intensity-modulated radiotherapy (IMRT) or volumetric-modulated arc therapy (VMAT) and, in selected cases, 3D conformal radiotherapy will be used alone or in combination with IMRT/VMAT. In both instances, the physician will attempt to deliver an even dose to the target tissue and minimize doses to surrounding normal structures. The use of customized blocks or multileaf collimation for field shaping is strongly recommended.

3. Localization requirements: All patients will be immobilized and simulated in the treatment position prior to the start of induction chemotherapy and after induction chemotherapy within 1-2 weeks after the last cycle of chemotherapy. A contrast-enhanced

CT simulation scan (or PET-CT simulation scan) with immobilization is required for planning. Slice thickness should be optimally 3 mm and no greater than 5 mm. The pre- and post-chemotherapy diagnostic scans will be fused to define the targets below. Patients must be reproducibly immobilized. Radio-opaque markers may be used whenever possible to delineate the surgical scars, extent of nodal disease, skin involvement, and any gross disease.

4. Target volumes: Appropriate volumes will be delineated at the time of simulation to treat the pre-chemotherapy extent of gross disease and areas of potential microscopic disease.

- GTV will be all gross tumor and involved lymph nodes identified by physical exam, additional clinical information, and radiographic studies prior to induction chemotherapy.
- CTV1 will be an isotropic expansion of GTV by 1.0 cm and may be modified at the discretion of the treating physician to respect anatomic boundaries to spread of tumor (e.g., bone or air).
- PTV1 will be an isotropic expansion of the CT1 by 0.5 cm.
- CTV2 will be delineated only for standard CRT patients. This will include CTV1 plus the next echelon of uninvolved but at risk lymph nodes that include the nodal stations at risk for microscopic spread as described in the tables in section 6.5.5. Inclusions of the retropharyngeal nodes will be at the discretion of the treating radiation oncologist. CTV2 may be modified at the discretion of the treating physician to respect anatomic boundaries to spread of tumor (e.g., bone or air).
- PTV2 will be an isotropic expansion of the CTV by 0.5 cm.

5. Dose and fractionation

For patients treated with CRT on the TFHX platform

- De-escalated CRT: PTV1 will be treated to 66 Gy (1.5 Gy BID) over the course of 4.5 cycles. There will be no PTV2 volume for these patients with ≥ 50% response to induction chemoimmunotherapy. Chemoradiation will be given on an alternating week basis during the first 4 cycles, and no concurrent chemotherapy will be given during the final 4 fractions of radiation. There should be a minimum of 6 hours between fractions. All fields will be treated each day. In the case of a mechanical failure or a holiday, one day of BID radiotherapy can be replaced with a single daily fraction of 2 Gy. Accordingly, the final cumulative dose will be slightly less.
- Standard CRT: PTV1 will be treated to 75 Gy (1.5 Gy BID) over the course of 5 cycles and PTV2 will be treated to 45 Gy (1.5 Gy BID) over the first 3 cycles of CRT. Chemoradiation will be given on an alternating week basis. There should be a minimum of 6 hours between fractions. All fields will be treated each day. In the case of mechanical failure or a holiday, one day of BID radiotherapy can be

replaced with a single daily fraction of 2 Gy. Accordingly, the final cumulative dose will be slightly less.

6. Field size: Appropriate volumes will be determined at the time of simulation to treat gross disease and areas of potential microscopic disease as indicated. The optimal field arrangements will be determined on the treatment planning techniques employed. All fields must be treated during each treatment session.

7. Treatment technique: Blocking will be individualized for each patient. Either custom Cerrobend blocks or multileaf collimator will be acceptable.

- Intensity Modulation Radiotherapy: Optimal IMRT planning will depend on the planning system employed. We anticipate the optimal plan will use 7-11 gantry positions. Acceptable plans will encompass the PTV with the 95% prescribed dose. No more than 1% of the PTV should receive less than 95% of the prescribed dose. Plans should be reviewed to ensure that any part of the PTV getting less than 95% of the prescribed dose is at the edge of the volume. In no case should a central area of the PTV receive less than 95% of the prescribed dose. No more than 1% of the PTV should receive more than 110% of the prescribed dose.
- 3D Conformal Radiotherapy: The neck should be treated with opposed lateral fields using a half-field technique. The lower neck should be treated with an anterior field prescribed to a depth of 3 cm. Opposed fields for the lower neck are permitted in order to improve PTV coverage and increase homogeneity. Wedges, tissue compensators, or segmented fields should be used to ensure uniformity of PTV coverage. Electron boosts of the posterior neck are permitted to limit the dose to the spinal cord. Electron fields shall be prescribed to the depth of maximum dose with the energy and field size chosen so that the target volume is encompassed within 90% of the prescribed isodose line. A cord block is permitted on the anterior or lateral fields provided it does not block tumor. Feathering the match line is permitted in cases where a cord block would block the tumor. For 3D techniques, acceptable plans will encompass the PTV within the 95% isodose line. The dose variation in the PTV will be +7% and -5% of the prescription point dose.

8. Normal Tissue Constraints/Dose Volume Histogram: Isodose calculations in the axial, sagittal, or coronal planes are required. In addition, dose volume histograms for the planning treatment volumes and the spinal cord are required. The dose limit to the spinal cord will vary depending upon the technique used. Attempts should be made to limit the spinal cord dose to < 45 Gy in all cases.

9. Adaptive Re-planning: Patients on the standard CRT arm treated on the TFHX platform will undergo repeat CT simulation during cycle 3 for adaptive replanning of treatment volumes.

10. Surrounding critical normal structures should be outlined for study purposes. Including the brainstem, spinal cord, superior/inferior constrictor muscles, optic nerves/chiasm, parotid and submandibular glands, temporo-mandibular joints and cochlea, oral cavity, mandible, eyes, lens, brachial plexus, esophagus (including postcricoid pharynx) and glottic larynx. The normal tissues will be contoured and considered as solid organs. DVH plots must be generated for relevant critical normal structures, any corresponding PRVs, and the unspecified tissues. Institutions that use PRVs must clearly define them as such. Ultimate inclusion of the normal structures and exceptions from the above guidelines will be made at the discretion of the treating radiation oncologist.

11. Special situations: 3D conformal treatment techniques may be preferable to IMRT in certain situations. Some large primary tumors and some large neck nodes may extend up to the skin. In these situations, it may not be possible to add a sufficient margin to the GTV to account for variability in the patient set up. In such a situation, 3D conformal treatment techniques may be preferable to IMRT.

6.5.5 Nodal Planning Target Volume Delineation for Standard CRT Patients

Lateralized Base of Tongue

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II, III, SCV	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	II	II	II	II	II	IB	II	IB	II, IV	II, III, SCV	II, III

Base of Tongue Crossing Midline

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II, III, SCV	II, III	IA, IB, II	II	II	II	II	II

Contralateral	IA	II	II	II	II	II	IB	IA, II	IB, III	II, IV	II, III, SCV	II, III

Soft Palate

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II, III, SCV	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	II	II	II	II	II	IB	IA, II	IB, III	II, IV	II, III, SCV	II, III

Lateralized Tonsil: No Base of Tongue Invasion

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II, III, SCV	II, III	IA, IB, II	II	II	II	II	II
Contralateral	IA	---	---	---	---	---	IB	IA, II	IB, III	II, IV	II, III, SCV	II, III

Tonsil with Base of Tongue Invasion

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	IB, III	II, IV	II, III, SCV	II, III	IA, IB, II	II	II	II	II	II

Contralateral	IA	II	II	II	II	II	IB	II	IB, III	II, IV	II, III, SCV	II, III

Oropharynx involving Larynx

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	III	II, IV	II, III, SCV	II, III	IA, IB, II	II	II	III	III	II
Contralateral	IA	II	II	II	II	II	IB	IA, II	IB, III	II, IV	II, III, SCV	II, III

Oropharynx involving Oral Cavity (Lateralized)

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IA, IB, II, III, IV, SCV	IA, IB, II, III	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II
Contralateral	IA, IB	---	---	---	---	---	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IA, IB, II, III, SCV	II, III

Oropharynx involving Oral Cavity (Crosses Midline)

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												

Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IA, IB, II, III, IV, SCV	IA, IB, II, III	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II
Contralateral	IB, II	IB, II	IB, II	IB, II	IB, II	IB, II	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IA, IB, II, III, SCV	II, III

Oropharynx involving Nasopharynx

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II VA	IA, II, VA	IB, III, VA	II, IV, VA	II, III, VA, SCV	II, III	IA, IB, II, VA	II, VA	II, VA	II, VA	II, VA	II, VA
Contralateral	IA	II	II	II	II	II	IB, VA	IA, II, VA	IB, III, VA	II, IV, VA	II, III, SCV, VA	II, III, VA

Larynx: T1-T2

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	III	II, IV	II, III	II, III	IA, IB, II	II	II	III	III	II
Contralateral	IA	---	II	II	II	II	IB	II	III	II, IV	II, III	II, III

Larynx: T3-T4

	Adenopathy Level

	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	III	II, IV	II, III	II, III	IA, IB, II	II	II	III	III	II
Contralateral	IA	---	II	II	II	II	IB	II	III	II, IV	II, III	II, III

Hypopharynx

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	II, III	III, IV	II, IV	II, III	II, III, IV	IA, IB, II	II	II	III	III	II
Contralateral	IA	---	II, III	II, III	II, III	II, III	IB	II	III	II, IV	II, III	II, III

Lower Gingiva

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IA, IB, II, III	IA IB II III	IA, IB	IA, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II
Contralateral	IA, IB	---	---	---	---	---	IB, II	IA, II	IA, IB, III	IB, IA, II, IV	IA, IB, II, III	II, III

Retromolar Trigone

	Adenopathy Level	
	Ipsilateral	Contralateral

Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	IB, III	IB, II, IV	IB, II, III	IB II III	IA, IB	IA, II	IB, II	IB, II	IB, II	IB, II
Contralateral	IA, IB	---	---	---	---	---	IB, II	IA, II	IB, III	IB, II, IV	IB, II, III	II, III

Lateralized Oral Tongue

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IB, IA, II, III	IA IB II III	IA, IB, II	IA, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II
Contralateral	IA, IB	---	---	---	---	---	IB, II	IA, II	IA, IB, III	IB, IA, II, IV	IA, IB, II, III	II, III

Oral Tongue Crossing Midline

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IB, IA, II, III	IA IB II III	IA, IB, II	IA, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II
Contralateral	IA, IB	IA, IB	IA, IB	IA, IB	IA, IB	---	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IA, IB, II, III	II, III

Floor of Mouth

	Adenopathy Level											
	Ipsilateral						Contralateral					
Involved Nodes	IA	IB	II	III	IV	V	IA	IB	II	III	IV	V
CTV2												
Ipsilateral	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IA, IB, II, III	IA IB II III	IA, IB, II	IA, II	IA, IB, II	IA, IB, II	IA, IB, II	IA, IB, II
Contralateral	IA, IB	IA, IB	IA, IB	IA, IB	IA, IB	--	IB, II	IA, II	IA, IB, III	IA, IB, II, IV	IA, IB, II, III	II, III

6.6 Consolidative Immunotherapy Details and Guidelines

Nivolumab will be given at 480 mg flat dose every 28 days (9 doses total, 9 months of consolidation treatment). The goal of consolidative nivolumab is to re-activate a potential anti-tumor response triggered during the induction phase after chemoradiation and to eradicate micro-metastatic residual disease.

6.7 Supportive Guidelines during Chemoradiation

- Anti-emetics will be ordered at the discretion of the attending physician.
- Use of growth factor support (G-CSF) during induction as above. During the TFHX regimen G-CSF may be used during the off week at the treating physician's discretion.
- A double lumen venous access device is recommended prior to initiation of therapy, although peripheral IV access is acceptable.
- Use of a feeding device is recommended for high-risk patients. Placement of a feeding device is left to the discretion of the treating physician/investigator. Commonly applied criteria for feeding device placement include:
  - Loss of > 10% of body weight from the start of therapy
  - Dehydration or inability to maintain adequate oral hydration
  - Inability to maintain intake of 25+ kcal/kg of ideal body weight
- During chemoradiotherapy patients should receive instructions for oral hygiene and prescriptions to include standard of care treatment typical for the care of HNSCC patients undergoing chemoradiation:
  - Oral nystatin or fluconazole (100 mg daily)
  - Viscous lidocaine HCl and/or Grade I mouthwash 10 mL QID, swish and spit
    - Grade 1 Mouthwash contains 50 mL 2% viscous lidocaine, 50 mL diphenhydramine elixir (12.5 mg/5 mL), 100 mL sodium bicarbonate injection, and 500 mL normal saline irrigation for a total volume of 700 mL

  - Normal saline mouthwash 10 mL QID swish and spit
  - Natural Care Gel (or similar product) BID during chemoradiotherapy and TID during rest week
  - Vigilon (or similar product) to be applied to open wounds during chemoradiotherapy
  - Silvadene cream to open wounds followed by zinc oxide cream and then Telfa dressings BID during rest week (discontinue Silvadene and zinc oxide creams 1 day prior to radiotherapy)
  - Aquaphor (or similar brand) cream to lips PRN
  - Adequate analgesia is essential to maintain oral intake and patient comfort. Narcotic analgesics are usually necessary and should be used at the physician/investigator discretion.
  - Therabite for trismus if appropriate.
  - Replacement for electrolyte imbalances when applicable.
- Prior to discharge of the patients after a cycle of chemoradiation, a CBC and platelet count, and determination of serum electrolytes, including creatinine will be performed.
- A visit to the treating physician is strongly recommended between cycles of chemoradiation (i.e., days 6-14).
- Use of IV home hydration is strongly recommended in patients with inadequate oral intake: normal saline 1000 mL IV daily during rest weeks (days 6-14).
- If Hb < 10, patients should generally be transfused an amount sufficient to increase Hb to > 10. The Hb level should be maintained > 10 mg/dL for the duration of chemoradiotherapy in all patients.
- The use of amifostine during chemoradiotherapy is not permitted.

6.8 Post-Therapy Follow-Up

Every patient should be followed clinically until taken off study. Patients will be seen in clinic for evaluation by Medical Oncology, Radiation Oncology, and Otolaryngology approximately 4 weeks after completing locoregional therapy. Repeat imaging of the head and neck with a PET/CT at 12 weeks post-completion of locoregional therapy will be obtained. Neck dissection or repeat biopsy may be indicated by 12-week post-treatment imaging findings (upon review in multidisciplinary tumor board).

Patients should undergo clinical and radiographic disease evaluation every 3 months in year 1, every 6 months in years 2 and 3, and annually in years 4 and 5 after completion of definitive chemoradiation. Radiographic assessment should include imaging of the head, neck, and optionally, the chest. Laboratory evaluation should consist of at least a CBC, serum electrolytes, serum creatinine, liver enzymes, serum calcium, and serum albumin. TSH should be measured at least annually. This schedule can be altered according to the

physician's discretion. Suspicion of progressive disease should be evaluated by radiographic studies whenever possible.

6.9 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue for the allotted treatment time period (as described above) or until one of the following criteria applies:

- Disease progression.
- Intercurrent illness that prevents further administration of treatment.
- Unacceptable adverse event(s).
- Patient decides to withdraw from the study.
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.10 Criteria for Discontinuation/Withdrawal of Informed Consent

Patients may be discontinued from trial treatment at any time, at the discretion of the investigator(s). Specific reasons for discontinuing a patient from study treatment include:

- Objective progression of disease if deemed inappropriate for further study treatment
- Unacceptable adverse events including abnormal laboratory values
- Abnormal test procedure result(s)
- Protocol non-compliance
- Study closure
- Patient decision to withdraw from the study
- Patient lost to follow-up
- In the judgment of the investigator, further treatment would not be in the best interest of the patient
- Death

6.11 Late Toxicity Assessment

6.11.1 Late Toxicity Assessment Schedule

Swallowing function and speech will be assessed pre-treatment, at first follow-up after completion of definitive locoregional therapy, and then at 3, 6, 12, and 24 months after completion of definitive chemoradiation.

6.11.2 Assessment of Late Toxicity

Performance measures will be assessed by determining swallowing function and speech. Voice will be assessed as a simple yes/no response from patients as to whether their voice

has returned to normal. Swallowing will be determined by a patient's ability to swallow table food. A formal swallow evaluation will be done on patients experiencing dysphagia. Additionally, late toxicity will be determined by evaluating presence and degree of xerostomia, dental decay, osteoradionecrosis, as well as the presence of enteral or tracheostomy dependence.

6.11.3 Quality of Life Assessments

The proposed regimen aims to decrease treatment toxicity without compromising outcomes. Thus, quality of life and performance are important treatment endpoints. The objective is to describe these dimensions prospectively, pre-treatment, through treatment, to long-term follow-up. Specific aims are to document patient's experience of treatment effects; evaluate changes in quality of life and performance as a function of treatment regimen; determine extensiveness and persistence of quality of life and function-related treatment effects; and describe the pattern, timing and extent of recovery of function and quality of life.

Quality of life and performance measures to be used in this protocol include:

- Performance Status Scale for Head and Neck Cancer Patients (PSS-HN)
- Functional Assessment of Cancer Therapy – Head and Neck Version 4 (FACT – H&N)

The PSS-HN is a clinical rated instrument consisting of three subscales: Normalcy of Diet, Eating in Public, and Understandability of Speech. It has been demonstrated to be reliable and valid in head and neck cancer patients.

The FACT-H&N is a multidimensional, self-report quality of life instrument specifically designed for use with head and neck cancer patients. The core scale (FACT-G) consists of 27 core items assessing patient well-being in four areas: Physical, Social/Family, Emotional, and Functional. The core scale is supplemented with site-specific modules of which the head and neck version (12 items) will be employed here.

These surveys can be found in the appendix.

These instruments will be administered on paper pre-treatment (pre-induction), post-induction, at first follow-up (4 weeks) after completion of definitive locoregional therapy, and then at 3, 6, 12, and 24 months after completion of definitive chemoradiation.

7 EXPECTED ADVERSE EVENTS, RISKS AND DOSE MODIFICATIONS

7.1 Expected Adverse Events

7.1.1 Nivolumab (during induction and consolidative therapy)

- Central nervous system: Fatigue, malaise
- Dermatologic: Skin rash
- Endocrine and metabolic: Hyperglycemia, hypothyroidism
- Gastrointestinal: Diarrhea, nausea
- Hematologic and oncologic: Lymphocytopenia, anemia
- Hepatic: Increased serum AST, ALT, bilirubin, and alkaline phosphatase
- Respiratory: Pneumonitis
- Miscellaneous: Febrile reaction, infusion reaction
- Please see investigational brochure for full list of side effects

7.1.2 Carboplatin (during induction therapy)

- Dermatologic: Alopecia (includes other agents in combination with carboplatin)
- Endocrine & metabolic: Hypomagnesemia, hypokalemia, hyponatremia, hypocalcemia; less severe than those seen after cisplatin (usually asymptomatic)
- Gastrointestinal: Nausea, vomiting, stomatitis, diarrhea, anorexia
- Hematologic: Myelosuppression is dose related and is the dose-limiting toxicity; thrombocytopenia is the predominant manifestation, with a reported incidence of 37% in patients receiving 400 mg/m2 as a single agent and 80% in patients receiving 520 mg/m2; leukopenia has been reported in 27% to 38% of patients receiving carboplatin as a single agent (nadir: ~21 days following a single dose)
- Hepatic: Alkaline phosphatase increased, AST increased (usually mild and reversible)
- Otic: Hearing loss at high tones (above speech ranges, up to 19%); clinically-important ototoxicity is not usually seen
- Renal: Increases in creatinine and BUN have been reported; most of them are mild and they are commonly reversible; considerably less nephrotoxic than cisplatin
- Neuromuscular & skeletal: Peripheral neuropathy (4% to 6%; up to 10% in older and/or previously-treated patients)
- <1% (Limited to important or life-threatening): Neurotoxicity, urticaria, rash, nephrotoxicity, secondary malignancies, anaphylaxis, malaise, hypertension

7.1.3 Paclitaxel (during induction and TFHX concurrent chemoradiation)

- Cardiovascular: Flushing, edema, hypotension
- Central nervous system: Peripheral neuropathy
- Dermatologic: Alopecia, rash, nail changes
- Gastrointestinal: Nausea, vomiting, diarrhea, mucositis
- Hematologic and oncologic: Neutropenia, leukopenia, anemia, thrombocytopenia
- Hepatic: Increased alkaline phosphatase, increased serum AST

- Hypersensitivity: Hypersensitivity reaction
- Neuromuscular and skeletal: Arthralgia, myalgia
- May cause a hypersensitivity reaction which often occur within the first 10 minutes of an infusion

7.1.4 5-Fluorouracil (during TFHX concurrent chemoradiation)

- Gastrointestinal: Diarrhea, mucositis, nausea, and vomiting
- Hematologic: Myelosuppression
- Dermatologic: Photosensitivity, skin dryness, hand-foot syndrome, increased pigmentation of skin, increased pigmentation of veins used for infusion, nail changes
- Cardiac: myocardial ischemia, arrhythmias
- Allergic reactions
- Neurologic: Acute cerebellar syndrome, disorientation, headache
- Eye: Lacrimal duct stenosis, lacrimation, photophobia, and visual changes
- May cause birth defects and should not be used in pregnant women.
- A known radiation sensitizer and may potentiate side effects of radiation

7.1.5 Hydroxyurea (during TFHX concurrent chemoradiation)

- Cardiovascular: Edema
- Gastrointestinal: Nausea, vomiting, diarrhea, constipation
- Hematologic and oncologic: Leukopenia, bone marrow depression
- Renal: Increased blood urea nitrogen, increased serum creatinine
- It may aggravate the inflammation of mucous membranes secondary to irradiation.
- Less common side effects include: dysuria or impairment of renal tubular function, rare neurological disturbances (headaches, dizziness, disorientation, hallucination, and convulsion.

7.1.6 Cisplatin (during cisplatin concurrent chemoradiation)

- Central nervous system: Peripheral neuropathy
- Gastrointestinal: Nausea, vomiting
- Hematologic and oncologic: Anemia, leukopenia, thrombocytopenia
- Hepatic: Increased liver enzymes
- Otic: Ototoxicity
- Renal: Nephrotoxicity

7.1.7 Filgrastim

- Cardiovascular: Chest pain
- Central nervous system: Fatigue
- Gastrointestinal: Nausea
- Hematologic and oncologic: Thrombocytopenia

- Hepatic: Increased serum alkaline phosphatase
- Neuromuscular and skeletal: Ostealgia, back pain
- Miscellaneous: Fever

7.1.8 Radiation

- Radiation to the head and neck will cause skin irritation, dry mucous membranes due to salivary gland dysfunction, mucositis, and stomatitis. The concomitant administration of chemotherapy will aggravate these side effects. Long-term side effects include myelitis, osteoradionecrosis, hoarseness, hypothyroidism, trismus, swallowing dysfunction, fibrosis of soft tissues, and enteral tube dependency.

7.2 Dose Modifications

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 5 for toxicity and Adverse Event reporting. A copy of the CTCAE Version 5.0 can be downloaded from the CTEP home page. This section discussed the general dose modifications in the setting of the most commonly observed adverse events with systemic therapy and radiation therapy. These are general guidelines to be followed, but deviations from the listed dose modifications are allowed at the discretion of the treating physician.

7.2.1 Induction Chemotherapy Dose Modifications

7.2.1.1 Hematologic Toxicity

- Patient should not begin a new cycle of induction therapy unless the ANC is ≥ 1500 cells/mm^3 and the platelet count is ≥ 100,000 cells/mm^3. Repeat counts should be obtained weekly until resolved. In the setting of low blood counts as specified above, dose reductions on subsequent cycles are provided in the table below.
- A delay in therapy of up to 2 weeks is permitted for count recovery
- If ANC are < 1500 or platelets < 100,000 on day 8 or 15 of each cycle, reduce all subsequent doses of paclitaxel and carboplatin (if any) to one dose reduction of the previous dose. Withhold treatment until counts recover to an absolute neutrophil count of at least 500 cells/mm^3 or platelets of at least 50,000 on days 8 or 15 of the cycle. Growth factor support should then be used with subsequent cycles.
- Dose reduction per the table below:

Adverse Reaction	Occurrence	Paclitaxel Dose (mg/m^2)	Carboplatin Dose (AUC mg·min/mL)
ANC < 1500/mm^3 OR ANC < 500/mm^3 for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 100,000/mm^3	First	75	4.5
	Second	Discontinue Treatment	

7.2.1.2 Neurotoxicity (Peripheral)

- Patients with grade 1 peripheral neuropathy should be carefully watched for progression of symptoms. A dose reduction is not necessary in this setting
- In the setting of grade 2 peripheral neuropathy – paclitaxel should be dose reduced according to the table below.
- Withhold paclitaxel for grade 3-4 peripheral neuropathy. Paclitaxel at reduced doses can be resumed when peripheral neuropathy improves to grade 1.
- Dose reduction table below:

Adverse Reaction	Occurrence	Paclitaxel Dose (mg/m^2)
Severe sensory neuropathy	First	75
	Second	50
	Third	Discontinue Treatment

7.2.1.3 Ototoxicity

- If grade 2 hearing loss, subsequent doses of cisplatin may be replaced by carboplatin AUC 6. For grade 3 ototoxicity, discontinue carboplatin.

7.2.1.4 Hypersensitivity

- In case of paclitaxel hypersensitivity reactions, the investigator should institute treatment measures medically appropriate per institutional guidelines.
- For grade 1 allergic reactions, supervise at the bedside without further treatment. Consider decreasing rate of infusion until recovery from symptoms.
- For grade 2 reactions, interrupt the infusion of paclitaxel, and resume upon recovery of symptoms. The infusion should be resumed at a slower rate and if no further symptoms appear, complete the administration of the dose. If symptoms recur, discontinue infusion and follow guidelines below.
- For grade 3-4 reactions, stop the infusion and administer additional doses of H1 and H2 blockers intravenously. Administer IV steroids and consider epinephrine and bronchodilators as clinically indication.
- For recurrent grade 2 or grade 3 reactions, prior to re-challenge and with all subsequent cycles, consider both an H1 and H2 blocker intravenously plus dexamethasone 20 mg x2 doses (orally or IV) 12 and 6 hours pre-paclitaxel.

- Grade 4 reactions are considered severe hypersensitivity reactions, and rechallenge is contraindicated.

7.2.1.5 Hepatic

- Mild impairment (AST or ALT < 10 times ULN or bilirubin ≤ 1.25 times ULN): No adjustments
- Moderate impairment (AST or ALT < 10 times ULN or bilirubin 1.26-2 times ULN): Reduce paclitaxel dose by 25%.
- Severe impairments (AST or ALT < 10 times ULN or bilirubin 2.01-5 times ULN): Reduce paclitaxel dose to 50%. May increase up to a reduction of 25% in subsequent cycles if liver impairment improves to either moderate or mild impairment.
- AST or ALT > 10 times ULN or bilirubin > 5 times ULN: Discontinue paclitaxel.

7.2.1.6 Other Toxicities

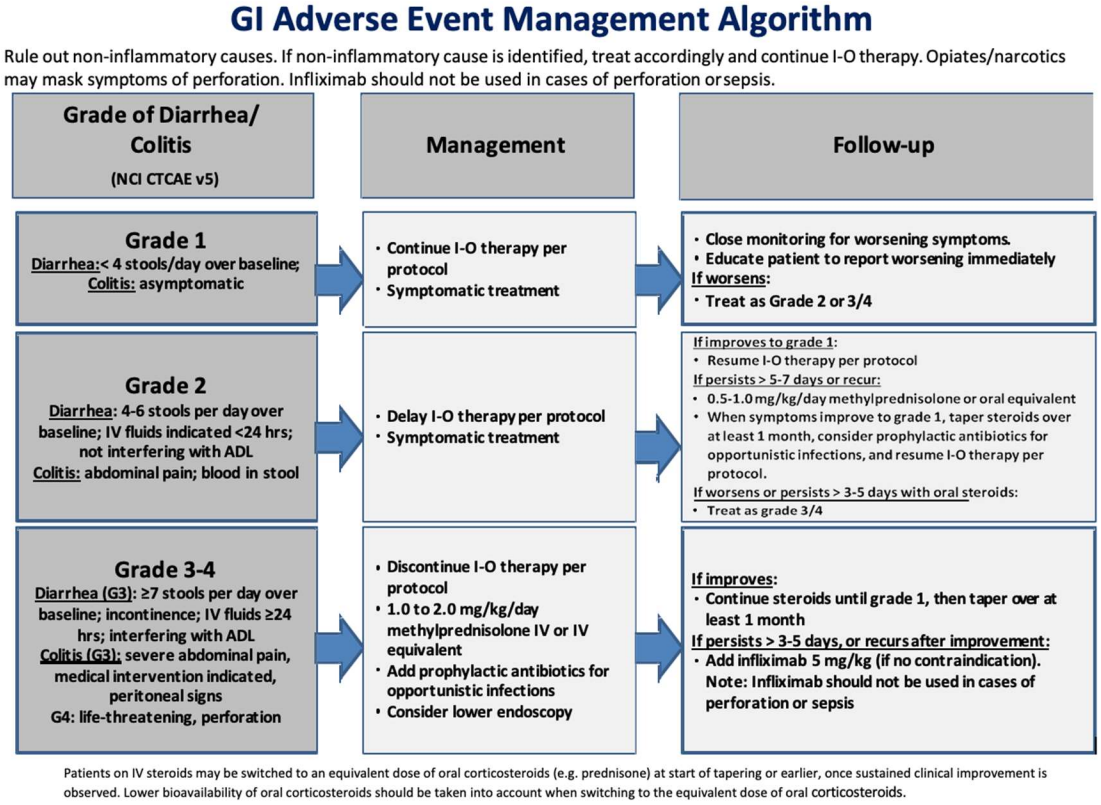
- For all other grade 3+ toxicities (except alopecia, nausea, vomiting, fatigue and anorexia), reduce carboplatin and paclitaxel by 25% for all subsequent doses during induction.
- In the event of recurrent grade 3 or 4 toxicity attributed to chemotherapy (excluding transaminase elevation, nausea, vomiting, alopecia) reduce carboplatin and paclitaxel by a further 25% during induction.

7.2.2 Nivolumab Dose Modifications during Induction Phase and Consolidative Phase

There will be no dose adjustments for nivolumab, however treatment can be held or discontinued based on occurrence of immune related adverse events. Please refer to the below tables/guidelines for guidance as well as investigator brochure for most up to date detailed management guidelines.

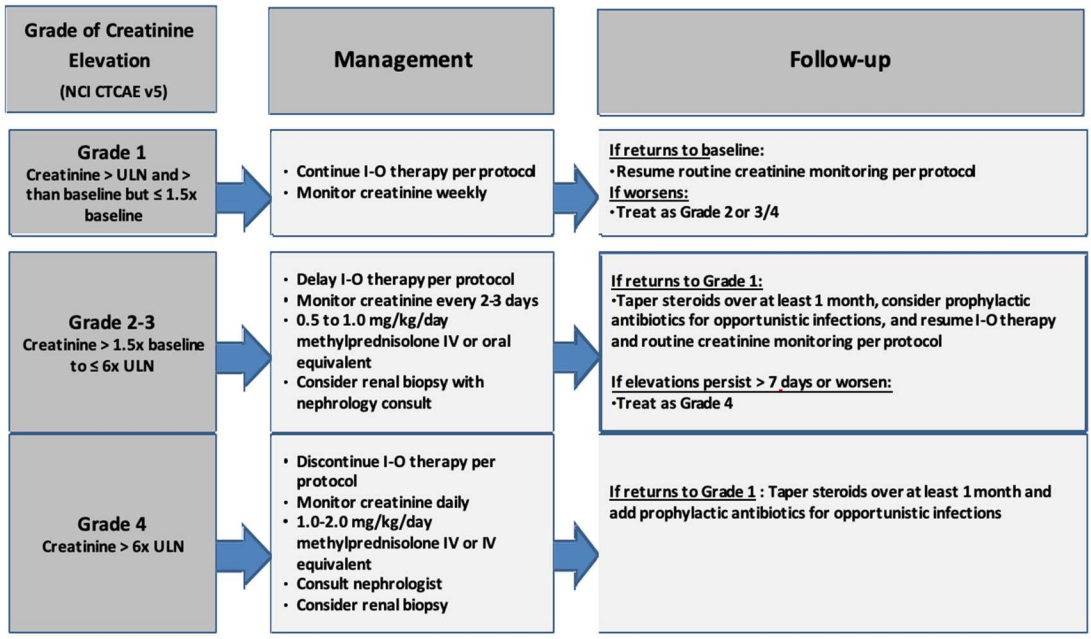
Guidelines for permanent discontinuation or withholding of doses are described below.

7.2.3 Nivolumab Adverse Event Management Algorithms



Renal Adverse Event Management Algorithm

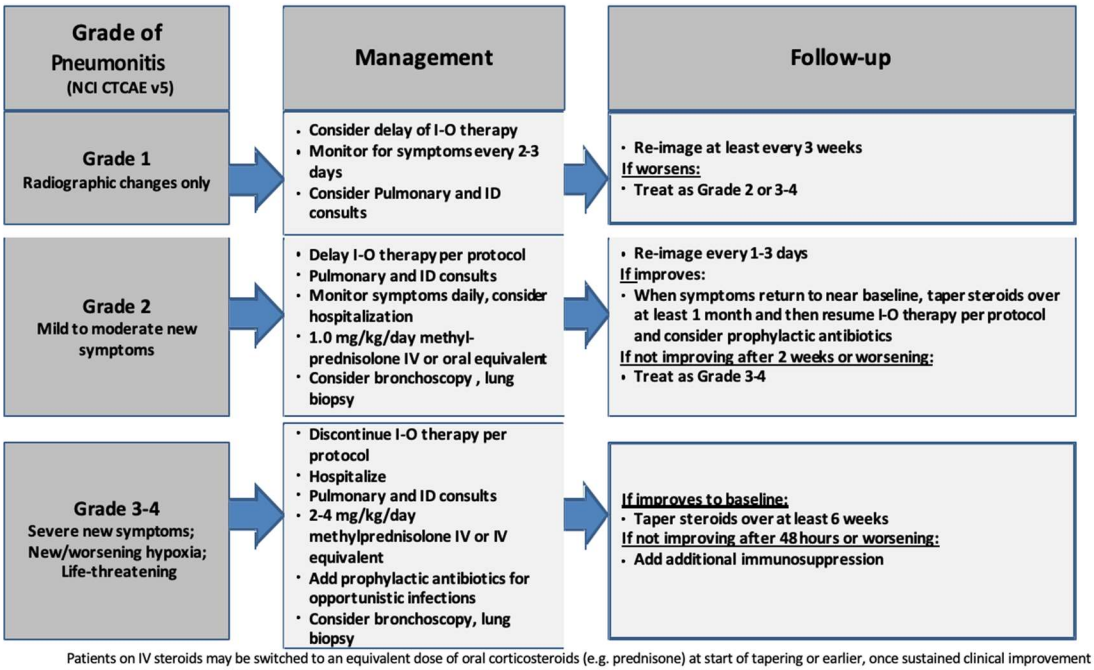
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Pulmonary Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids

Hepatic Adverse Event Management Algorithm

Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider imaging for obstruction.

Grade of Liver Test Elevation (NCI CTCAE v5)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*The recommended starting dose for grade 4 hepatitis is 2 mg/kg/day methylprednisolone IV.

Endocrinopathy Adverse Event Management Algorithm

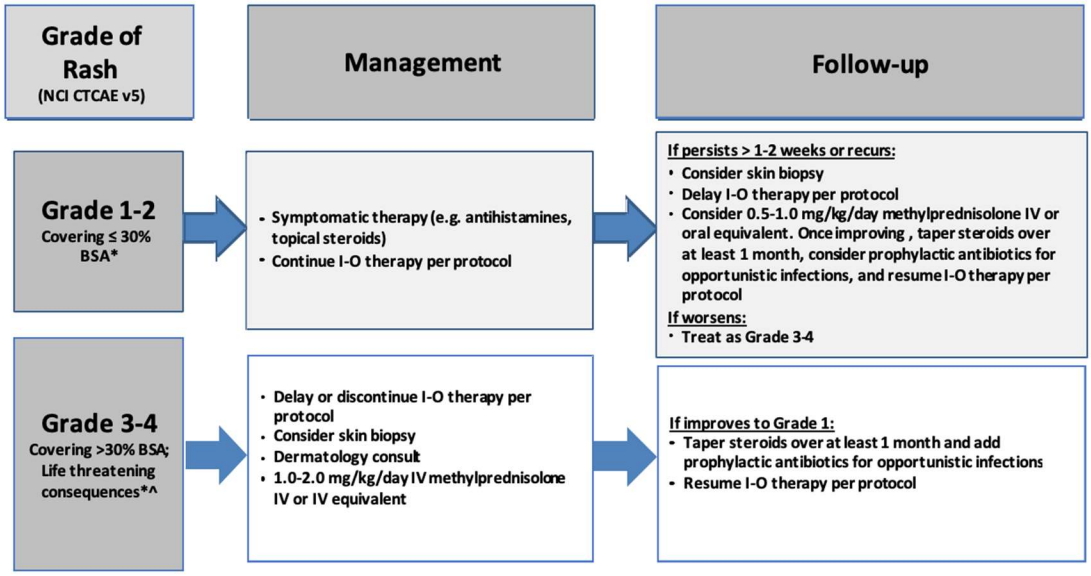
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.

Asymptomatic TSH elevation	• Continue I-O therapy per protocol • If TSH < 0.5 x LLN, or TSH > 2 x ULN, or consistently out of range in 2 subsequent measurements: include fT4 at subsequent cycles as clinically indicated; consider endocrinology consult	
Symptomatic endocrinopathy	• Evaluate endocrine function • Consider pituitary scan Symptomatic with abnormal lab/pituitary scan: • Delay I-O therapy per protocol • 1-2 mg/kg/day methylprednisolone IV or PO equivalent • Initiate appropriate hormone therapy No abnormal lab/pituitary MRI scan but symptoms persist: • Repeat labs in 1-3 weeks / MRI in 1 month	If improves (with or without hormone replacement): • Taper steroids over at least 1 month and consider prophylactic antibiotics for opportunistic infections • Resume I-O therapy per protocol • Patients with adrenal insufficiency may need to continue steroids with mineralocorticoid component
Suspicion of adrenal crisis (e.g. severe dehydration, hypotension, shock out of proportion to current illness	• Delay or discontinue I-O therapy per protocol • Rule out sepsis • Stress dose of IV steroids with mineralocorticoid activity • IV fluids • Consult endocrinologist • If adrenal crisis ruled out, then treat as above for symptomatic endocrinopathy	

Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Skin Adverse Event Management Algorithm

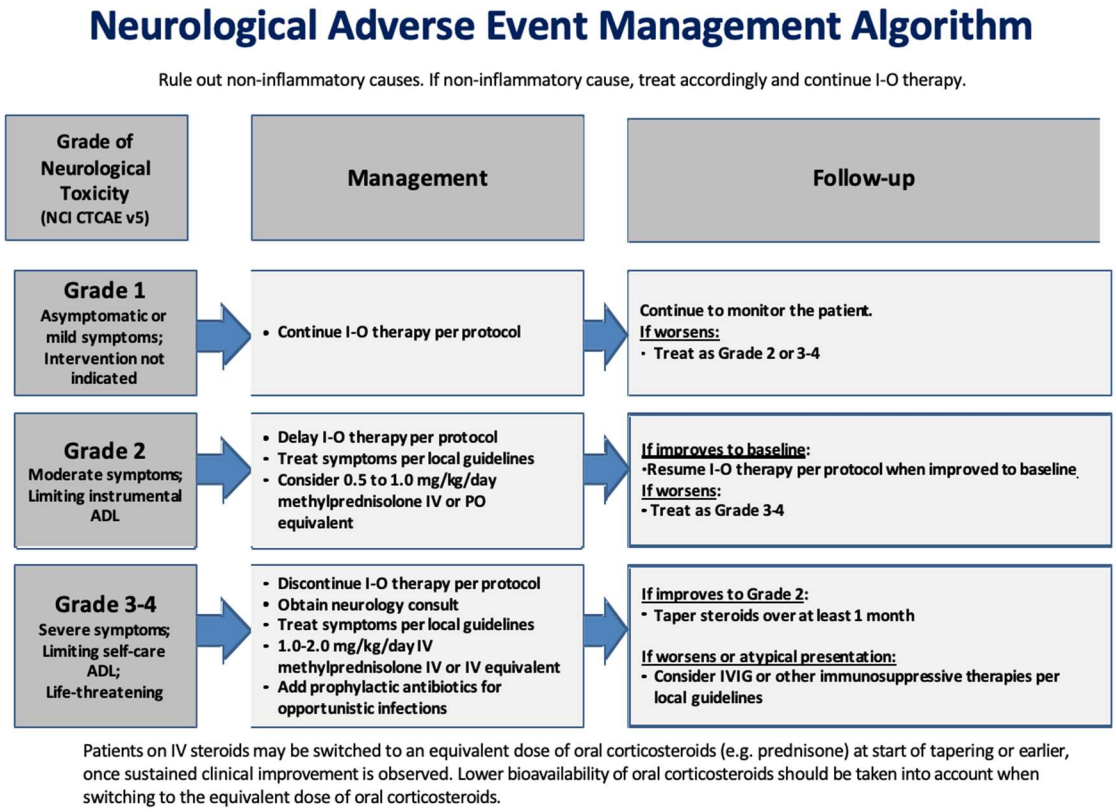
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

*Refer to NCI CTCAE v4 for term-specific grading criteria.

^If SJS/TEN is suspected, withhold I-O therapy and refer patient for specialized care for assessment and treatment. If SJS or TEN is diagnosed, permanently discontinue I-O therapy.



7.2.3.1 Nivolumab Dose Delay Criteria

Because of the potential for clinically meaningful nivolumab-related adverse events requiring early recognition and prompt intervention, management algorithms have been developed for suspected adverse events of selected categories. These algorithms are specified above. Dose delays will occur when nivolumab-related AEs have not resolved upon the next cycle of treatment or the patient remains on an equivalent of 10 mg prednisone or higher. In the setting of an adverse event likely due to nivolumab, the treating physician has the option to continue induction therapy with carboplatin and paclitaxel while holding nivolumab.

In the event there are adverse events related to carboplatin or paclitaxel that require holding treatment, nivolumab must also be held and delayed until chemotherapy can resume.

Nivolumab should also be permanently discontinued for grade 2 or 3 immune-related adverse reactions that persist despites treatment modifications or for inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day.

7.2.3.2 Treatment of Nivolumab Infusion Reaction

Since nivolumab contains only human IgG protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, blood pressure shifts, bronchospasms, or other symptoms. All grade 3, 4, or 5 infusion reactions should be reported within 24 hours to the primary investigator and reported as an SAE. Infusion reactions should be graded according to NCI CTCAE v 5.0 guidelines.

Treatment recommendations are provided below and may be modified based on local treatment standards and guidelines as appropriate:

- **For Grade 1 symptoms:** (Mild reaction; infusion interruption not indicated; intervention not indicated). Remain at bedside and monitor patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations.
- **For Grade 2 symptoms**: (Moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids); prophylactic medications indicated for 24 hours).
  Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.
- **For Grade 3 or Grade 4 symptoms:** (Severe reaction, Grade 3: prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization

indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)). Grade 4: (life threatening; pressor or ventilatory support indicated). Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the patient as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine, or corticosteroids).

7.2.4 Dose Modifications During Concurrent Chemotherapy

7.2.4.1 Hematologic Dose Modifications for Hydroxyurea

- Neutropenia: If the absolute neutrophil count (ANC) is between 500 and 1000 on day 0 – 5 of each cycle, decrease hydroxyurea to 50% of the full dose. On subsequent cycles, a reduced starting dose of hydroxyurea should be used. For ANC of ≤ 500/µl on Day 0 – 5 of any cycle, omit hydroxyurea, and administer 600 mg/m^2/day of 5-FU and radiotherapy only. On subsequent cycles, a reduced starting dose of hydroxyurea by 50% should be used.
- Thrombocytopenia: For a platelet count of 50,000/ µl to 74,000/µl on Day 0 – 5 of each cycle, decrease hydroxyurea to 50% of full dose. On subsequent cycles, a reduced starting dose of hydroxyurea may be used. For a platelet count ≤ 50,000/µl on Day 0 – 5 of any cycle, omit hydroxyurea, and administer 600 mg/m^2/day of 5-FU and radiotherapy only. On subsequent cycles, a reduced starting dose of hydroxyurea by 50% should be used.

7.2.4.2 Hematologic Dose Modifications for Paclitaxel

- For ANC ≤ 1000 or platelets count of 50-74 on day 0-5 of each cycle, decrease paclitaxel by one dose level. For ANC ≤ 500 or platelet count of less than 50 on day 0 -5 of any cycle, hold paclitaxel for that cycle and decrease by one dose level in subsequent cycles. Discontinue paclitaxel if further dose reduction is required. Dose level 0 = 100 mg/m^2; dose level -1 = 75 mg/m^2; dose level -2 = 50 mg/m^2, dose level -3 = discontinue

7.2.4.3 Non-Hematologic Dose Modifications for 5-FU, Hydroxyurea, and Paclitaxel

- Mucositis, Dysphagia, Dermatitis, Diarrhea: Treatment cycles should not be delayed for mucositis, dysphagia, dermatitis, or diarrhea. For grade 4 mucositis,

dysphagia, and dermatitis exceeding 7 days duration or persisting on Day 1 of a subsequent cycle, decrease 5-FU to 500 mg/m^2/day. For grade 4 diarrhea exceeding 7 days duration or persisting on Day 1 of a subsequent cycle, decrease 5-FU to 500 mg/m^2/day. Doses will not be increased on subsequent cycles.

- Nephrotoxicity: If grade 2 renal toxicity, administer 50% hydroxyurea dose. If grade 3 or 4 renal toxicity, hold hydroxyurea.
- Hepatotoxicity: If grade 3 or 4 on day 0, hold hydroxyurea and adjust paclitaxel according to section 7.2.1.5.
- Peripheral neuropathy: For paclitaxel, refer to section 7.2.1.2.
- Chemoradiotherapy should not be interrupted for non-hematologic toxicity except as judged necessary on a case-by-case basis by the treating radiation, medical oncologists, and Principal Investigator.
- In the presence of a persisting fever ≥ 38C or other clinically apparent infection a cycle can be postponed for 1 week or interrupted (if treatment cycle has already started) if this is necessary in the opinion of the treating medical and radiation oncologists.
- Cutaneous vasculitic toxicities, including vasculitic ulcerations and gangrene, have occurred in patients with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported most often in patients with a history of, or currently receiving, interferon therapy. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in patients with myeloproliferative disease, hydroxyurea should be discontinued if cutaneous vasculitic ulcerations develop.
- Geriatric Use: Elderly patients may be more sensitive to the effects of hydroxyurea, and may require a lower dose regimen. This drug is known to be excreted by the kidney, and the risk of toxic reactions to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

7.2.4.4 Dose Modifications for Cisplatin

- Nephrotoxicity: If CrCl 46-60, 25% dose reduction. If CrCl 31-45, 50% dose reduction
- Myelosuppression: If the ANC is < 1000 on day 1 of each cycle, hold cisplatin and when counts recover > 1000 ANC, then decrease cisplatin 25%. On subsequent cycles, a reduced starting dose of cisplatin should be used.
- Peripheral Neuropathy: If grade 2, then decrease cisplatin 25%. On subsequent cycles, a reduced starting dose of cisplatin should be used. If grade 3 or more, hold cisplatin and when neuropathy recovers to grade 2 or better, then decrease cisplatin 25%. On subsequent cycles, a reduced starting dose of cisplatin should be used.

7.2.4.5 General Toxicity Information

- Any other significant toxicity that is felt to be potentially drug related should be discussed between the PI and the treating physician and dose reduction can be implemented for the benefit and safety of the patient.
- Radiotherapy should not be interrupted for non-hematologic toxicities except when judged necessary on a case-by-case basis by the treating radiation and medical oncologist in consultation with the PI.
- All interruptions or changes to study drug administration must be recorded.
- It will be documented whether or not each patient completed the clinical study. If for any patient either study treatment or observations were discontinued the reason will be recorded. Reasons that a patient may discontinue participation in a clinical study are considered to constitute one of the following: 1) adverse events, 2) abnormal laboratory value(s), 3) abnormal test procedure result(s), 4) disease progression, 5) protocol violation, 6) patient withdrew consent, 7) lost to follow-up, 8) death

8 PHARMACEUTICAL INFORMATION

8.1 Carboplatin

- Supply: supplied commercially as a sterile lyophilized powder available in single-dose vials containing 50 mg, 150 mg and 450 mg of carboplatin. Each vial contains equal parts by weight of carboplatin and mannitol. Please refer to package insert for information on preparation.
- Side effects: listed in section 7.1.2. Please refer to the package insert for full prescribing information.
- Preparation: Immediately before use, the content of each vial must be reconstituted with either sterile water for injection, USP, 5% dextrose in water, or 0.9% sodium chloride injection, USP to produce a carboplatin concentration of 10 mg/ml. When prepared as directed, carboplatin solutions are stable for 8 hours at room temperature. Since no antibacterial preservative is contained in the formulation, it is recommended that carboplatin solutions be discarded 8 hours after dilution.
- Storage and Stability: Unopened vials of carboplatin are stable for the life indicated on the package when stored at controlled room temperature and protected from light.
- Administration: Administer over 30-60 minutes after completing the paclitaxel infusion. The Calvert Equation (Dose=AUC (CC+25) will be used to achieve the desired dose where CC = Wt*(140-age)/72/creatinine (if female use 85%).

8.2 Fluorouracil

- Commercially available as 10 ml ampules containing 500 mg/10 ml. No dilution is necessary for administration, but it may be further diluted in D5W or normal saline. It is stored at room temperature and is stable for 24 hours. It will be administered by intravenous continuous infusion as described in section 7.1.4. Please refer to the package insert for full prescribing information.

8.3 Hydroxyurea

- Hydroxyurea (Bristol-Myers Squibb, Princeton, NJ): commercially available as 500 mg capsules. It is stored at room temperature and will be administered. Please refer to the package insert for solution preparation and expected AE. Please refer to the package insert for full prescribing information.

8.4 Paclitaxel

- Chemistry: Paclitaxel is a natural product with antitumor activity. The chemical name for paclitaxel is 5,20-Epoxy-1,2 hexahydroxytax-11-en 9-one 4, 10 diacetate 2- benzoate 13-ester with (2R,3S)-N-benzoyl-3-phenylisoserine. Paclitaxel is a white to off-white crystalline powder with the empirical formula C47H51NO14 and a molecular weight of 853.9. It is extremely lipophilic and melts at around 216-217°C. Paclitaxel is highly insoluble in water.
- Mechanisms of Action: Microtubules have been demonstrated to be very strategic targets for antineoplastic agents; however, few antimicrotubule agents have been discovered and encompassed into standard chemotherapeutic regimens. Paclitaxel, a diterpenoid plant product extracted from the bark of the western yew (Taxus brevifolia), has a unique mechanism of action. Unlike other antimicrotubule agents in clinical use (e.g. colchicine, vincristine, and vinblastine) that shift the equilibrium between microtubules and tubulin subunits toward microtubule disassembly, paclitaxel promotes assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization. These microtubules are stable even when treated with low temperatures or calcium, conditions that usually promote disassembly. This unusual stability results in the inhibition of the normal dynamic reorganization of the microtubule network that is essential for vital interphase and mitotic cellular functions. In addition, paclitaxel induces abnormal arrays or "bundles" of microtubules during mitosis.
- Human Toxicology: The dose limiting toxicities and MTD of paclitaxel administered on a variety of schedules to patients with solid neoplasms were previously evaluated in phase I trials. In these studies, paclitaxel was infused over 1, 3, 6, and 24 h, but severe acute reactions, characterized by bronchospasm, hypotension, stridor, tachy- and bradyarrhythmias, and death, resulted in the temporary discontinuation of all trials. These reactions were attributed to paclitaxel's Cremophor vehicle, since identical reactions were observed with other

drugs formulated with it and when the vehicle alone was administered to animals. Since a higher incidence of these acute reactions was observed with shorter durations of infusion, studies that used shorter infusions were permanently discontinued, and trials that evaluated longer infusion durations (24 h) were resumed using antiallergic pre-medications consisting of corticosteroids, H1- and H2- histamine antagonists. These modifications were associated with a marked reduction in the incidence of acute reactions. Neutropenia was the major dose-limiting toxicity for paclitaxel in phase I solid tumor trials. In addition, a sensory neuropathy, characterized by a glove-and-sock distribution of numbness and paresthesias, was observed at higher doses. Nausea and vomiting, myalgias, mucositis, total-body alopecia, diarrhea, and phlebitis were also observed.

- Pharmaceutical Data: Formulation: Paclitaxel (TAXOL®) for Injection Concentrate is a clear colorless to slightly yellow viscous solution. It is commercially supplied as a solution in a nonaqueous medium. It is intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Paclitaxel is available in 30 mg (5mL) vials. Each mL of sterile non-pyrogenic solution contains 6 mg paclitaxel, 527 mg of Cremophor®EL (polyoxyethylated castor oil) and 49.7% (v/v) dehydrated alcohol, USP.
- Storage and Stability: Unopened vials of Paclitaxel for Injection Concentrate are stable until the date indicated on the package when stored under refrigeration, 2°-8°C (36°47° F). Refrigeration is not required for shipping. Freezing does not adversely affect the concentrate. Solutions for infusion which are prepared as recommended are stable at ambient temperature and lighting for up to 27 hours.
- Administration: Commercially available. Paclitaxel should be given after the patient has received the appropriate premedication as per institutional standards. Paclitaxel: supplied in 5 ml vials containing 30 mg of drug (6mg/ml). Please refer to the package insert for information on preparation and for full prescribing information.
- Drug interactions: There is a potential for interaction with Ketoconazole, which might interfere with paclitaxel metabolism.
- Contraindications: Known hypersensitivity to either paclitaxel or Cremaphor EL.

8.5 Cisplatin

- Formulation: Cisplatin is a sterile aqueous solution, each mL containing 1 mg cisplatin and 9 mg sodium chloride. Cisplatin is supplied in multidose vials of 50 mg and 100 mg cisplatin. Please refer to package insert for information on preparation. NOTE: Aluminum reacts with cisplatin causing precipitate formation and loss of potency; therefore, needles or intravenous sets containing aluminum parts that may come in contact with the drug must not be used for the preparation or administration of cisplatin.

- Storage: Store at 15C to 20C. Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days from light or for 7 days under fluorescent room light.
- Availability: Commercially available. Administration should follow institutional guidelines and may depend on renal function, and ability to give pre- and post-hydration as appropriate. Typically, a bolus injection will be given over 2-3 hours, but injection time may be extended to minimize adverse events. Pre- and post-hydration is required.

8.6 Filgrastim

- Packaging and Formulation: G-CSF (Filgrastim) is commercially available. Filgrastim is a sterile, clear, colorless, preservative-free liquid for parenteral administration, containing Filgrastim at a specific activity of 1.0 ± 0.6 x 108 U/mg (as measured by a cell mitogenesis assay). The product is available in single use vial form and prefilled syringe. The single use vial contains 480 mcg Filgrastim at a fill volume of 1.6 mL. The formulation is: 480 mcg of Filgrastim (r-methHuG-CSF), containing acetate (0.94 mg), sorbitol (80.0 mg), Tween® 80 (0.004%), sodium (0.056 mg) in water for injection, USP q.s. ad (1.6 mL). The single use prefilled syringe contains 0.6 mg Filgrastim at a fill volume of 0.8 mL. The formulation is: 480 mcg of Filgrastim (r-methHuG-CSF), containing acetate (0.472 mg), sorbitol (40.0 mg), Tween® 80 (0.004%), sodium (0.028 mg) in water for injection, USP q.s. ad (0.8 mL).
- Storage Conditions and Stability: Filgrastim should be stored in the refrigerator at 2o to 8oC (36o to 46o F). Avoid shaking. Prior to injection, Filgrastim may be allowed to reach room temperature for a maximum of 24 hours. Any vial or pre-filled syringe left at room temperature for greater than 24 hours should be discarded. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit; if particulate or discoloration are observed, the container should not be used. At a concentration of 5 mcg/ml or greater in D5W, filgrastim is stable for 7 days at room or refrigerator temperatures. At dilutions from 5 to 15 mcg/ml, albumin in a final concentration if 2mg/ml should be added to protect against adsorption to plastic materials. Addition of albumin is unnecessary when the drug is diluted to a concentration greater than 15 mcg/ml in D5W. Dilutions in D5W are stable in glass bottles, polyvinyl chloride, polyolefin or polypropylene bags and IV sets, and Travenol Infusors. Dilution of Neupogen® to a final concentration of less than 5 mcg/mL is not recommended at any time. Do not dilute with saline at any time because the product may precipitate.
- Preparation and Administration: If using the vial, draw the appropriate dose into a syringe for subcutaneous injection. If using the pre-filled syringe, select the

appropriate pre-filled syringe for subcutaneous injection. Inject only the appropriate dose, discard the unused drug. Incompatibilities: Normal saline.

- Adverse Reactions: The following events are associated with Filgrastim and meet the regulatory definition of "expected." The only consistently observed clinical toxicity described with Filgrastim is medullary bone pain. Other clinical adverse events that have been described include skin rash, and cutaneous vasculitis. Since commercial introduction of Neupogen®, there have been rare reports of allergic-type reactions. Biochemical abnormalities that may occur include increases in alkaline phosphatase, uric acid, and lactate dehydrogenase.
- Overdosage: The maximum amount of Filgrastim that can be safely administered has not been determined. Efficacy was demonstrated at doses of 4 to 8 mcg/kg/day in the phase 3 study of nonmyeloablative chemotherapy. Patients in bone marrow transplant studies received up to 138 mcg/kg/day without toxic effects, although there was a flattening of the dose response curve above daily doses of greater than 10 mcg/kg/day. In Filgrastim clinical trials of cancer patients receiving myelosuppressive chemotherapy, WBC > 100,000/mm3 have been reported in less than 5% of patients but were not associated with any reported adverse clinical effects. In cancer patients receiving myelosuppressive chemotherapy, discontinuation of Filgrastim therapy usually results in a 50% decrease in circulating neutrophils within 1 to 2 days, with a return to pretreatment levels in 1 to 7 days.
- Toxicity/Warnings: Filgrastim is contraindicated inpatients with known hypersensitivity to E coli-derived proteins, pegfilgrastim, Neupogen®, or any other component of the product. Rare cases of splenic rupture have been reported following the administration of colony stimulating factors, including Filgrastim, for peripheral blood progenitor cell (PBPC) mobilization in both healthy donors and patients with cancer. Some of these cases were fatal. Individuals receiving Filgrastim who report abdominal or shoulder tip pain, particularly healthy donors receiving Filgrastim for PBPC mobilization, should be evaluated for an enlarged spleen or splenic rupture. Adult respiratory distress syndrome (ARDS) has been reported in neutropenic patients with sepsis receiving Filgrastim and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic patients receiving Filgrastim who develop fever, lung infiltrates, or respiratory distress should be evaluated for the possibility of ARDS. In the event that ARDS occurs, Filgrastim should be discontinued until resolution of ARDS and patients should receive appropriate medical management for this condition. Allergic-type reactions occurring on initial or subsequent treatment have been reported in < 1 in 4000 patients treated with Filgrastim. These have generally been characterized by systemic symptoms involving at least 2 body systems, most often skin (rash, urticaria, facial edema), respiratory (wheezing, dyspnea), and cardiovascular (hypotension, tachycardia). Some reactions occurred on initial exposure. Reactions tended to occur within the first 30 minutes after

administration and appeared to occur more frequently in patients receiving Filgrastim IV. Rapid resolution of symptoms occurred in most cases after administration of anti-histamines, steroids, bronchodilators, and/or epinephrine. Symptoms recurred in more than half the patients who were rechallenged. Severe sickle cell crisis has been reported in patients with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle/beta+ thalassemia) who received Filgrastim for PBPC mobilization or following chemotherapy. One of these cases was fatal.

- Pregnancy and Lactation: Since there are no adequate and well-controlled studies in pregnant women, the effect, if any, of Filgrastim on the developing fetus or the reproductive capacity of the mother is unknown. It is not known whether Filgrastim is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when Filgrastim is administered to a nursing woman.
- Drug Interactions: No formal drug interaction studies between pegfilgrastim and other drugs have been performed. Drugs which may potentiate the release of neutrophils, such as lithium, should be used with caution. Patients receiving lithium and Filgrastim should have more frequent monitoring of neutrophil counts.
- Nursing Guidelines: Filgrastim should be kept in the refrigerator until needed and the vials or Pre-filled Syringe should not be shaken. The drug should be administered at the same time each day. Vials and Pre-filled Syringes of filgrastim are single-dose and the remaining drug should be discarded. Refer to protocol text for information regarding requirements for documentation of doses administered, temperatures, side effects, etc. Acetaminophen is the recommended analgesic for mild bone pain. Duration of therapy will be determined by the return of blood counts (WBC/ANC) to specific values.

8.7 Nivolumab

- Supply: Nivolumab is investigational and supplied by BMS
- Storage Conditions and Handling: Nivolumab should be stored at between 2-8 degrees Celsius (36-46 degrees Fahrenheit), and protected from light and freezing. If any temperature excursions are encountered during storage, they should be reported to BMS. As with all injectable drugs, care should be taken when handling and preparing Nivolumab. Whenever possible, Nivolumab should be prepared in a laminar flow hood or safety cabinet using standard precautions for the safe handling of intravenous agents applying aseptic technique. Partially used vials should be disposed at the time following procedures for the disposal of anticancer drugs.
- Preparation and Administration: Nivolumab injection is to be administered using a volumetric pump with a 0.2/0.22 micron pore size, low protein binding polyethersulfone membrane in-line filter at the protocol-specific doses. The line

should be flushed at the end of the infusion with sufficient quantity of normal saline per institution SOC. Nivolumab is not to be administered as an IV push or bolus injection. At the dose of 360 or 480mg, the total dose needed will be diluted to a minimum total volume of 100 ml in 0.9% Sodium Chloride injection solution. Care must be taken to assure sterility of the prepared solution as the produce not contain any anti-microbial preservative or bacteriostatic agent. Nivolumab should be administered over 30 minutes but 60 minutes would still be acceptable; infusions will be controlled by a volumetric pump. No incompatibilities between Nivolumab and polyolefin bags have been observed. IV bags/containers should specify they are made of polyolefin. If this is not clearly specified, please check with the manufacturer of the IV bag/container. 1) Allow the appropriate number of vials of Nivolumab to stand at room temperature for approximately 5 minutes before preparation. 2) Ensure that Nivolumab solution is clear, colorless, and essentially free from particulate matter. 3) Aseptically withdraw the require volume of Nivolumab into a syringe and dispense into an IV bag. a. Add the appropriate volume of 0.9% Sodium Chloride injection solution. b. Mix by gently inverting several times. DO NOT shake. c. Record the time the Nivolumab was prepared on the IV bag label. d. Attach the IV bag containing the Nivolumab solution to the infusion set, in-line filter, and infusion pump. e. The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 30-60 minutes. f. At the end of the infusion period, flush the line with a sufficient quantity of 0.9% Sodium Chloride injection solution. 4) Pharmacy supplies required: a. Empty IV bags-50mg, 100mL, 200 mL b. 0.9% NaCl bags c. 0.2 or 0.22 micron in line filter and infusion tubing d. Volumetric infusion pumps.

- Use Time/Stability: After preparation, nivolumab infusion should be stored at room temperature for no more than 8 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion. An alternation option is storage under refrigeration at 2-8 degrees Celsius for no more than 24 hours from the time of infusion preparation. Do not freeze.
- Investigational supply of Nivolumab is obtained from Bristol Myers Squibb. Drug supplies will be kept in a secure, limited access storage area under the storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.
- The responsible person must maintain records of the product's delivery to the study site, the inventory at the site and the use by each patient. The Principal Investigator (and participating site investigators) are responsible for all destructions/disposals of partially used and unused supplies. Supplies are not to be shipped back to BMS. A copy of the drug destruction certificate must be maintained for provision to BMS at the end of the study.

- These records will include dates, quantities, batch/serial numbers, expiry ("use by") dates, and study patients. The responsible person will maintain records that document adequately that the patients were provided the doses specified by the CSP and reconcile all investigational product(s) received from BMS.

9 CORRELATIVE STUDIES

9.1 Objectives

Correlative studies will be explorative in nature and will focus on tissue (serial samples) as well as blood based markers. The overreaching goal is in a descriptive manner to identify changes to the tumor microenvironment with chemoimmunotherapy using serial samples, and also evaluating potential predictive candidate biomarkers.

We will collect plasma samples to monitor treatment progress using cell free circulating tumor DNA (ctDNA). This will be monitored by measuring somatic mutations. In addition to providing a marker of treatment efficacy, it will also be used to assess patients after treatment serially to assess any evidence of early recurrence but will not be used for clinical decision making at this point.

9.2 Correlative Analysis

9.2.1 Tissue

Baseline archival (or if not available alternatively fresh) tissue will be collected on all patients as well as a biopsy around day 8 of cycle 2 to assess synergistic immunotherapy relevant changes in the tumor micro-environment. In the curative intent setting, biopsy is readily doable in virtually all head and neck cancer patients with stage IV HNSCC as enrolled in this trial.

9.2.1.1 Multicolor immunofluorescence based assessment of immune microenvironment

Using both archival or fresh tumor samples and then the on-treatment paired biopsy during induction chemoimmunotherapy, we will analyze dynamic changes in the immune microenvironment.

The analyses may include determination of CD8, PD-L1, FOXP3, IDO, CD168 and other immune related markers via immunofluorescence. Results will be digitally assessed, and results descriptively compared with results from flow cytometry and mRNA analysis.

9.2.1.2 mRNA Analysis / Immune Signatures

Analysis will be performed using the Nanostring Counter (or similar approach) using the Nanostring immune panel. Briefly, from 3-5 FFPE slides, RNA will be extracted using the Qiagen RNA/DNA FFPE kit and protocol.

9.2.1.3 Tumor DNA Analysis

Exome sequencing from tumor and normal blood white cells will be performed on the tumor samples for an exploratory analysis of correlation of genetic aberrations, immune phenotype, tumor response, and tumor mutational burden. In addition, tumor RNAseq analysis will be performed from tumor tissue. Specific processing information will be made available in a continually updated SOP for tissue collection and processing.

9.2.1.4 Germline DNA Analysis

Blood will be obtained from all patients for exome sequencing of normal DNA. Specific processing information will be made available in a continually updated SOP for tissue collection and processing.

9.2.1.5 Analysis of Tumor Digests

Fresh tumor samples will be digested using a protocol for tumor digestion employing the Miltenyi GentleMACS system available in the HIM Core facility. Single cell suspension will be stored for subsequent FACS or similar analysis. Specific processing information will be made available in a continually updated SOP for tissue collection and processing.

9.2.2 Blood

9.2.2.1 ctDNA Analysis

Using cell free circulating DNA (ctDNA), we will measure somatic mutations. This will be assessed as a candidate marker of treatment efficacy e.g. during induction with chemoimmunotherapy (baseline versus 3 weeks into treatment (cycle 2, day 1)).

Furthermore, it will also be used to assess patients after treatment serially to assess any evidence of early recurrence (early detection) but will not be used for clinical decision making at this point. Especially as part of a de-escalation protocol, early detection in the future may prove invaluable in order to identify patients at risk for recurrence who may benefit from additional therapy.

The option to add time points to ctDNA exists at the discretion of the primary investigator with the permission of the patient.

9.2.2.2 RNA Analysis

Blood samples will be obtained at baseline and after 3 weeks (cycle 2, day 1). Samples will be processed for RNA extraction (e.g. using the PAXgene RNA kit/tubes). RNA will be analyzed by Nanostring or RNAseq in an exploratory fashion comparing baseline with on-treatment inflammatory markers. Specific processing information will be made available in a continually updated SOP for tissue collection and processing.

9.3 Sample and Tissue Procurement

9.3.1 Archival Tumor Collection

All patients at the time of enrollment need to provide 10 or more 5-micron un-stained slides for correlative analysis. Patients who cannot fulfill this requirement will need to undergo a new biopsy prior to enrollment on study.

9.3.2 Tissue Biopsy

Tumor biopsy will be performed prior to starting therapy or archival tissue will be obtained for all patients. At the time of surgical resection or biopsy, tissue in excess of what is necessary for diagnostic purposes will be obtained < 15 min after removal from the patient. Furthermore, an optional on-treatment biopsy during induction chemoimmunotherapy will be performed sometime around day 8 of cycle 2 as clinically feasible.

Tissues will be instantaneously frozen and stored anonymously with a unique barcode at -80C in a locked freezer in Biospecimen Shared Resource (Tissue Bank) at the University of Chicago. Additional alternative processing (e.g. tissue digestion) and cell suspension generation for flow analyses is also acceptable.

After obtaining sample:

- Write study number, patient initials, and date on plastic cryomold
- Weigh or estimate sample weight and slice sample into less than 0.5 cm thick fragments
- Place tissue into cryotube labeled with study number, patient initials, and date filled with RNAlater reagent from Qiagen
- Freeze over liquid nitrogen vapors or in -80C freezer

9.3.3 Blood Isolation

Blood will be obtained from all patients enrolled in the study for pharmacogenomics and biomarker evaluation. Investigation of the relevant polymorphisms will take place in germline DNA extracted from peripheral whole blood (10 mL) collected in EDTA (purple top) plastic vacutainer tubes (i.e. BD catalog #366643). Investigation of cytokine markers will be from peripheral blood (10 mL) collected in a red top vacutainer tube. Blood should

be stored at -80C and sent to Biospecimen Shared Resource (Tissue Bank) at the University of Chicago for DNA extraction and plasma isolation following standard HTRC protocols.

Isolated DNA will be stored anonymously with a unique barcode at -80C at the University of Chicago for future genotype analysis.

Patients will have blood samples collected prior to induction chemoimmunotherapy and 2-3 weeks into induction therapy. Samples will also be collected prior to radiotherapy initiation, and 4 and 12 weeks post-chemoradiation.

Plasma will be used for identification of cell free circulating tumor DNA, e.g. for somatic mutations to be assessed as a candidate biomarker for monitoring during treatment for efficacy and surveillance after completion of treatment for detection of early recurrence.

10 STUDY CALENDAR

		Induction Chemotherapy									CRT						Post-treatment Follow Up		
	Pre-Study$	C1 D1	C1 D8	C1 D15	C2 D1	C2 D8	C2 D15	C3 D1	C3 D8	C3 D15	Pre-RT	RT C1	RT C2	RT C3	RT C4	RT C5	4 weeks post-chemoRT (15)	12 weeks post-chemoRT (15)	Q3-6 mo f/u 2 years post-chemoRT (15)
Scheduling Window (Days)	**-28 to -1**	±3	±3	±3	±3	±3	±3	±3	±3	±3		±3	±3	±3	±3	±3		±10	
Induction Chemo		X	X	X	X	X	X	X	X	X									
CRT(1)												X	X	X	X	X			
Adjuvant nivolumab																	Q4 weeks for 9 months (13)		
Panendoscopy (14)	X																		
Biopsy(2)	X					X													
PET/PET-CT(3)	X										X*							X	
MRI/CT Neck	X										X*								X(11)
CT Chest	X																		X(11)
Metastatic workup (4)	X																		
Correlative blood(5)	X				X						X						X	X	
Informed consent	X																		
Medical History	X																		
Concurrent Meds	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Swallowing Eval. (6)	X																X	X	
Dental Exam (6)	Anytime before CRT																		
Vital Signs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Height	X																		
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Performance Status	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
TSH(7)	X							X				X						X	X
CBC	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Chemistries (8)	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
AE evaluation	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Tumor Measurement	X										X						X		
QoL Evaluations	X										X						X	X	X
b-hCG(9)	X										X						X	X	
HPV testing	X																		
Surgery(10)											X						X		

$All baseline testing is to be conducted within 4 weeks prior to start of protocol therapy unless otherwise specified.
*Pre-chemoradiation imaging should occur on or within 10 days of cycle 3 day 15
(1)CRT: Please refer to dedicated treatment section. Briefly, RT duration varies depending on allocated treatment arm and choice of regimen – cisplatin-RT vs TFHX.
(2)Biopsy should be performed if no adequate archival tissue is available pre-study. A second optional biopsy for purposes of correlative tissue analysis should be performed around cycle 2 day 8 of induction chemotherapy.
(3) At baseline PET/PET-CT is optional. On study PETs between induction/chemoRT and after chemoRT are optional.
(4) As appropriate per treating physician – this may include but is not limited to abdominal imaging, PET, bone scan.
(5) Correlative blood draws will occur pre-treatment, day 1 of cycle 2, pre-chemoradiation, and at 4 and 12 weeks after chemoradiation.
(6) These tests can occur at any time before radiation starts – before start of induction therapy or during induction therapy.
(7) TSH should be repeated q2mo while on consolidative nivolumab, and annually after post-CRT, and as part of standard of care considered to be continued beyond this protocol.
(8) Standard comprehensive metabolic panel includes electrolytes, kidney function, liver function, glucose, and calcium
(9) To be done within 24 hr of starting therapy.
(10) Although unlikely to be necessary, an option for surgical neck dissection will be allowed after induction therapy prior to radiation to reduce the radiotherapy field size. In addition, biopsy and/or salvage surgical procedures may be indicated for persistent disease after completion of definitive chemoradiation.
(11) Follow up imaging of the head, neck, and optionally, the chest via CT and/or MRI is indicated after completion of chemoradiation every 3 months for the first year, every 6 months for years 2-3, and annually for years 4-5.
(13) A chemistry and CBC will be drawn every 4 weeks (at each dose) of consolidative nivolumab. These are the only required tests specific for consolidative visits. Imaging and TSH may occur on these visits if they fall in line with the post-chemoradiation imaging schedule.

(14) If clinically indicated by multidisciplinary tumor board.
(15) The first post-chemoRT follow up scan should occur three months after completing chemoRT. The remaining follow up imaging may occur within 1 month of the specified time points.
(16) HPV testing is required prior to C1D1 for oropharyngeal primary tumor patients only. Other anatomic sites will be classified as HPV- unless requested per treating physician.
(17) CT chest required only if PET/CT not performed.

11 CRITERIA FOR OUTCOME ASSESSMENT/THERAPEUTIC RESPONSE

11.1 Outcome Response

All baseline evaluations will be performed within the first 28 days. For subsequent evaluation, the method of assessment and techniques will be the same as those used at baseline. We will use radiographic response rates per RECIST v1.1 and we will further quantify tumor shrinkage ≥ 50% defined as deep response.

11.2 Therapeutic Response

Response will be evaluated in this study using the international criteria proposed by the RECIST committee for measurable disease. Patients will be evaluated for response according to the guidelines below.

11.2.1 Response Evaluation Criteria in Solid Tumors (RECIST)

Response and progression will be evaluated in this study using the new international criteria proposed by the revised RECIST guideline (version 1.1). Changes in the largest diameter (uni-dimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.2.1.1 Disease Parameters

- Measurable disease: Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) on radiography or by calipers on clinical exam.
- 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. At baseline and in follow-up, only the short axis will be measured and followed.
- Non-measurable disease: All other lesions (or sites of disease), including small lesions (longest diameter < 10 mm or pathological lymph nodes with ≥ 10 to < 15 mm short axis), are considered non-measurable disease.
- Target lesions: All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest 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 for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added to the sum. The baseline sum diameters will be used as a reference to further characterize any objective tumor regression in the measurable dimension of the disease.

- Non-target lesions: All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.2.1.2 Methods for Evaluation of Measurable Disease

All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of 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 is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are accessible by clinical exam.

Clinical Lesions. Clinical lesions will only be considered measurable when they are superficial (e.g. skin nodules and palpable lymph nodes) and ≥ 10 mm diameter as assessed using calipers (e.g. skin nodules).

Conventional CT and MRI: Diagnostic imaging plays an important role in the assessment of head and neck squamous cell carcinomas before and after treatment. Currently, computed tomography (CT) with contrast, fluorodeoxyglucose positron emission tomography (FDG-PET), and magnetic resonance imaging (MRI) are routinely used to evaluate patients with this type of cancer.

11.2.1.3 Evaluation of Target Lesions

- Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
- Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Deep Response (DR): At least a 50% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.
- Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum 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 is also considered progression.

- Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

12 REGULATORY AND REPORTING REQUIREMENTS

12.1 Regulatory Guidelines

Food and Drug Administration (FDA) Approval

This study will be conducted under an IND held by Dr. Everett Vokes at the University of Chicago. The University of Chicago CCTO will be responsible for facilitating all communications with the FDA on behalf of the IND holder. Participating sites should not communicate directly with the FDA.

New Protocol Distribution and IRB Submission

Once final BMS and University of Chicago (U of C) IRB approval is received, the protocol and consent form will be distributed to the participating affiliate institutions electronically. Upon receipt of the email, the affiliate institution is expected to do the following:

- The affiliate institution is expected to submit the protocol to their IRB as soon as possible after receipt.
- The U of C version date must appear on the affiliate consent form and on the affiliate IRB approval letter. The version dates can be found on every page of the protocol and consent form.

Before the study can be initiated at any site, the following documentation must be provided to the Cancer Clinical Trials Office (CCTO) at the U of C Comprehensive Cancer Center.

- A copy of the official local 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 institutions lab normal values
- Investigational drug accountability standard operating procedures
- Additionally, before the study can be initiated at any site, the required executed research contract/subcontract must be on file with the University of Chicago.

Amendment Distribution and IRB Submission

All modifications to the protocol, consent form, will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form (if applicable) to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.
- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment must be IRB approved by the institution within 3 months from the date that it was received.
- The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter. The version dates can be found on the header of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.
- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

Annual IRB Renewals, Continuing Review and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the affiliates' IRBs at least once a year for the duration of the study. The annual IRB renewals for the affiliate institution should be emailed promptly to the Regulatory Affairs Administrator. If the institution's IRB requires a new version of the consent form with the annual renewal the consent form should be included with the renewal letter.

Departure from the Protocol

An investigator cannot modify the protocol without satisfying procedures in this protocol as outlined in the study calendar. Any changes in research activity, except those necessary to remove an apparent, immediate hazard to the study subject, must be reviewed and approved by the local IRB. When a variation from the protocol is deemed necessary for an individual subject, the principal investigator or study chair must be contacted by phone or email (**Everett Vokes, 773-702-9306 / 312-823-7990**, evokes@medicine.bsd.uchicago.edu). Such contact must be made as soon as possible to permit a decision as to whether or not the subject is to continue in the study.

The principal investigator or study chair must be informed of all intentional or unintentional departures from the protocol and will decide whether or not the subject is to continue in the study (**Everett Vokes, 773-702-9306 / 312-823-7990**, evokes@medicine.bsd.uchicago.edu). All departures from the protocol, intentional and unintentional, along with the decision of the principal investigator will be submitted to the local and University of Chicago IRB per institutional guidelines.

12.2 Adverse Event Characteristics

CTCAE term (AE description) and grade

The descriptions and grading sales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5 will be utilized for AE reporting. All appropriate treating areas will have access to a copy of the CTCAE version 5. A copy of the CTCAE version 5 can be downloaded from the CTEP web site http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

Attribution of the AE

- Definite (5) – The AE is *clearly related* to the study treatment.
- Probable (4) – The AE is *likely related* to the study treatment.
- Possible (3) – The AE *may be related* to the study treatment.
- Unlikely (2) – The AE is *doubtfully related* to the study treatment.
- Unrelated (1) – The AE is *clearly NOT related* to the study treatment.

12.3 Adverse Event Definitions

12.3.1 Adverse Event

An adverse event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product that does not necessarily have a causal relationship with the treatment. An adverse event can be any unfavorable and unintended sign (including a laboratory finding), symptom or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

At each evaluation patients should be interviewed in a non-directed manner to elicit potential adverse reactions from the patient. The occurrence of an adverse event will be based on changes in the patient's physical examination, laboratory results, and/or signs and symptoms, and review of the patient's own record of adverse events.

Adverse events will be followed until resolution while the patient remains on-study. Once the patient is removed from study, events thought to be related to the study medication will be followed until resolution or stabilization of the adverse event, or until the patient

starts a new treatment regimen, or death, whichever comes first. Patients will be followed for AEs/SAEs for 100 days after their last dose of study drug(s).

12.3.2 Serious Adverse Events (SAE)

An adverse event is considered serious if it results in ANY of the following outcomes

- Death
- Life-threatening (e.g. places patient at immediate risk of death, this does not include events that might have caused death if they occurred a greater severity)
- Results in inpatients hospitalization or prolongation of existing hospitalization for ≥ 24 hours
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
- A congenital anomaly/birth defect

Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, bloody dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

In addition to those events meeting the definitions above, the following will be considered an SAE for the purposes of this study:

- Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug
- Pregnancy within 6 months completion of chemoradiation or the last dose of consolidative nivolumab, whichever occurs latest
- Overdose to any medication required for cancer treatment or supportive measures
- Grade 3 or more infusion reaction due to nivolumab

12.3.3 Relatedness

The definition of "related" being that there is a reasonable possibility that the drug caused the adverse experience.

12.3.4 Adverse Reactions

An adverse event is considered to be an adverse reaction if there is evidence to suggest a causal relationship to the study agent. This may include a single occurrence of an event strongly associated with drug exposure (e.g. Stevens-Johnson Syndrome), one or more occurrence of an event otherwise uncommon is the study population, or an aggregate analysis of specific events occurring at greater than expected frequency.

12.4 Adverse Event Reporting Requirements

12.4.1 Routine Adverse Event Reporting

All adverse events must be reported in routine study data submissions. AEs reported using the Serious Event Reporting Form and/or MedWatch Form discussed below must also be reported in routine study data submissions.

All adverse events (except grade 1 and 2 laboratory abnormalities that do not require an investigation), regardless of causal relationship**,** are to be recorded in the case report form and source documentation. The Investigator must determine the intensity of any adverse events according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 5.0 and their causal relationship.

12.4.2 Serious Adverse Event Reporting to Coordinating Center

Use the UC CCC protocol number and the protocol-specific patient ID assigned during trial registration on all reports.

All serious adverse events (as defined in section 12.3.2) occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UCCCC). The responsible Research Nurse or other designated individual at the treating site should report the SAE to the Study Lead Investigator, the University of Chicago CRC, and the CCTO by the end of the business day when the team becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm the next business day. Reports should be made using the "Serious Event Report" Form. Please scan and send via email (preferred) or fax to the following:

University of Chicago Phase II CRA General:
PhaseIICRA@medicine.bsd.uchicago.edu
Fax: 773-702-4889

UC CCC Cancer Clinical Trials Office Quality Assurance:
qaccto@bsd.uchicago.edu

All unexpected adverse reactions must be reported to the IND holder so that the University of Chicago CCTO can inform the FDA. The responsible Research Nurse or other designated individual at the treating site should provide a complete written report using the FDA MedWatch 3500A from. The completed form should be sent to the CCTO at qaccto@bsd.uchicago.edu and to the Phase II CRA at PhaseIICRA@medicine.bsd.uchicago.edu within the specified timelines below regardless of whether all information regarding the event is available. If applicable, a follow-up report should be provided to the CCTO if additional information on the event becomes available.

Participating sites should not forward any adverse event reports directly to the FDA. The CCTO will report all events to the FDA as per the current FDA guidelines.

All serious adverse events should also be reported to the local IRB of record according to their policies and procedures.

12.4.3 Serious and Unexpected Adverse Event Reporting by the Coordinating Center

The designated UC CCC Regulatory Manager will notify all participating sites of all unexpected and serious adverse reactions that occur on this clinical trial and which are reported to the FDA and/or UC Institutional Review Board (IRB). When reported to the FDA, a copy of the completed Form 3500A (MedWatch) will be provided to the responsible Regulatory Manager by the CCTO IND Coordinator for distribution to all participating sites.

12.4.4 Serious Adverse Event Reporting to BMS

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours of investigator knowledge of the event. SAEs must be recorded on BMS or an approved form; pregnancies on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com
SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.) If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to the BMS (or designee) using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization.

If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form. The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharamacovigilance (WoldwideWorldwide.Safety@bms). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

12.5 Data Submission

Data reporting will be performed utilizing the RedCap electronic data capture system. The University of Chicago CRC will provide you with the applicable user registration information.

All required data must be recorded in the RedCap database at the completion of each cycle. AEs are to be entered in real time. SAEs are to be entered on the Serious Event Form within 24 hours of the site's knowledge of the event and sent via email (preferred) or fax to the University of Chicago (PhaseIICRA@medicine.bsd.uchicago.edu or qaccto@bsd.uchicago.edu; Fax: 773-702-4889). All case report forms must be completed by designated study personnel.

Each screened (consented) patients is to be entered into RedCap within 48 hours of patient registration. The site will prepare and maintain adequate and accurate source documents. Source records are original documents, data, and records (e.g. medical records, raw data collection forms, pharmacy dispensing records, recorded data from automated instruments, laboratory data) that are relevant to the clinical trial. These documents are designed to record all observations and other pertinent data for each patient enrolled in this clinical trial. Source records must be adequate to reconstruct all data transcribed onto the case report form.

12.6 Data and Safety Monitoring

This study will be monitored by the designated University of Chicago Clinical Research Coordinator (CRC) in accordance with the University of Chicago, Section of Hematology/Oncology standard operating procedure titled Monitoring of Multi-Institutional Investigator Initiated Clinical Trials.

Prior to subject recruitment, and unless otherwise specified, a participating site will undergo a Site Initiation Teleconference to be conducted by the designated University of Chicago research team. The site's principal investigator and their study staff must attend the site initiation meeting.

Monitoring will be conducted to verify the following:

- Adherence to the protocol
- Completeness and accuracy of study data and samples collected
- Compliance with regulations
- Submission of required source documents

Participating sites will also undergo a site close-out teleconference upon completion, termination or cancellation of a study to ensure fulfillment of study obligations during the

conduct of the study, and to ensure that the site Investigator is aware of his/her ongoing responsibilities.

Unless otherwise specified, this protocol will undergo weekly review at the multi-institutional data and safety monitoring teleconference as per procedures specified by the UC CCC NCI-approved Data and Safety Monitoring Plan. The conference will review:

- Enrollment rate relative to expectations, characteristics of participants
- Safety of study participants (Serious Adverse Event & Adverse Event reporting)
- Adherence to protocol (protocol deviations)
- Completeness, validity and integrity of study data
- Retention of study participants

Protocol deviations are to be documented using the Protocol Deviation Form and sent via email to PhaseIICRA@medicine.bsd.uchicago.edu. Deviations that are considered major because they impact subject safety or alter the risk/benefit ratio, compromise the integrity of the study data, and/or affect subjects' willingness to participate in the study must be reported within 7 days. Please contact the University of Chicago CRA (PhaseIICRA@medicine.bsd.uchicago.edu) if you have questions about how to report deviations. All major protocol deviations should also be reported to the local IRB of record according to their policies and procedures.

12.7 Auditing

In addition to the clinical monitoring procedure, the University of Chicago Comprehensive Cancer Center (UCCCC) will perform routing Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UCCCC DSM Plan. Audits provide assurance that trials are conducted and study data are collected, documented and reported in compliance with the protocol. Further, quality assurance audits ensure that study data are collected, documented and reported in compliance with Good Clinical Practices (GCP) Guidelines and regulatory requirements. The audit will review patients enrolled at the University of Chicago in accordance with audit procedures specified in the UCCCC Data and Safety Monitoring plan. For institutions who are formal members of the Personalized Cancer Care Consortium (PCCC), the UC CCC will conduct on site quality assurance audits on average every two years during the enrollment and treatment phase of the study.

A regulatory authority (e.g. FDA) may also wish to conduct an inspection of the study, during its conduct or even after its completion. If an inspection has been requested by a regulatory authority, the site investigator must immediately inform the University of Chicago Cancer Clinical Trials Office and Regulatory Manager that such a request has been made.

13 STATISTICAL PLAN

13.1 Analysis Populations

- All Enrolled Patients: All patients who sign an informed consent form and are registered onto the trial
- Safety Population: All patients who receive at least one dose of chemo- or immunotherapy (i.e. carboplatin, paclitaxel, and nivolumab).
- Evaluable Population: All patients who receive at least one dose of carboplatin, paclitaxel, and nivolumab.

13.2 Endpoints

13.2.1 Primary Endpoint

- Objective: To intensify induction chemotherapy with the addition of an immune checkpoint inhibitor aimed at increasing the proportion of patients achieving a deep tumor response in order to subsequently allow risk-adapted definitive chemoradiotherapy in advanced stage HPV negative head and neck squamous cell cancer patients.
- Definition: Deep Response Rate (DRR) is defined as a 50% or greater response to induction therapy based on RECIST v1.1 criteria.
- Analysis: The proportion of patients who achieve a deep response will be calculated along 95% exact confidence intervals for ORR on binomial distribution.
- Sample Size: The DRR will be compared against a historical control of a platinum/taxane induction regimen. The DRR of our historical control is 22%[11]. This trial consisted of HPV positive and negative patients receiving induction cisplatin, paclitaxel, everolimus, and cetuximab. As noted in the study, there were 89 evaluable patients who completed induction therapy. In unpublished data, 32 of the 89 patients who completed induction therapy were HPV negative. Seven of those 32 patients had a deep response. To further provide evidence of response rate to induction therapy, we recently completed a phase I induction therapy trial using carboplatin, paclitaxel, and veliparib. Eighteen HPV negative patients were enrolled on this portion of the trial. Four of the 18 (22%) had a deep response to this regimen. Our hypothesis is that the addition of immunotherapy will increase the deep response rate to 40% based on the ~15% response rate seen with nivolumab in the metastatic setting. In addition, an increase from 38% to 58% was recently reported in a trial evaluating the addition of a PD-1 inhibitor to carboplatin and paclitaxel in squamous cell lung cancer.[49] Assessment of DRR will occur within 1-2 weeks of receiving the final dose of paclitaxel (the final dose of induction therapy). We will use a Simon two-stage design to test the null hypothesis that $P \leq 0.220$ versus the alternative that $p \geq 0.400$ has an expected sample size of 22.32 and a probability of early termination of 0.687. If the drug is

actually not effective, there is a 0.090 probability of concluding that it is (the target for this value was 0.100). If the drug is actually effective, there is a 0.197 probability of concluding that it is not (the target for this value was 0.200). After testing the drug on 17 patients in the first stage, the trial will be terminated if 4 or fewer have a deep response. If the trial goes on to the second stage, a total of 34 patients will be studied. If the total number responding is less than or equal to 10, the drug is rejected. Two additional patients will be enrolled to account for drop out prior to starting any treatment.

13.2.2 Secondary Endpoints

- Objective: Assess survival outcomes in all patients receiving induction chemoimmunotherapy and compare survival between radiation arms.
    - Endpoint: Progression free survival at 24 months after completing chemoradiation.
        - Definition: Progression-free survival will be defined as the time from registration to the date of first documented disease progression, clinical progression, or death due to any cause, whichever occurs first.
        - Analysis: PFS will be estimated by Kaplan-Meier methodology in all evaluable patients. PFS will be calculated for the entire cohort and for each radiation treatment arm. Comparison between the two radiation treatment arms will be made using the log-rank test. Patients who died without reported progression will be considered to have progressed on the date of their death. Patients who did not progress or die will be censored on the date of their last evaluable tumor assessment. Patients who started any subsequent anti-cancer therapy, including tumor-directed radiotherapy and tumor-directed surgery outside of the context of this trial, without a prior reported progression will be censored at the last evaluable tumor assessment prior to/on initiation of the subsequent anti-cancer therapy. For patient who have not progressed or are still alive, the date of documented last follow-up will be recorded.
    - Endpoint: Overall survival at 24 months after completing chemoradiation.
        - Definition: Overall survival will be defined as the time between the date of registration and the date of death.
        - Analysis: OS will be estimated by Kaplan-Meier methodology in all evaluable patients. OS will be calculated for the entire cohort and for each radiation treatment arm. Comparison between the two radiation treatment arms will be made using the log-rank test. For

patients without documentation of death, overall survival will be censored on the last date the patient was known to be alive.

- Objective: Assess disease control in all patients receiving induction chemoimmunotherapy and compare disease control between radiation arms.
    - Endpoint: Locoregional control at 24 months after completing chemoradiation.
        - Definition: Locoregional control will be defined as the time from registration to the date of first documented disease progression in the head and neck.
        - Analysis: Locoregional control will be estimated by Kaplan-Meier methodology in all evaluable patients. Locoregional control will be calculated for the entire cohort and for each radiation treatment arm. Comparison between the two treatment arms will be made using the log-rank test.
    - Endpoint: Distant control at 24 months after completing chemoradiation
        - Definition: Distant control will be defined as the time from registration to the date of first documented disease progression below the clavicles.
        - Analysis: Distant control will be estimated by Kaplan-Meier methodology in all evaluable patients. Distant control will be calculated for the entire cohort and for each radiation treatment arm. Comparison between the two radiation treatment arms will be made using the log-rank test.

13.2.3 Exploratory Endpoints

- Objective: Assess long-term/late toxicities including enteral tube dependence in all patients receiving induction chemoimmunotherapy.
- Objective: Assess acute and long-term toxicity in patients who received risk-adapted chemoradiotherapy after deep response to induction chemoimmunotherapy.
    - Endpoint: Acute and late toxicity during treatment and at 1 month, 3 months, and 1 year post-chemoradiation
        - Definition: Acute and late toxicities will be defined using the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) v5.0
        - Analysis: Acute and late toxicity will be assessed in the safety population and for each radiation treatment arm. All AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using the worst grade by CTCAE v5.0 by system and organ class. Comparisons will be made using Fisher's exact test.

    - Endpoint: Enteral tube dependency at 3 months and 1 year
        - Definition: Enteral tube dependency will be defined as continued necessity of any nutrition through enteral tube to maintain weight.
        - Analysis: The incidence of enteral tube dependency will be described within the safety population and among each radiation treatment arm. Comparisons will be made using Fisher's exact test.
- Objective: Evaluate quality of life in patients who receive dose-reduced chemoradiotherapy after a deep response to induction therapy.
    - Endpoint: Overall and domain subset scores of the PSS-HN and FACT H&N quality of life assessments
        - Analysis: Quality of life assessments will be measured in the safety population. Results will be tabulated and compared using Fisher's exact test.
- Objective: Interrogate and understand the immune micro-environment at baseline and 2-3 weeks into induction therapy with extensive immunohistological and serum biomarkers.
    - Analysis: Potential relationships between biomarker data and efficacy will be investigated as part of an exploratory analysis aimed at identifying baseline biomarkers that may be used to prospectively identify patients likely or not likely to respond to induction carboplatin, paclitaxel, and nivolumab. These exploratory predictive biomarker analyses will be completed with biomarkers measured in the blood and in tumor samples obtained prior to and near completion of induction therapy. The main tumor biomarkers measured will be PD-L1, tumor mutation burden, and T-cell activated gene signatures. Cell free DNA will also be collected via peripheral blood. Associations between biomarkers and efficacy measures will be analyzed on all evaluable patients with available biomarker data. The relationship between binary measures and candidate biomarkers will be investigated using logistic regression. Models to predict clinical activity based on combinations of biomarkers may also be investigated. Additional post hoc statistical analyses not specified in the protocol, such as alternative modeling approaches or unmentioned biomarkers may be completed. Details are outlined in section 8.0.

13.3 Accrual Rate and Study Duration

- We will accrue up to 36 patients to this trial to account for any drop out prior to starting therapy. Based on the number of patients seen at our institution, we hope to accrue over the course of 1.5-2 years.
- The study will end 2 years after the final patient has completed chemoradiation.
- Continued follow up will be allowed beyond the end of the trial.

13.4 Safety Analysis Plan

- The safety of adding nivolumab to induction chemotherapy will be assessed by evaluation of nivolumab exposure, adverse events, serious adverse events, deaths, and changes from baseline in laboratory determinations. Safety analyses will be performed for all patients who take at least one dose of study drug.

13.5 Handling of Missing Data

- Every attempt will be made to obtain data at the defined time points as described in the primary and secondary endpoints. For time points that have no data, we will evaluate whether or not the other time points can be used to fulfill the primary and secondary data. If the data are not sufficient to analyze specific endpoints, the participant's data may be excluded entirely or partially, depending on the specific endpoints in questions and in consultation with the biostatistician. No missing data will be imputed. Whenever possible, all available data will be included in the analysis. A sample size for each analysis will be clearly stated along with the reason for exclusion, if any participant is excluded from the analysis due to missing data.

14 STUDY MANAGEMENT AND REGULATORY AFFAIRS

14.1 Multicenter Guidelines

The specific responsibilities of the Principal Investigator and the Coordinating Center are presented in section 16.3. Clinical studies coordinated by The University of Chicago must be conducted in accordance with the ethical principles that are consistent with Good Clinical Practices (GCP) and in compliance with other applicable regulatory requirements

The Study Lead PI/Coordinating Center is responsible for distributing all official protocols, amendments, and IND Action Letters or Safety Reports to all participating institutions for submission to their individual IRBs for action as required.

14.2 Institutional Review Board (IRB) Approval and Consent

Unless otherwise specified, each participating institution must obtain its own IRB approval. It is expected that the IRB will have the proper representation and function in accordance with federally mandated regulations. The IRB should approve the consent form and protocol.

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

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

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

14.3 Food and Drug Administration (FDA) Approval

This study will be conducted under an investigator-held IND held at the University of Chicago. The University of Chicago CCTO will be responsible for facilitating all communications with the FDA on behalf of the IND holder. Participating sites should not communicate directly with the FDA.

14.4 Amendments to the Protocol

All modifications to the protocol, consent form, and/or questionnaires will be submitted to the University of Chicago IRB for review and approval. A list of the proposed modifications or amendments to the protocol and/or an explanation of the need of these modifications will be submitted, along with a revised protocol incorporating the modifications. Only the Study Lead PI can authorize any modifications, amendments, or termination of the protocol. Once a protocol amendment has been approved by the University of Chicago IRB, the Regulatory Manager will send the amended protocol and consent form (if applicable) to the affiliate institutions electronically. Upon receipt of the packet the affiliate institution is expected to do the following:

- The affiliate must reply to the email from the Regulatory Manager indicating that the amendment was received by the institution and that it will be submitted to the local IRB.

- The amendment should be submitted to the affiliate institution's IRB as soon as possible after receipt. The amendment **must** be IRB approved by the institution **within 3 months** from the date that it was received.

- **The University of Chicago version date and/or amendment number must appear on the affiliate consent form and on the affiliate IRB approval letter.** The version dates can be found on the footer of every page of the protocol and consent form. The amendment number can be found on the University of Chicago IRB amendment approval letter that is sent with the protocol/amendment mailing.

- The IRB approval for the amendment and the amended consent form (if amended consent is necessary) for the affiliate institution must be sent to the designated UC Regulatory Manager as soon as it is received.

14.5 Annual IRB Renewals, Continuing Review and Final Reports

A continuing review of the protocol will be completed by the University of Chicago IRB and the participating institutions' IRBs at least once a year for the duration of the study. The annual IRB renewal approvals for participating institutions should be forwarded promptly to the Regulatory Manager. If the institution's IRB requires a new version of the consent form with the annual renewal, the consent form should be included with the renewal letter.

14.6 Record Retention

Study documentation includes all CRFs, 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 patient consent forms).

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

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

14.7 Obligations of Study Site Investigators

the site in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Study Site Principal Investigator is responsible for personally overseeing the treatment of all study patients. He/she 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 Study Site Principal Investigator at each institution or site will be responsible for assuring that all the required data will be collected and entered into the CRFs. Periodically, monitoring visits or audits will be conducted and he/she must provide access to original records to permit verification of proper entry of data.

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16 APPENDIX

16.1 PSS-HN

PERFORMANCE STATUS SCALE FOR HEAD & NECK CANCER PATIENTS - PSS-HN

Suggestions for Administration

These performance scales may be rated by health professionals (e.g., physicians, nurses, nutritionists) or other personnel (e.g., clerks, data managers). Ratings are determined through use of an unstructured interview format.

Normalcy of Diet
Begin by asking the patient what kinds of foods (s)he has been eating. Ask what foods are difficult to eat. Based on the patient's response, choose an item at the low end of the scale. Move up the scale giving examples of foods in each category and asking the patient if (s)he is eating those food items. Even if the patient says that (s)he eats everything, inquire about specific items beginning with 50, soft chewable foods and moving upwards. Stop at the item at, and above which the patient cannot eat. The patient then receives the score **below** that. If the patient indicates that (s)he is eating a full diet, also inquire whether (s)he needs to drink more liquids than usual with meals; eating a full diet with intake of extra fluids is scored 90. If the patient can take foods orally, but is also using a feeding tube, score based on solid food.

Public Eating
Score the Public Eating scale by asking the patient where (s)he eats (in a restaurant, at home, at friends/relatives' homes, etc.) and with whom (s)he eats (always alone, with family/friends, etc). Ask patient if (s)he chooses different foods (softer, less messy, etc.) when eating with others. When was the last time the patient ate in a restaurant, cafeteria, MacDonald's, picnic, family reunion? Choose the score beside the description that best fits the patient. A patient on a restricted diet, (e.g., tube feeding, pureed foods) who does not eat in public but will join others in a public eating setting should be rated 75. Score 999 for inpatients.

Understandability of Speech
This scale is scored based on the interviewer's ability to understand the patient during conversation (in this case, based on conversation about patient's diet and social activities). Choose the score beside the description that best fits the patient. See if you can understand the patient if you are looking away while (s)he is talking.

Special Considerations for Inpatients: Administration of the PSS-HN varies somewhat for inpatients. Score the Normalcy of Diet and Understandability of Speech Scale as indicated. The Eating in Public Scale is not applicable as inpatients generally have little opportunity to eat with others or leave their hospital rooms. Inpatients receive a score of 999 on the Eating in Public Scale.

PERFORMANCE STATUS SCALE FOR HEAD AND NECK CANCER PATIENTS: PSS-HN

Patient Name_____ ID# /__/__/ /__/__/ /__/__/__/ Date /_/_/_/_/_/

NORMALCY OF DIET /__/__/__/

100	Full diet (no restrictions)
90	Full diet (liquid assist)
80	All meat
70	Raw carrots, celery
60	Dry bread and crackers
50	Soft chewable foods (e.g., macaroni, canned/soft fruits, cooked vegetables, fish, hamburger, small pieces of meat)
40	Soft foods requiring no chewing (e.g., mashed potatoes, apple sauce, pudding)
30	Pureed foods (in blender)
20	Warm liquids
10	Cold liquids
0	Non-oral feeding (tube fed)

PUBLIC EATING /_/_/

100	No restriction of place, food or companion (eats out at any opportunity)
75	No restriction of place, but restricts diet when in public (eats anywhere, but may limit intake to less "messy" foods (e.g., liquids)
50	Eats only in presence of selected persons in selected places
25	Eats only at home in presence of selected persons
0	Always eats alone
999	Inpatient

UNDERSTANDABILITY OF SPEECH / / / /

100	Always understandable
75	Understandable most of the time; occasional repetition necessary
50	Usually understandable; face-to-face contact necessary
25	Difficult to understand
0	Never understandable; may use written communication

List MA, Ritter-Sterr C, Lansky SB. A Performance Status Scale for Head and Neck Cancer Patients. Cancer. 66:564-569, 1990

16.2 FACT H&N

FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are important**. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4
	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness.....	0	1	2	3	4
GE3	I am losing hope in the fight against my illness.....	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4
	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4
GF3	I am able to enjoy life.....	0	1	2	3	4
GF4	I have accepted my illness.....	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
H&N1	I am able to eat the foods that I like	0	1	2	3	4
H&N2	My mouth is dry	0	1	2	3	4
H&N3	I have trouble breathing	0	1	2	3	4
H&N4	My voice has its usual quality and strength	0	1	2	3	4
H&N5	I am able to eat as much food as I want	0	1	2	3	4
H&N6	I am unhappy with how my face and neck look.....	0	1	2	3	4
H&N7	I can swallow naturally and easily	0	1	2	3	4
H&N8	I smoke cigarettes or other tobacco products	0	1	2	3	4
H&N9	I drink alcohol (e.g. beer, wine, etc.).....	0	1	2	3	4
H&N 10	I am able to communicate with others	0	1	2	3	4
H&N 11	I can eat solid foods.....	0	1	2	3	4
H&N 12	I have pain in my mouth, throat or neck	0	1	2	3	4

16.3 Multicenter Guidelines

Responsibility of the Study Lead PI

- The Study Lead PI will be the single liaison with regulatory and data management staff, outside sponsor/s, FDA, and funding agencies The Study Lead PI is responsible for the coordination, development, submission, and approval of the protocol as well as its subsequent amendments. The protocol must not be rewritten or modified by anyone other than the Study Lead PI. There will be only one version of the protocol, and each participating institution will use that document. The Study Lead PI is responsible for assuring that all participating institutions are using the correct version of the protocol.
- The Study Lead PI is responsible for the overall conduct of the study at all participating institutions and for monitoring its progress. All reporting requirements are the responsibility of the Study Lead PI.
- The Study Lead PI is responsible for the timely review of Adverse Events (AE) to assure safety of the patients.
- The Study Lead PI will be responsible for the review of and timely submission of data for study analysis.

Responsibilities of the Coordinating Center

- The Coordinating Center is responsible for maintaining copies of IRB approvals from each participating site.
- The Coordinating Center is responsible for central patient registration. The Coordinating Center is responsible for assuring that IRB approval has been obtained at each participating site prior to the first patient registration from that site.
- The Coordinating Center is responsible for the preparation of all submitted data for review by the Study Lead PI.
- The Coordinating Center will maintain documentation of AE reports. The Coordinating Center will submit AE reports to the Study Lead PI for timely review.