A phase II trial of nivolumab/nab-paclitaxel/carboplatin induction chemotherapy followed by response-stratified locoregional therapy for patients with locoregionally advanced HPV-related oropharyngeal cancer – the OPTIMA II Trial

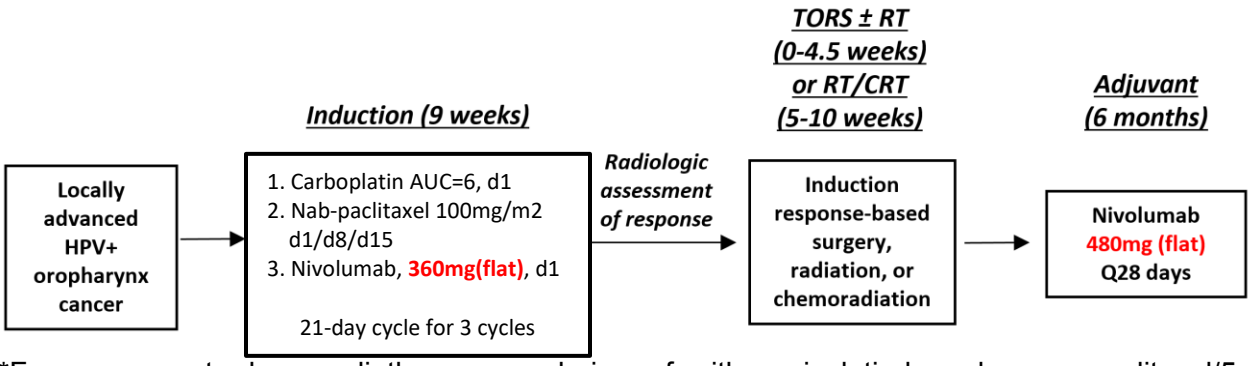
OPTIMA = O*ro***P***haryngeal* **T***umor* **I***nduction chemotherapy and response-stratified locoregional therapy trial in order to* **M***inimize long-term* **A***dverse events*

UCCCC IRB Number:	*IRB17-0104*
Coordinating Center:	The University of Chicago
Principal Investigator:	Everett Vokes Section of Hematology/Oncology, University of Chicago Medical Center 5841 S Maryland Avenue; MC6092, Chicago, IL 60637 Phone: 773-702-9306 E-mail: evokes@medicine.bsd.uchicago.edu
Co-Investigators:	Alexander T. Pearson Daniel Haraf (Radiation Oncology PI) Nishant Agrawal (ENT PI) Michael Spiotto Zhen Gooi Louis Portugal Elizabeth Blair Nicole Cipriani Mark Lingen
Statistician:	Theodore Karrison
Research Nurse:	Courtney Mccampbell
Study Coordinator:	Elaine Klema
Data Manager:	Melody Jones

Table of Contents

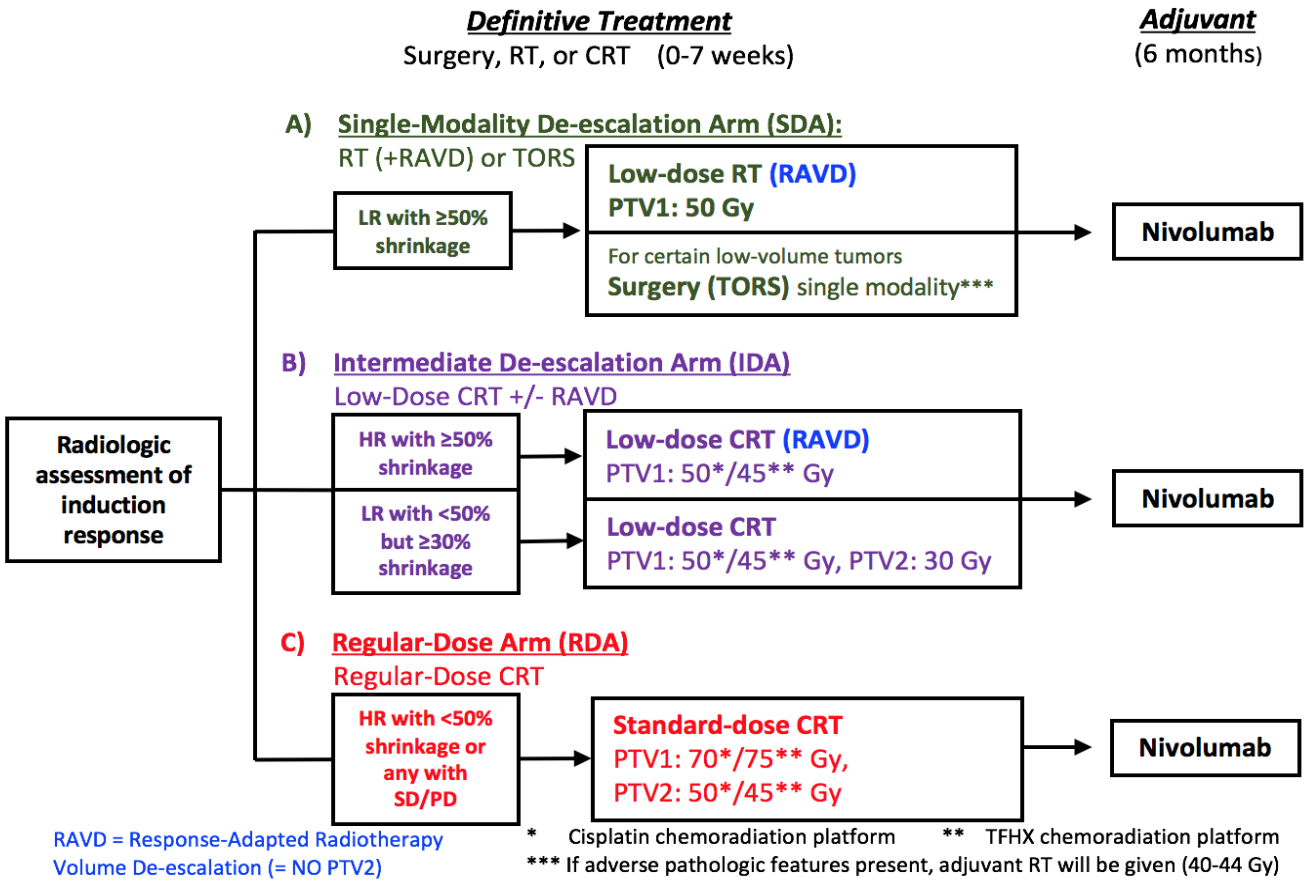
1 PROTOCOL SYNOPSIS & SCHEMATA

1.1 Brief Trial Schema



*For concurrent chemoradiotherapy a choice of either cisplatin-based or a paclitaxel/5-FU/hydroxyurea-based backbone is acceptable. Both regimens are considered equivalent choices and are dependent on physician/subject preference (dealer's choice).

1.2 Brief Schema for Response-Stratified Locoregional Therapy



1.3 Brief Overview of Risk Classification

Low Risk (LR) *(→ ALL of the below)*	High Risk (HR) *(→ ANY of the below)*
T1-T3	T4
N0-2b (unless N3 equivalent LN conglomerate)	N2c-N3 (or N2b with N3 equivalent conglomerate)
≤20 pack years smoking	>20 pack years smoking
HPV16	Non-HPV16 HPV type

→ N3/bulky nodal disease is defined radiologically or on clinical exam.

1.4 Brief Trial Design Overview

A phase II trial in human papillomavirus (HPV)-positive oropharyngeal squamous cell cancer (as determined by p16 immunohistochemistry with confirmatory ISH or PCR) to determine radiologic response to induction chemotherapy with nivolumab. Subjects will undergo evaluation by a multidisciplinary team prior to risk assessment. The subjects will be assigned to high or low risk groups based on tumor size, lymph node involvement, and smoking history. Subjects will be assigned to treatment with induction chemotherapy with carboplatin, nab-paclitaxel, and nivolumab. Radiologic response to induction chemotherapy according to RECIST measurement of tumor shrinkage will then be used for therapeutic stratification of locoregional therapy, consisting of either transoral robotic surgery (TORS) or radiation with or without chemotherapy . Subjects with low risk disease (see table above) and small volume tonsillar/BOT disease (T1-2 primary, non-bulky N2A-N2B nodal status) who have ≥50% reduction by RECIST following induction chemotherapy will undergo TORS for primary site resection and selective nodal dissection as a definitive treatment if technically feasible with adjuvant radiation for adverse pathologic features. Subjects with other low risk tumors e.g. with higher volume disease, or who refuse surgery, who also have ≥50% reduction by RECIST following induction chemotherapy will be given de-intensified treatment with radiation alone to 50 Gy (no chemotherapy). Subjects with low risk features and <50% but ≥30% reduction OR high risk features (T4, bulky N2B or N2C-N3, >20 pack-years tobacco use) with ≥50% reduction will receive de-intensified chemoradiation with concurrent cisplatin-RT to 50 Gy (5 weeks) or TFHX to 45 Gy (3 cycles/6 weeks). Subjects with low risk features and <30% reduction OR high risk disease with <50% reduction or any subjects with progressive disease during induction chemotherapy will undergo chemoradiotherapy with concurrent cisplatin-RT to 70 Gy (7 weeks) or TFHX to 75 Gy (5 cycles/10 weeks). Subjects with both high and low risk features who have ≥50% reduction will receive locoregional therapy targeting the pre-chemotherapy extent of disease only. Adjuvant nivolumab will be offered

to all subjects for 6-months post completion of definitive therapy (7 doses given as a flat dose of 480mg, every four weeks).

1.5 Brief Background and Rationale

The incidence of HPV-positive oropharyngeal cancer is rising rapidly in the United States and Europe.[1] HPV-positive tumors occur in younger, healthier subjects often with higher socioeconomic status. Subjects with HPV-positive tumors have excellent prognosis and we may be currently over-treating this younger subject population.[2,3] Recently, it has been shown that induction chemotherapy may be used for treatment stratification in HPV-positive subjects.[4,5] A good response to induction chemotherapy indicates improved prognosis overall with decreased risks of locoregional and distant recurrence.[6] As such, subjects with favorable response to induction chemotherapy may be candidates for de-intensified locoregional therapy. The goal of de-intensified locoregional therapy is to decrease the late toxicity associated with treatment.

In our recently published response-adapted volume de-escalation (RAVD) trial, treatment was stratified based on response to induction chemotherapy.[5] Subjects with favorable response to induction chemotherapy received concurrent chemotherapy and radiation targeted to only gross disease. In this novel approach, elimination of elective nodal coverage did not compromise outcomes and resulted in significantly improved late toxicity. In a specific subset analysis of HPV-positive oropharynx subjects, outcomes were excellent with 2-year locoregional control and progression-free survival rates of 100% and 93%, respectively, in good responders to induction chemotherapy.

In a subsequent study (OPTIMA I), we sought to further decrease the toxicity of definitive chemoradiation for HPV-positive oropharyngeal cancer by decreasing the radiotherapy dose.[7] In this study, subjects were first stratified based on subject and tumor characteristics. Treatment for each strata was then determined by response to an induction chemotherapy regimen consisting of nab-paclitaxel and carboplatin. In this trial, low-risk subjects with favorable response to induction chemotherapy received definitive radiation and high-risk subjects received chemoradiation. Both low- and high-risk subjects with favorable response to induction chemotherapy received radiotherapy dose de-escalation. Preliminary data based on post-treatment pathology specimens indicate a high degree of control using this approach although an analysis of the complete cohort is still pending.

Monoclonal antibodies targeting the programmed death (PD)-1 immune checkpoint receptor have shown remarkable activity in multiple cancer types including head and neck cancer.[8,9] The goal of PD-1 blockade is to promote tumor recognition and destruction by the immune system. Nivolumab, a PD-1 inhibitor, is approved in melanoma, Hodgkin lymphoma, lung carcinoma, and renal cell carcinoma, and has recently been approved by the U.S. Food and Drug Administration (FDA) for head and neck cancer. Results of the phase III CheckMate-141 study investigating nivolumab after platinum-based chemotherapy were recently published.[8] In this trial, the ORR was 13.3% with nivolumab and a 2.4 month benefit in median overall survival (OS) was observed versus investigator's choice of therapy (P = 0.01).

Given the above, we hypothesize that the addition of the checkpoint inhibitor nivolumab to induction chemotherapy will increase the response rate to neoadjuvant therapy and therefore increase the proportion of subjects who may qualify for de-intensified locoregional therapy. Additionally, we believe that further de-intensification of locoregional therapy compared to Optima I by limiting treatment to only the pre-chemotherapy extent of disease (in subjects with ≥50% induction response) will further reduce the toxicity associated with curative-intent therapy without compromising disease control. An additional goal of this trial will be to assess the comparative efficacy and toxicity profiles of locoregional therapy with TORS versus RT in low-risk subjects with favorable induction response.

1.6 Brief Definition of Subject Population

- Subjects with HPV-positive HNSCC

1.7 Brief Overview of Objectives

Primary Objectives:

- To measure the deep response rate (DRR) to induction chemotherapy with carboplatin/nab-paclitaxel/nivolumab and determine its activity compared to the DRR using carboplatin/nab-paclitaxel in the Optima I trial.

- In the predecessor Optima 1 study, deep responses were defined as ≥50% tumor shrinkage by RECIST 1.1 and this is believed to approximate a clinical complete response (CR) as utilized in the ECOG 1308 study (which was the primary outcome for E1308). Hence in this study, deep responses are also defined as ≥50% tumor shrinkage by RECIST 1.1. Linked to this we will evaluate the overall percentage of subjects treated with dose-reduced radiotherapy or TORS.

Secondary Objectives:

- To determine the tolerability of the nivolumab/carboplatin/nab-paclitaxel induction chemotherapy regimen and its impact on subsequent receipt of definitive chemoradiotherapy.

- To determine 2-year progression-free survival (PFS) for the entire cohort and all arms and compare them to the entire cohort and corresponding arms in Optima I.

- To determine 2-year overall survival (OS) for the entire cohort and all arms and compare them to the entire cohort and corresponding arms in Optima I.

- To determine 2-year rates of locoregional and distant control for the entire cohort and all arms and compare them to the entire cohort and corresponding arms in Optima I.

- To determine rates of acute and late toxicity and compare them to rates of G-tube dependency on the Optima I and RAVD trials.

- To determine quality of life scores in subjects and compare them to quality of life scores on the RAVD trial.

- To determine the comparative efficacy and toxicity profiles of TORS versus RT for management of low risk disease.

1.8 Key Inclusion Criteria

- Subjects with locoregionally advanced HPV-positive squamous cell carcinoma. HPV positivity will be determined by p16 IHC and HPV PCR for validation and HPV type determination.

- Normal organ function

- Measurable disease by RECIST 1.1

- No previous radiation or chemotherapy for a head and neck cancer

- ECOG performance status 0-1 (Karnofsky ≥80%)

- Age ≥18 years

- Ability to obtained informed consent

- Availability of baseline tissue (as listed below in section 4.0)

1.9 Brief Overview of Treatment Plan

Induction therapy: All enrolled subjects will receive three 21-day cycles of chemotherapy consisting of nab-paclitaxel (100 mg/m^2 on days 1, 8, 15; 9 doses total), carboplatin (AUC 5 on day 1; 3 doses total), and nivolumab (360 mg on days 1; 3 doses total). Growth factor support will be provided using G-CSF administered on days 16-18 if clinically indicated.

TORS/RT/CRT: The subjects will be assigned to treatment arms based on response to induction chemotherapy and high or low risk status. High or low risk status is based on tumor size, lymph node involvement, and smoking history at enrollment on study.

Risk Status:

Low Risk Status (all of the below):

- T1-3
- N0-N2B (unless N3 equivalent lymph nodal conglomerate*)
- ≤20 pack year history tobacco use
- HPV16

High Risk Status (any of the below):

- T4
- N2C-N3
- Bulky N2B disease with N3 equivalent nodal conglomerate*
- >20 pack year history tobacco use
- Non-HPV16 HPV type (e.g. HPV31, 18, etc)

*N3/bulky nodal disease is defined radiologically or on clinical exam.

Response Stratified Grouping:

Subjects will be assigned to TORS, RT, or CRT based on response to induction chemotherapy and risk category (see schemas 1.1 and 1.2). Decision between RT or TORS in the single modality arm (SDA) will be individualized (see details below). Chemoradiation will be done using either outpatient cisplatin (100mg/m2 every 3 weeks), or alternatively the inpatient TFHX platform consisting of 2-week cycles of paclitaxel (100 mg/m^2, day 1), 5-FU (continuous infusion at 600 mg/m^2/day $\times$ 5 days), and hydroxyurea (500 mg PO BID days 0-5, 11 doses/cycle) with twice daily radiation (150 cGy per fraction). Both chemoradiation platforms are considered equivalent and treatment on either regimen will depend on subject preference.

Group A1: Single-Modality De-escalation Arm (SDA) --TORS

Subjects with low risk and small volume tonsillar disease (T1-T2, non-bulky N2A-N2B with ≤2 non-lower neck lymph nodes measuring ≤5 cm in size) or base of tongue disease (T1-2 with lateralized primary ≤3 cm, non-bulky N2A-N2B with ≤2 non-lower neck lymph nodes measuring ≤5 cm in size) who have ≥50% reduction by RECIST following induction chemotherapy will undergo TORS and selective nodal dissection. De-intensified adjuvant RT will be given for adverse pathologic features. Subjects may refuse TORS treatment (see treatment next paragraph).

Group A2: Single-Modality De-escalation Arm (SDA) –RT

Subjects with low risk, who do not qualify for TORS (due to volume of disease or poor visualization/access) or refuse TORS, who have ≥50% reduction by RECIST following

induction chemotherapy will be given de-intensified treatment with radiation alone to 50 Gy (see schema page 5).

Group B: Intermediate De-escalation Arm (IDA) – Low dose CRT
Subjects who have low risk disease with <50% but ≥30% reduction of tumor by RECIST with induction chemotherapy will receive CRT to 50 Gy with concurrent bolus cisplatin (x2 doses) or TFHX to 45 Gy (3 cycles).

Subjects who have high risk disease and ≥50% reduction of tumor by RECIST with induction chemotherapy will receive CRT to 50 Gy with concurrent bolus cisplatin (x2 doses) or TFHX to 45 Gy (3 cycles).

Group C: Regular Dose Arm (RDA) – Standard dose CRT:
Subjects who have low risk disease and <30% reduction of tumor by RECIST with induction chemotherapy will receive CRT to 70 Gy with concurrent bolus cisplatin (x3 doses) or TFHX to 75 Gy (5 cycles).

Subjects who have high risk disease and <50% reduction of tumor by RECIST with induction chemotherapy will receive CRT to 70 Gy with concurrent bolus cisplatin (x3 doses) or TFHX to 75 Gy (5 cycles).

Any subject who has progressive disease will receive CRT to 70 Gy with concurrent bolus cisplatin (x3 doses) or TFHX to 75 Gy (5 cycles).

Adjuvant therapy: Adjuvant nivolumab 480mg iv every 4 weeks will be offered to all subjects for 6-months post completion of locoregional therapy (= doses).

1.10 Brief Summary of Treatment Duration

Induction chemotherapy: 9 weeks
Definitive radiation therapy: 5 weeks
Definitive chemoradiotherapy: 5-10 weeks
Adjuvant radiation therapy (if indicated after TORS): 4-4.5 weeks
Adjuvant immunotherapy: 6 months (=7 doses)

1.11 Brief Overview of Statistical analysis

Subjects will receive induction chemotherapy for three cycles followed by radiologic evaluation and response-based allocation to definitive locoregional therapy.

Response will be assessed after completion of induction chemotherapy by radiological examination.

We expect to enroll and start treatment in 3-5 subjects per month for a total of 56 subjects over a period of approximately 18 months. This study is designed to accrue

56 evaluable subjects for the primary endpoint to allow sufficient statistical power. However the trial is to be extended to up to 74 patients to fulfull sufficient enrollment on the RT-alone (A1) and TORS (A2) arms (at least 10 subjects each, unless the trial reaches N=74 subjects first).

Overall Primary Objective: To demonstrate an increased rate of deep responses (deep response rate=DRR) to induction chemotherapy with the addition of nivolumab to the carboplatin/nab-paclitaxel backbone used in the Optima I trial.

- In the predecessor Optima 1 study, deep responses were defined as ≥50% tumor shrinkage by RECIST 1.1 and this is believed to be equivalent to a clinical complete response (CR) as utilized in the ECOG 1308 study (which was the primary outcome for E1308). Hence in this study, deep responses are also defined as ≥50% tumor shrinkage by RECIST 1.1.
- We will employ a superiority test in which the objective is to establish that the response rate to carboplatin/nab-paclitaxel/nivolumab induction chemotherapy is 15% higher than the response rate of 60% in Optima I which utilized a carboplatin/nab-paclitaxel induction regimen.
- We will test: H_0: DRR=60% (based on data from Optima 1 trial) vs H_A: DRR=75% with addition of nivolumab to the carboplatin/nab-paclitaxel induction regimen.
- Using Power Analysis and Sample Size (PASS v11) software, a sample of 56 subjects will provide 87% power to test this hypothesis using a (one-sided) type I error rate of 0.10. Essentially, H_0 will be rejected and nivolumab/carboplatin/nab-paclitaxel based induction regimen declared superior if the lower, one-sided 90% confidence limit for the response rate exceeds 75%. No interim analysis will be conducted.

NB: A minimum of 10 patients will be enrolled on the RT only and also TORS arm to allow for descriptive interpretation of the pathology results in tabular form. The overall trial may overenroll up to 18 patients (N=74) to fulfill this enrollment goal for the RT-only and TORS arms.

2 OBJECTIVES

2.1 Primary Objective

- To measure the deep response rate (DRR) to induction chemotherapy with carboplatin/nab-paclitaxel/nivolumab and determine its activity compared to the DRR using carboplatin/nab-paclitaxel in the Optima I trial.

- In the predecessor Optima 1 study, deep responses were defined as ≥50% tumor shrinkage by RECIST 1.1 and this is believed to approximate a clinical complete response (CR) as utilized in the ECOG 1308 study (which was the primary outcome for E1308). Hence in this study, deep responses are also defined as ≥50% tumor shrinkage by RECIST 1.1. Linked to this we will evaluate the overall percentage of subjects treated with dose-reduced radiotherapy or TORS.

2.2 Secondary Objectives

- To determine the tolerability of the nivolumab/carboplatin/nab-paclitaxel induction chemotherapy regimen and its impact on subsequent receipt of definitive chemoradiotherapy.
- To determine 2-year progression-free survival (PFS) for the entire cohort and all arms and compare them to the entire cohort and corresponding arms in Optima I.

- To determine 2-year overall survival (OS) for the entire cohort and all arms and compare them to the entire cohort and corresponding arms in Optima I.

- To determine 2-year rates of locoregional and distant control for the entire cohort and all arms and compare them to the entire cohort and corresponding arms in Optima I.

- To determine rates of acute and late toxicity and compare them to rates of G-tube dependency on the Optima I and RAVD trials.

- To determine quality of life scores in subjects and compare them to quality of life scores on the RAVD trial.

- To determine the comparative efficacy and toxicity profiles of TORS versus RT for management of low risk disease. A minimum of 10 patients will be enrolled on the RT only and also TORS arm to allow for descriptive interpretation of the pathology results in tabular form. The overall trial may overenroll up to 18 patients (N=74) to fulfill this enrollment goal for the RT-only and TORS arms.

2.3 Laboratory Objectives

- To evaluate quantitative HPV titers pre-treatment, post-induction, and post-definitive locoregional therapy at defined intervals on blood and saliva samples. This will be used to assess treatment efficacy (e.g. during nivolumab based induction chemotherapy), as well as a potential marker for early recurrence.

- To evaluate changes in the immune micro-environment at a) baseline and b) during combined anti-PD-1/chemotherapy induction (paired biopsies). This will performed in an exploratory fashion:
    - Multicolor IF to assess changes in the immune microenvironment
    - mRNA analysis (Nanostring)
    - Mutational Load
    - Blood based markers over time

2.4 Exploratory Objectives

- To evaluate the efficacy and utility of a visual aid used during the consent process by anonymous and optional subject and provider questionnaires.

- To determine whether MRI (namely diffusion weighted imaging, and radiomics) can predict response to induction (chemotherapy + immunotherapy).

3 BACKGROUND

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.[10] The majority (90-95%) of these cases are squamous cell carcinomas of the head and neck (HNSCC) and approximately two-thirds are locoregionally advanced cancers (AJCC Stage III-IV). Despite advances in the multimodality treatment of locoregionally advanced HNSCC (LA-HNSCC) over the past two decades, these subjects 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 subjects developed metastatic disease and nearly one-fifth of these subjects died of distant metastases without evidence of locoregional recurrence.[11-14]

3.2 Chemoradiotherapy

Given the discouraging outcomes with surgery and radiation, investigators became increasingly interested in the incorporation of chemotherapy for the treatment of LA-HNSCC. The feasibility of a non-surgical, organ preservation approach with concomitant chemoradiation was first established by the landmark Veterans Affairs Laryngeal Cancer Study.[15,16] 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 subjects with locoregionally advanced un-resectable disease.[17-22] The positive effects on 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.[23] This 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.[24] However, other treatment-related morbidities such as dysphagia are still problematic. Rates of feeding tube dependence at 1-year in the 3D-conformal era have been reported to be approximately 25%.[25] This is particularly significant given recent data that quality of life among subjects with HNSCC treated with radiotherapy is substantially affected by swallowing dysfunction and the need for enteral nutrition support.[26] 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 stricture formation with doses ≥50 Gy.[27] Single-institution reports of treatment of oropharyngeal cancer in the IMRT-era demonstrate long-term feeding tube dependence rates of approximately 5-10%.[28]

3.2.1 CRT Platforms: Concurrent Cisplatin-Radiation or TFHX

Chemoradiotherapy with concurrent bolus cisplatin (100 mg/m2 delivered q3weeks) and conventionally fractionated radiotherapy remains the commonly accepted standard of care for the treatment of LA-HNSCC. This is due to the prevalence of randomized studies, including the Head and Neck Intergroup trial and RTOG 91-11, which observed that concurrent chemoradiotherapy with every-3-weeks cisplatin improved locoregional control and overall survival for unresectable HNSCC and resectable laryngeal cancers, respectively.[29,30]

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).[31,32] Both chemotherapy agents have known systemic activity and have been shown to act as radiation enhancers in vitro and in vivo.[14,33,34] Cytotoxic activity is synergistic as hydroxyurea modulates the activity of 5-FU by depleting cellular pools of deoxyuridine monophosphate (dUMP) and facilitating binding of the 5-FU metabolite 5-FdUMP to its target enzyme thymidylate synthase.[35] Paclitaxel was subsequently added to the FHX regimen (TFHX) and the radiation scheme changed to twice daily to further intensify the treatment.[36-39]

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.[38,40] Since surgery was used primarily as a salvage procedure, excellent organ preservation was also achieved. Acute toxicities were severe in a majority of subjects but were considered tolerable overall. Mucositis (84% grade 3/4), “in-field” dermatitis (38% grade 3/4), leukopenia (34% grade 3/4), and anemia (22% required transfusion) were the most common serious side effects. At 1 year post-treatment, 61% of subjects 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.[6,41] 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 treatment goal that was not achieved optimally with the chemotherapy doses applied during concomitant chemoradiotherapy. Indeed, approximately 20% of subjects were noted to recur distantly, despite the addition of cytotoxic chemotherapy to radiation therapy as part of the TFHX regimen.

3.3 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.[42] Systemic disease progression was noted in 7% of subjects; 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/fluorouracil (5-FU) combination and published phase III trials demonstrating the superiority of induction docetaxel, cisplatin, and 5-fluorouracil over cisplatin and 5-fluorouracil when followed by radiotherapy or chemoradiotherapy.[21,43-45]

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.[46-48] Additionally, recent data demonstrate that TPF and carboplatin/paclitaxel seem to have equivalent activity while the latter platform is associated with decreased toxicity.[49] Two studies evaluating carboplatin/paclitaxel induction demonstrated 82% and 87% response rates compared to our DeCIDE trial 64% response to TPF.[41,42,50]

Paclitaxel and nab-paclitaxel have the same activity based on response rates with better delivery and a favorable toxicity profile (especially with nab-paclitaxel). Compared with solvent-based paclitaxel, nab-paclitaxel delivers 33% higher drug concentration to tumors in preclinical xenograft models, and demonstrates enhanced transport across endothelial cell monolayers.[51] The Cremophor-free medium enables nab-paclitaxel to be given in a shorter duration without the need for premedication to prevent solvent-related hypersensitivity reactions. Standard IV bags and tubing may be used for the delivery of nab-paclitaxel. Preliminary data from our Optima I trial using a nab-paclitaxel/carboplatin induction backbone indicate a high degree of tolerability and efficacy with a deep response rate of approximately 60%. Importantly with relation to immunotherapy, nab-

paclitaxel can be administered without steroid premedication, and concerns exist for immunotherapy efficacy with steroid pre-medication.

3.4 Human Papillomavirus (HPV) and HNSCC

Both epidemiologic and molecular evidence have elucidated the causative role of HPV in oropharynx SCC over the past decade. The incidence of oropharyngeal cancer has risen dramatically over the past two decades and it is now the most common HNSCC.[1] Both seropositivity and oral infection with high-risk type HPV (HPV-16) have been shown to increase the risk of developing oropharyngeal cancer (OPC).[52,53] HPV-positive tumors have a unique molecular profile: wild-type p53, upregulated p16, and downregulated pRb.[54] There is direct evidence that HPV-16 is oncogenic, mechanistically driving the development and viability of cancer cells.[55-57]

There is concern for an HNSCC-epidemic due to HPV. Extrapolating recent trends, the annual number of HPV-positive OPC is expected to surpass the annual number of cervical cancers by the year 2020.[1,58] This is especially concerning in light of the fact that subjects with HPV-related OPC are approximately ten years younger on average than their HPV-negative OPC counterparts.[59]

Recently, studies have demonstrated that subjects with HPV-related OPC have superior response to therapy and survival compared to HPV-negative OPC. In retrospective analyses of survival and HPV status from three phase III trials, unprecedented overall survival of approximately 80-90% at three years was obtained.[2,60,61] Improved survival in these studies was largely due to markedly improved local-regional control as a biologic consequence of the HPV-origin of these tumors. With the improvement in locoregional control, distant metastasis is now gaining recognition as a leading cause of death in HPV-positive subjects and the rate of distant relapse is the same for both HPV-related OPC and non-HPV related tumors.[2,3,62]

Recursive partitioning analysis has helped to stratify HPV-related OPC subjects for both risk of death and distant relapse. In a retrospective analysis of the association between tumor HPV status and survival among subjects with stage III/IV OPC who were enrolled in a randomized trial comparing accelerated-fractionation radiotherapy with standard-fractionation radiotherapy as part of concomitant chemoradiation with cisplatin, HPV status of the tumor was the major determinant of overall survival, followed by the number of pack-years of tobacco smoking (≤10 vs >10), and then nodal stage (N0-N2A vs N2B-N3) for HPV-positive tumors.[2] In another retrospective analysis of the association between tumor HPV status and distant metastatic risk in a prospectively assembled cohort of OPC subjects treated with radiotherapy alone or concurrent chemoradiotherapy, the distant control rates for HPV-positive, low-risk N0-2A or less than 10 pack-year N2B subjects were similar for RT alone and CRT, but the rate was lower in the N2C subset managed by RT alone.[3] Subsequent studies however have found a higher threshold of 20-pack years, which is now commonly used, and other studies have found no relationship with tobacco use at all, and hence tobacco use was not integrated into the

new staging system for HPV-positive OPC subjects (ICONS-S / AJCC 8th edition) for that reason.[3,64]

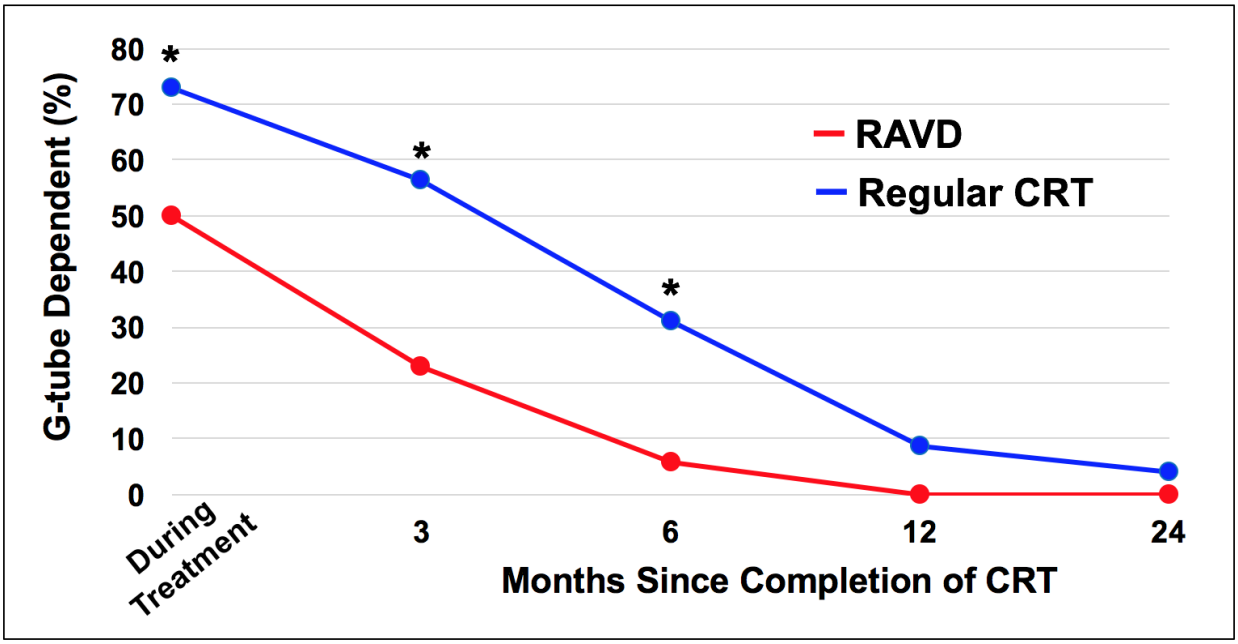
Preliminary results of our Optima I trial indicate that risk stratification using nodal stage (N0-N2B vs N2C-N3), tumor size (T0-3 vs T4), and tobacco use history (≤10 vs >10 pack years) appropriately selected subjects for de-intensified locoregional therapy without compromising outcomes. Additionally, this risk stratification is echoed in recent proposals for a new staging classification for HPV-related OPC as part of the AJCC 8th edition.[63,64] In a multi-institutional development and validation study, adjusted hazard ratio methods were found to best model a proposed staging system in which T1-T2/N0-N2B is classified as stage I (5-year survival 85%), T3/N2C is classified as stage II (5-year survival 78%), and T4/N3 is classified as stage III (5-year survival 53%).[64] Additionally, there are recent data demonstrating the prognostic significance of HPV-genotype, with superior survival outcomes for subjects with HPV-16.[65]

3.5 Response-Adapted Volume De-escalation (RAVD)

It has been shown that subjects with favorable response to IC have superior prognosis and are less likely to experience locoregional failure after definitive chemoradiation.[6] Strategies to decrease the late toxicity associated with CRT have focused on radiotherapy (RT) 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 RT treatment volume.[66]

Conventional head and neck RT elective nodal volumes are based on historic surgical data regarding the risk of occult LN involvement. Several series have investigated decreasing elective nodal RT coverage. For subjects with limited tonsillar cancer, elimination of contralateral elective neck RT has shown to be feasible.[67] Additionally, it has recently been shown that elimination of elective RT to the retropharyngeal and high level II lymph nodes in the contralateral uninvolved neck is feasible and results in decreased toxicity.[68] In our RAVD trial, we utilized radically reduced RT volumes entirely omitting elective nodal coverage in good responders to IC and significantly decreasing coverage in non-responders.[5]

Outcomes of the RAVD trial were specifically investigated in subjects with HPV+ oropharyngeal SCC. 2-year PFS and OS for HPV+ oropharynx good responders were 93.1% and 92.1%, respectively. 2-year PFS and OS for HPV+ oropharynx non-responders were 74.0% and 95.2%, respectively. The majority of locoregional failures (12/13—92.3%) in this trial were in-field failures within the RT treatment volume and 11/12 (91.7%) occurred in the highest-risk PTV1. With respect to late toxicity, non-responders were significantly more likely to undergo G-tube placement during treatment (50.0% GR vs 73.5% NR, P = 0.040) and be G-tube dependent at 3-month (22.9% GR vs 57.1% NR, P = 0.002) and 6-month follow-up (5.7% GR vs 32.6% NR, P = 0.005). On multivariate analysis, good response to IC was the only significant predictor of G-tube dependency on treatment (OR 0.36, P = 0.028) and at 3-month (OR 0.22, P = 0.002) and 6-month follow-up (OR 0.12, P = 0.009).



3.6 Dose De-escalation for HPV-related Oropharynx Cancer

Given the excellent cancer control and survival in HPV-associated oropharynx cancer, there has been a wave of recent efforts to decrease the intensity of treatment without compromising cancer control. Alternative dose de-intensification strategies have been recently published or presented.

In the University of North Carolina/University of Florida experience, subjects with favorable-risk HPV-associated oropharynx cancer were treated with weekly cisplatin and 60 Gy RT (10 Gy dose de-escalation) followed by pathologic evaluation.[69] The pathologic complete response rate was 86% and non-inferior to the null hypothesis of 87%. In the ECOG 1308 trial, subjects with resectable stage III/IV disease received induction chemotherapy followed by risk-stratified locoregional therapy (54 Gy with cetuximab for complete responders versus 69.3 Gy for partial responders).[4] Preliminary results of this trial indicate a 2-year progression-free survival of 84% and locoregional control greater than 90%. Additionally, preliminary results of our Optima I trial significantly de-escalating dose for both high and low risk HPV-related oropharynx cancer after favorable response to induction chemotherapy indicate a high degree of control without compromised efficacy.

3.7 Transoral Robotic Surgery (TORS)

Compared to traditional open surgical approaches, transoral robotic surgery (TORS) has been shown to improve Quality of Life (QOL) outcomes and functional outcomes in speech and swallowing, while maintaining good oncologic outcomes.[70] Favorable gastrostomy tube rates (0-9,5% at one year and 0% at 2 years after treatment) have been

reported following TORS. T1-2 tumors of the oropharynx, especially those arising within the tonsillar fossa and lateral pharyngeal wall, glossopharyngeal sulcus, and lateral tongue base, are amenable to TORS when adequate oral access can be obtained.

There are limited retrospective and no randomized data comparing TORS versus RT/CRT for definitive treatment of oropharynx cancer. A recently published meta-analysis suggests equivalent efficacy of both TORS and RT in terms of disease control for early stage oropharyngeal SCC.[71] A small retrospective analysis of quality of life outcomes published by the UCLA group showed similar quality of life among subjects treated by transoral surgery or chemoradiotherapy.[72] The currently accruing ORATOR phase II study which randomizes subjects with early-stage SCC of the oropharynx to RT of TORS will provide valuable prospective data.[73]

A novel approach using induction chemotherapy followed by transoral surgery was recently published by the George Washington University group.[74] In this series of 17 subjects with advanced oropharyngeal cancer who were treated with neoadjuvant chemotherapy followed by transoral surgery of the pre-chemotherapy extent of disease plus selective neck dissection, 16/17 subjects were alive without recurrence at median follow-up of 31 months (3-year disease-specific survival 94.1%).

Additionally, multiple trials are currently examining the role of adjuvant therapy de-intensification for subjects with HPV-related oropharynx cancer after TORS. Standardly, post-operative RT is delivered to a dose of 60-66 Gy for adverse features including extracapsular extension (ECE), positive surgical margins, perineural invasion (PNI), or lymphovascular invasion (LVI). Concomitant chemotherapy is also added for subjects with ECE or positive margins, based on joint analysis of the EORTC and RTOG trials demonstrating a significant survival benefit for this subset.[75]

The Eastern Cooperative Group (ECOG) 3311 trial is examining transoral surgery followed by low-dose of standard-dose RT with or without chemotherapy for subjects with HPV-related stage III/IVA oropharynx cancer.[76] Subjects with intermediate adverse features (≤1 mm ECE, 2-3 involved nodes, PNI, or LVI) are randomized to RT alone to 50 Gy versus 60 Gy. Subjects with high risk adverse features (positive margins, >1 mm ECE, or ≥4 involved nodes) are treated to 66 Gy with concurrent cisplatin (40 mg/m2). In the phase II trial from the Mayo Clinic, subjects with p16-positive oropharynx cancer with less than a ten pack-year smoking history who have had a complete surgical resection are also treated with de-intensified adjuvant therapy.[77] Subjects with intermediate risk disease (≥T3, ≥N2, LVI, or PNI) are treated with 30 Gy RT (1.5 Gy BID) and concurrent weekly docetaxel while subjects with ECE receive a similar treatment regimen but also have the nodal level with positive ECE concurrently boosted to 36 Gy in 1.8 Gy twice-daily fractions.

In this trial we are seeking to use TORS as a substitution for XRT in good prognosis cases with excellent response to induction with reduced longterm toxicities (such as fibrosis, xerostomia, dental issues, and dysphagia, etc (see 5.11.2).

3.8 Positron Emission Tomography (PET)-Based Surveillance

Post-chemoradiotherapy neck dissection can be associated with significant morbidity because of the associated scarring and fibrosis. In our published experience at the University of Chicago, 10% of subjects developed wound healing complications and other complications occurred in 16% of subjects and included need for tracheotomy, nerve transection and paresis, and permanent hypocalcemia.[78]

Computed tomography (CT) has been previously shown to spare subjects with radiographic complete response from post-RT neck dissection, regardless of initial nodal stage.[79] This has been adopted as the routine post-CRT surveillance at the University of Chicago over the past decade. Recently, positron emission tomography (PET)-CT has been adopted at several institutions as a method of avoiding neck dissection after definitive chemoradiotherapy.

A prospective, randomized, controlled trial, assessing the noninferiority of PET-CT guided surveillance (performed 12 weeks after the end of chemoradiotherapy, with neck dissection performed only if PET-CT showed an incomplete or equivocal response) to planned neck dissection in subjects with stage N2 or N3 disease was recently published.[80] The hazard ratio for death slightly favored PET-CT–guided surveillance and indicated noninferiority. Survival was similar among subjects who underwent PET-CT–guided surveillance and those who underwent planned neck dissection, but surveillance resulted in considerably fewer operations and it was more cost-effective.

3.9 Nivolumab / anti-PD-1

Nivolumab is a fully humanized, IgG4 (kappa) isotype monoclonal antibody (mAb) that binds the programmed death receptor-1 (PD-1).[81] PD-1 is a transmembrane protein primarily expressed on activated immune cells. In its usual function, the binding of PD-1 (found on activated T-cells) to its ligands PD-L1 (B7-H1) and PD-L2 (B7-DC) 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.[82] 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 approved by the U.S Food and Drug Administration (FDA) in melanoma, Hodgkin lymphoma, lung carcinoma, and renal cell carcinoma. It has received approval for head and neck cancer based on the results of the CheckMate 141 study.[8] 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. Subjects were randomized to receive nivolumab (3 mg/kg IV q2week) versus investigator's choice of therapy. Approximately one-quarter of subjects enrolled were p16 positive. 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). For subjects with p16 positive disease, the HR for overall survival was 0.56 (95% CI 0.32-0.99). Overall, nivolumab was well-tolerated with 3.8% of subjects not continuing treatment due to study drug toxicity and 13.1% of subjects 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%).

Currently, there is great interest in integrating nivolumab into the curative-intent setting. The Radiation Therapy Oncology Group (RTOG) will soon activate a phase III trial with a phase I dose finding lead-in study to evaluate whether the addition of nivolumab will improve the overall survival for subjects with newly diagnosed intermediate-risk or high-risk HNSCC when treated with radiation therapy and cisplatin-based or cetuximab-based chemotherapy or with radiation alone.[83]

Chemotherapy leads to tumor lysis and release of tumor antigens, which may prime the immune system for checkpoint inhibitors. The combination of a taxane and immune checkpoint inhibitor has been reported to improve response in non-small cell lung cancer (NSCLC). In a recently presented phase I study of nivolumab with nab-paclitaxel and carboplatin in advanced NSCLC (ABI-007-ST-001), subjects received 4 cycles of nab-paclitaxel (100 mg/m2 on days 1, 8, 15), carboplatin (AUC 6 on day 1 of a 21-day cycle), and nivolumab (5 mg/kg on day 15 starting at cycle 1).[84] No dose-limiting toxicities were observed. The most frequent grade ≥3 treatment-related adverse events were neutropenia (28.6%) and anemia (19%). No pneumonitis has been reported to date.

3.10 Study Rationale

HPV-positive oropharynx cancer is a distinct clinical entity based on differing demographics, biology, and prognosis. The overall survival benefit in subjects with HPV-related oropharynx cancer is due largely to a marked improvement in locoregional control. Given the younger demographic and the significant long-term morbidity incurred with standard locoregional therapy, treatment de-intensification is currently an area of active investigation.

Multiple approaches for treatment de-intensification of HPV-positive oropharynx cancer have recently been presented or are currently under investigation in multi-institutional settings. These strategies may be classified as follows:

1. Chemotherapy and RT dose de-escalation for select subjects with low-risk disease (UNC/UF study[69], NRG HN002[85])
2. Substitution of cetuximab in place of cisplatin as the concurrent agent (RTOG 1016[86], TROG 12.01[87])
3. Transoral surgical resection followed by de-intensified adjuvant therapy (ECOG 3311[76])
4. Induction chemotherapy followed by response-stratified locoregional therapy (ECOG 1308[4], University of Chicago RAVD[5] and Optima I[88] studies)

Our published results using induction chemotherapy to stratify subjects for receipt of radical radiotherapy volume de-escalation demonstrate excellent locoregional control and significantly improved treatment toxicity and quality of life outcomes.[5] Notably, subjects with both high- and low-risk HPV-positive oropharynx cancer, as well as HPV-negative HNSCC, were candidates for radical volume de-escalation in this trial. In the subset analysis of HPV-positive oropharynx subjects, outcomes were excellent with 2-year locoregional control and progression-free survival rates of 100% and 93%, respectively, for subjects with favorable response to induction chemotherapy in whom elective nodal coverage was omitted. Preliminary results of our subsequent study investigating significant RT dose de-escalation in subjects with response to induction chemotherapy also indicate a high degree of control without compromised outcomes.

Increasing the response rate to neoadjuvant therapy is an important endpoint to increase the proportion of subjects who qualify for de-intensified locoregional therapy. Monoclonal antibodies targeting the programmed death (PD)-1 immune checkpoint receptor have shown remarkable activity in multiple cancer types including head and neck cancer. The goal of PD-1 blockade is to promote tumor recognition and destruction by the immune system. Nivolumab has received breakthrough designation for head and neck cancer based on phase III results demonstrating a survival benefit with an objective response rate of 13.3%.[8]

Chemotherapy leads to tumor lysis and release of tumor antigens, which may prime the immune system for checkpoint inhibitors. Synergy of anti-PD-1 with chemotherapy is supported by early data combining nivolumab with nab-paclitaxel and carboplatin.[84] These data suggest a marked increase in the response rate and depth of response, perhaps related to the use of steroid sparing chemotherapy (in particular steroid sparing nab-paclitaxel) which allows for synergy with PD-1/PD-L1 checkpoint blockade.

Given the above, we hypothesize that the addition of a checkpoint inhibitor, nivolumab, to induction chemotherapy will increase the response rate to neoadjuvant therapy and therefore increase the proportion of subjects who may qualify for de-intensified locoregional therapy. Additionally, we hypothesize that de-intensified locoregional therapy for subjects with favorable response to induction chemotherapy (including TORS or dose- and volume- de-escalated C/RT) will not compromise control outcomes but will result in significantly decreased treatment toxicity.

In this study, we will specifically evaluate subjects with locoregionally advanced HPV-positive squamous cell cancer of the oropharynx. Subjects will be given 3 cycles of neoadjuvant nivolumab, carboplatin, and nab-paclitaxel followed by clinical and radiographic assessment of response. The subjects will be assigned to treatment arms based on response to induction chemotherapy and high or low risk status, as outlined below:

3.10.1 Risk Status

3.10.1.1 Low Risk Status (all of the below):

- T1-3
- N0-N2B (unless N3 equivalent lymph nodal conglomerate*)
- ≤20 pack year history tobacco use
- HPV16

3.10.1.2 High Risk Status (any of the below):

- T4
- N2C-N3
- Bulky N2B disease with N3 equivalent nodal conglomerate*
- >20 pack year history tobacco use
- Non-HPV16 HPV type (e.g. HPV18, HPV31, etc)

*N3/bulky nodal disease is defined radiologically or on clinical exam

3.10.2 Group A1: Single-Modality De-escalation Arm (SDA) -- TORS: Single-Modality De-escalation Arm (SDA) –RT

Subjects with low risk and small volume tonsillar disease (T1-T2, non-bulky N2A-N2B with ≤2 non-lower neck lymph nodes measuring ≤5 cm in size) or base of tongue disease (T1-2 with lateralized primary ≤3 cm, non-bulky N2A-N2B with ≤2 non-lower neck lymph nodes measuring ≤5 cm in size) who have ≥50% reduction by RECIST following induction chemotherapy will undergo TORS and selective nodal dissection. De-intensified adjuvant RT will be given for adverse pathologic features. Subjects may refuse TORS treatment.

3.10.3 Group A2: Single-Modality De-escalation Arm (SDA) –RT

Subjects with low risk, who do not qualify for TORS (due to volume of disease or poor visualization/access) or refuse TORS, who have ≥50% reduction by RECIST following induction chemotherapy will be given de-intensified treatment with radiation alone to 50 Gy (see schema page 5).

3.10.4 Group B: Intermediate De-escalation Arm (IDA) – Intermediate dose CRT

Subjects who have low risk disease with <50% but ≥30% reduction of tumor by RECIST with induction chemotherapy will receive CRT to 50 Gy with concurrent bolus cisplatin (x2 doses) or TFHX to 45 Gy (3 cycles).

Subjects who have high risk disease and ≥50% reduction of tumor by RECIST with induction chemotherapy will receive CRT to 50 Gy with concurrent bolus cisplatin (x2 doses) or TFHX to 45 Gy (3 cycles).

3.10.5 Group C: Regular Dose Arm (RDA) – Standard dose CRT:

Subjects who have low risk disease and <30% reduction of tumor by RECIST with induction chemotherapy will receive CRT to 70 Gy with concurrent bolus cisplatin (x3 doses) or TFHX to 75 Gy (5 cycles).

Subjects who have high risk disease and <50% reduction of tumor by RECIST with induction chemotherapy will receive CRT to 70 Gy with concurrent bolus cisplatin (x3 doses) or TFHX to 75 Gy (5 cycles).

Any subject who has progressive disease will receive CRT to 70 Gy with concurrent bolus cisplatin (x3 doses) or TFHX to 75 Gy (5 cycles).

3.10.6 Adjuvant Treatment with Nivolumab/anti-PD-1

Adjuvant nivolumab will be offered to all subjects for 6-months post completion of locoregional therapy for additional systemic activity.

4 SUBJECT SELECTION

4.1 Eligibility Criteria

- Subjects must have pathologically confirmed HPV-positive head and neck squamous cell carcinoma of the oropharynx. Confirmed HPV-positive disease of other subsites are uncommon but also eligible.

- HPV testing must be compliant with the following criteria:
    - p16 IHC positivity is sufficient to enroll and initiate treatment (p16 IHC interpretation to follow guidelines by *Jordan and Lingen et al*[89]).
    - p16 IHC positivity is to be validated using an HPV PCR during the induction phase. This is essential as HPV genotype influences treatment arm allocation, with non-HPV16 HPV strains being considered high risk.

- Availability of ≥10 unstained 5 micron slides (to be provided to HTRC at the University of Chicago). Subjects who cannot fulfill this requirement will need to undergo a new biopsy prior to enrollment on study.

- Subjects must be at least 18 years of age.

- Subjects with AJCC (7^{th} edition, 2010) N2-N3 nodal disease or T3-T4 primary tumor. Those with AJCC (8^{th} edition 2018) TXNX are also allowed.

- Measurable disease (either primary site and/or nodal disease) by RECIST 1.1 criteria.

- No previous radiation or chemotherapy for a head and neck cancer.

- 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 disease is acceptable).

- ECOG performance status 0-1 (Karnofsky ≥80%).

- Normal Organ Function
    - Leukocytes ≥3000/mm^3,
    - platelets ≥100,000/mm^3,
    - absolute neutrophil count ≥1,500,
    - hemoglobin >9.0 gm/dL,
    - AST and ALT ≤2.5 X ULN
    - alkaline phosphatase ≤2.5 X ULN
    - albumin >2.9 gm/dL,
    - total bilirubin ≤1.5 mg/dl,

- creatinine clearance >45 mL/min (or SCr ≤1.5 mg/dL), normal within 2 weeks prior to start of treatment.
  →The standard Cockcroft and Gault formula or the measured glomerular filtration rate must be used to calculate CrCl for enrollment or dosing

- Subjects must sign a study-specific informed consent form prior to study entry. Subjects should have the ability to understand and the willingness to sign a written informed consent document.

- Age, Sex, and Reproductive Status:
  a) Men and women, ages ≥ 18.
  b) Women of childbearing potential (WOCBP=premenopausal woman capable of becoming pregnant) 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.
  c) Women must not be breastfeeding.
  d) WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half-lives of study drug(s) plus 30 days (duration of ovulatory cycle) for up to 5 months post-treatment completion.
  e) Men who are sexually active with WOCBP must agree to follow instructions for method(s) of contraception for the duration of treatment with study drug(s) plus 5 half-lives of study drug(s) plus 90 days (duration of sperm turnover) for up to 7 months post treatment completion.
  f) Azoospermic males and WOCBP who are continuously not heterosexually active are exempt from contraceptive requirements. However, they must still undergo pregnancy testing as described in this section.

  Investigators shall counsel WOCBP and male subjects 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 subjects 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 subjects must agree to the use of one method of highly effective contraception as listed in Appendix E. In addition, male subjects are expected to use a condom as noted in Appendix E.

4.2 Exclusion Criteria

- Unequivocal demonstration of distant metastases (M1 disease).

- Unidentifiable primary site.

- Intercurrent medical illnesses which would impair subject tolerance to therapy or limit survival. Including but 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. Once clinically stable, as defined by the PI, they are eligible.

- Pregnant and nursing women are excluded because of the potential teratogenic effects and potential unknown effects on nursing newborns (please see above paragraph under inclusion criteria regarding WOCBP)

- 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 on study as outlined above

- Subjects receiving other investigational agents.

- Peripheral neuropathy >grade 1

- Has a 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.

- Has a known history of active tuberculosis (Bacillus Tuberculosis infection)

- Has hypersensitivity to nivolumab or any other drug used in this protocol.

- Has had a prior systemic anti-cancer treatment within the last 8 weeks

- 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 live expectancy in the subsequent 3 years without active treatment (e.g. low grade prostate cancer in absence of therapy).

- Has active autoimmune disease that has required systemic treatment in the past year (i.e. with use of 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.

- Has known history of, or any evidence of active, non-infectious pneumonitis.

- Has a history of Human Immunodeficiency Virus (HIV) (HIV 1/2 antibodies).

- Has known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). However, if eradicated subject is eligible.

- Has received a live vaccine within 28 days of planned start of study therapy.

    - *Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines, and are not allowed within 28 days prior to initiation of treatment.*

4.3 Criteria for discontinuation/withdrawal of informed consent

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

- Objective progression of disease if deemed inappropriate for further study treatment.

- Unacceptable adverse events.

- Protocol non-compliance.

- Study closure.

- Subject decision to withdraw from the study.

- In the judgment of the investigator, further treatment would not be in the best interest of the subject.

All deaths that occur within the trial period or within 100 days after administration of the last dose of trial drug are to be reported as SAEs.

All trial treatment-related toxicities and SAEs must be followed up until resolution. All subjects who have new or worsening CTCAE grade 3 or 4 laboratory values at the time of withdrawal must have additional testing performed for up to 12 months, and the results must be recorded in the subject's medical record. In these cases, the investigators must record their opinions regarding relationship to study treatment in the subject's medical record. Laboratory abnormalities should not be reported as adverse events unless a criterion for an SAE is fulfilled, the laboratory abnormality causes the subject to discontinue from the study, or the investigator insists the abnormality should be reported as an AE.

4.4 HPV testing

As this trial makes treatment decisions based on HPV status, the specificity of the HPV test used is of critical importance. Therefore, certain HPV testing requirements have to be met that take into account varying HPV performance characteristics in oropharyngeal primary tumors.

- p16 IHC positivity is sufficient to enroll and initiate treatment (p16 IHC interpretation to follow guidelines by *Jordan and Lingen et al*[89]).
- p16 IHC positivity is to be validated using an HPV PCR during the induction phase. This is essential as HPV genotype influences treatment arm allocation, with non-HPV16 HPV strains being considered high risk.

5 TREATMENT PLAN

5.1 General Considerations

Induction chemotherapy will be administered on an outpatient basis. Subjects receiving radiation therapy alone will be treated as outpatients whereas chemoradiotherapy may be administered on an inpatient basis (using the TFHX regimen) or outpatient basis (with cisplatin). Subjects receiving adjuvant nivolumab will receive this on an outpatient basis. All subjects will be evaluated by surgical, medical, and radiation oncologists prior to trial entry to determine optimal local treatment. Subjects will start induction chemotherapy within 4 weeks of signing consent. Three cycles of carboplatin, nab-paclitaxel, and nivolumab induction chemotherapy will be followed by response-adjusted locoregional therapy.

Subjects in Group A1 (Single-Modality De-escalation Arm) will undergo either TORS (with adjuvant radiation therapy 40-44 Gy for adverse features). Subjects in Group A2 will receive radiation therapy alone to 50 Gy in standard daily fractionation. Subjects in Group B (Intermediate De-escalation Arm) and Group C (Regular Dose Arm) will receive concurrent chemoradiation consisting of cisplatin 100mg/m2 for two (intermediate) or three (regular) doses with daily radiation, OR twice daily radiation with paclitaxel, 5-FU, and hydroxyurea (TFHX) given on an alternating week basis. Subjects should have a pre-induction chemotherapy CT simulation (or PET-CT simulation if available) performed. Cisplatin-radiation will be given to a total dose of 50 Gy for subjects in Group B and 70 Gy for subjects in Group C. TFHX will be given to a total dose of 45 Gy for subjects in Group B and 75 Gy for subjects in Group C. Adjuvant nivolumab will be offered to all subjects for 6 months on an outpatient basis.

5.2 Pre-treatment evaluation

Subjects must have completed the following within 4 weeks of signing consent unless noted (also see study calendar in section 9 for additional details) :

- Inclusion and exclusion criteria reviewed.
- Physical examination to define measurable disease.
- Pan-endoscopy with biopsy, tumor mapping, and documentation (if clinically indicated at PI's discretion).
- Biopsy proven squamous cell carcinoma of the oropharynx with HPV testing (IHC is sufficient for enrollment, but PCR needs to be completed during the first cycle of induction to confirm IHC).
- Baseline diagnostic CT or MRI scans of the head and neck that includes entire disease extent within 4 weeks before study entry.

- **PET/CT scan is recommended prior to start of induction chemotherapy, though not required.**

- 10 days prior to chemotherapy, 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 the end of induction.

- Speech and swallowing consultation during the first cycle of induction.

- Informed consent.

Refer to section 9 for a complete list of required baseline evaluations.

5.3 Study evaluations

Subjects will have the following exams and tests throughout the study at specified time points (please see study chart):

- Physical examination.

- Performance status evaluation.

- CBC with differential and platelet count.

- Complete metabolic panel.

- Toxicity and quality of life evaluations.

- Head and Neck staging evaluation and imaging with either MRI or CT within 4 weeks prior to induction chemotherapy.

- Repeat imaging of the head and neck after the 3rd cycle of induction chemotherapy week for stratification of locoregional therapy. In the case of TORS candidates, this can be delayed up to 3 weeks.

- Follow-up imaging with head and neck CT/MRI at 4 weeks post-locoregional therapy with or without re-staging PET/CT at 12 weeks post-locoregional therapy.

5.4 Induction Chemotherapy Details and Guidelines

Induction chemotherapy will be administered on an outpatient basis and concurrent chemoradiation will be administered on an inpatient basis. Expected adverse events (AEs) and appropriate dose modifications for these agents are described in Section 6. No other investigational agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

Carboplatin, nab-paclitaxel, and nivolumab combination will be administered for three cycles of three weeks duration each. TORS or RT/CRT will be performed after induction chemotherapy (i.e. day 64 of therapy). Dose delays and dose modifications should take place as outlined. **In no case should the three cycles of induction chemotherapy be given over a period exceeding twelve (12) weeks.**

Pre-medications: Premedication with dexamethasone should **not be** given due to the possibility of counteracting the effect of nivolumab, unless absolutely clinically necessary (after discussion with the PI).

Nivolumab: 360 mg flat dose on day 1, q21 days (3 doses total)

Nab-Paclitaxel: 100 mg/m^2 in 250 ml of NS (or similar per institutional standard) over 30 minutes on days 1, 8, and 15 (9 doses total)

Carboplatin: Start after completion of nab-paclitaxel, AUC 5 in 250 ml of D5W (or similar per institutional standard) over 30-60 minutes on day 1 (3 doses total)

A baseline creatinine level should be drawn within 1 week prior to starting chemotherapy.

Antiemetics: Pre-treatment with a 5 HT-3 antagonist [eg ondansetron hydrochloride (Zofran®), dolasetron mesylate (Anzemet®), or granisetron

Hydrochloride (Kytril®)] prior to chemotherapy on Day 1 is recommended. The use of additional antiemetics and the prevention of delayed emesis are left to the discretion of the treating physician. 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 (neupogen) is to be given at the discretion of the treating physician as clinically indicated.

5.5 Surgical Details and Guidelines

Subjects with low risk and small volume tonsillar disease (T1-T2, non-bulky N2A-N2B with ≤2 non-lower neck lymph nodes measuring ≤5 cm in size) or base of tongue disease (T1-2 with lateralized primary ≤3 cm, non-bulky N2A-N2B with ≤2 non-lower neck lymph

nodes measuring ≤5 cm in size) who have ≥50% reduction by RECIST following induction chemotherapy will undergo TORS and selective nodal dissection. De-intensified adjuvant RT will be given for adverse pathologic features. Subjects may refuse TORS treatment (see treatment next paragraph).

Subjects with low risk, who do not qualify for TORS (due to volume of disease or poor visualization/access) or refuse TORS, who have ≥50% reduction by RECIST following induction chemotherapy will be given de-intensified treatment with radiation alone to 50 Gy (see schema page 5).

Before induction chemotherapy, subjects will undergo examination under anesthesia and direct laryngoscopy to tattoo and photograph the primary tumor to plan the post-induction resection. Surgical resection should be performed within 2 weeks and no later than 4 weeks after completion of the third cycle of induction chemotherapy.

Primary site resection by TORS will be limited to the pre-induction extent of tumor (as defined with mapping and documentation at the time of pre-induction direct laryngoscopy). Selective nodal dissection of levels 2-4 and any other previously involved nodal levels as well as nodal levels that are clinically felt to be at risk will be performed.

5.5.1 Indications for Adjuvant Radiation post-operatively

In the absence of adverse pathologic features, subjects will not receive radiation based therapy.

Post-operative radiation will be given for adverse pathologic features as follows:

(1) 40 Gy in 2 Gy once daily fractions for PNI or LVI.
(2) 44 Gy in 2 Gy once daily fractions for ECE or positive surgical margins.

Post-operative RT volumes will be at the discretion of the treating physician, with approval from the Radiation PI, but generally will be targeted toward the surgical bed site with adverse pathology.

Post-operative RT should begin within 4 weeks and no later than 6 weeks after surgical resection.

5.6 Definitive Radiation/Chemoradiation Details and Guidelines

5.6.1 Risk Status

5.6.1.1 Low Risk Status (all of the below):

- T1-3

- N0-N2B (unless N3 equivalent lymph nodal conglomerate*)
- ≤20 pack year history tobacco use
- HPV16

5.6.1.2 High Risk Status (any of the below):

- T4
- N2C-N3
- Bulky N2B disease with N3 equivalent nodal conglomerate*
- >20 pack year history tobacco use
- Non-HPV16 HPV type (e.g. HPV18, HPV31 etc)

*N3/bulky nodal disease is defined radiologically or on clinical exam.

5.6.2 Response Stratified Grouping:

Subjects will be assigned to TORS, RT, or CRT based on response to induction chemotherapy.

Chemoradiation will be given with concurrent cisplatin or on the TFHX platform based on physician and subject preference, and are considered interchangeable.

- Cisplatin will be given at a dose of 100mg/m2, every 21 days for 2 (IDA arm, see below) or 3 doses (RDA arm, see below).

- Chemoradiation on the TFHX platform will consist of 14-day cycles of paclitaxel (100 mg/m^2 day 1 over 1 hour), 5-FU (continuous infusion at 600 mg/m^2/day $\times$ 5 days), and hydroxyurea (500 mg PO BID days 0-5, 11 doses/cycle) with twice daily radiation (150 cGy per fraction). Cisplatin-based chemoradiation on an outpatient basis will be offered as an alternative treatment platform.

5.6.2.1 Group A1: Single-Modality De-escalation Arm (SDA) – TORS

Subjects with low risk tumors and small volume tonsillar disease (T1-T2, up to N2B) *OR* base of tongue disease (T1-2 with primary ≤3cm, up to N2B) who have ≥50% reduction by RECIST following induction chemotherapy will undergo TORS and selective nodal dissection. De-intensified adjuvant RT will be given for adverse pathologic features. Subjects may refuse TORS treatment (see treatment next paragraph).

Subjects with low risk, who do not qualify for TORS (due to volume of disease or poor visualization/access) or refuse TORS, who have ≥50% reduction by

RECIST following induction chemotherapy will be given de-intensified treatment with radiation alone to 50 Gy (see schema page 5).

Surgical resection should be performed within 2 weeks and no later than 4 weeks after completion of the third cycle of induction chemotherapy.

Primary site resection by TORS will be limited to the pre-induction extent of tumor (as defined with mapping and documentation at the time of pre-induction direct laryngoscopy). Selective nodal dissection of at least the previously involved nodal levels will be performed.

Post-operative radiation will be given for adverse pathologic features as follows:

- **40 Gy in 2 Gy once daily fractions for PNI or LVI.**
- **44 Gy in 2 Gy once daily fractions for ECE or positive surgical margins.**

Post-operative RT volumes will be at the discretion of the treating physician, with approval from the Radiation PI, but generally will be directed toward the involved disease site.

Post-operative RT should begin within 4 weeks and no later than 6 weeks after surgical resection.

5.6.2.2 Group A2: Single-Modality De-escalation Arm (SDA) – RT

Subjects with low risk, who do not qualify for TORS (due to volume of disease or poor visualization/access) or refuse TORS, who have ≥50% reduction by RECIST following induction chemotherapy will be given de-intensified treatment with radiation alone to 50 Gy (see schema page 5).

5.6.2.3 Group B: Intermediate De-escalation Arm (IDA) – Low dose CRT

Subjects who have low risk disease with <50% but ≥30% reduction of tumor by RECIST with induction chemotherapy will receive CRT to 50 Gy with concurrent cisplatin (x2 doses) or 45 Gy on the TFHX platform (3 cycles).

Subjects who have high risk disease and ≥50% reduction of tumor by RECIST with induction chemotherapy will receive CRT to CRT to 50 Gy with concurrent cisplatin (x2 doses) or 45 Gy on the TFHX platform (3 cycles).

5.6.2.4 Group C: Regular Dose Arm (RDA) – Standard dose CRT:

Subjects who have low risk disease and <30% reduction of tumor by RECIST with induction chemotherapy will receive CRT to 70 Gy with concurrent cisplatin (x3 doses) or 75 Gy on the TFHX platform (5 cycles).

Subjects who have high risk disease and <50% reduction of tumor by RECIST with induction chemotherapy will receive CRT to CRT to 70 Gy with concurrent cisplatin (x3 doses) or 75 Gy on the TFHX platform (5 cycles).

Any subject who has progressive disease will receive CRT to 70 Gy with concurrent cisplatin (x3 doses) or 75 Gy on the TFHX platform (5 cycles).

Expected AEs and appropriate dose modifications for nab-paclitaxel, carboplatin, nivolumab, 5-FU, hydroxyurea, and radiation are described in sections 6.1 and 6.2 and Appendices B and C. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the subject's malignancy.

5.6.3 Concurrent Cisplatin-Radiation:

Cisplatin will be given on an every-3-weeks basis at a dose of 100mg/m2 IV over 3-4 hours day 1 (or 2) and 22 (or 23) for subjects on the *Intermediate Dose Arm*, and additionally on day 43 (or 44) for subjects on the *Regular Dose Arm*. Mannitol should be given to decrease risk of toxicity if clinically appropriate.

5.6.4 TFHX Regimen:

Subjects on the Intermediate or Regular Dose Arms will receive chemoradiation for 3-5 cycles (6-10 weeks) and chemotherapy should be administered during all weeks of radiotherapy.

Day 0

P.M.: start hydroxyurea at 500 mg PO q 12 hours $\times$ 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 P.M.: start continuous infusion of 5-FU at 600 mg/m^2/day $\times$ 5 days (120 hours).

Day 1 – 5 dexamethasone 20 mg PO (IV) in am Day 1, 1 hr prior to paclitaxel
famotidine 20 mg PO (IV) in am Day 1, 1 hr prior to paclitaxel
diphenhydramine 50 mg PO (IV) in am Day 1, 30 mins prior to paclitaxel

	Start paclitaxel 100 mg/m^2 after first RT fraction on day 1 of each cycle. Paclitaxel should be administered in 250 ml 0.9% NaCl over 60 minutes. Radiation therapy is administered twice daily at 150 cGy per fraction.
Days 6 – 13:	No chemoradiotherapy. **Subjects should be seen once on an outpatient basis during these non-treatment days to monitor for toxicity.**
For each cycle:	Administer 5 μg/kg subcutaneously (SQ) of G-CSF (filgrastim) daily, beginning on Day 6 through Day 12 at a minimum of 24 hours after completion of 5-FU in subjects who develop grade 3 neutropenia or who have neutropenia ≥ grade 2 on Day 0 of any cycle. In these subjects, 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.

5.6.5 Radiation Therapy Guidelines

1. All subjects 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) and, in selected cases, 3D conformal radiotherapy will be used alone or in combination with IMRT. 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 subjects 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. Subjects 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 identified by physical exam, additional clinical information, and radiographic studies prior to induction chemotherapy.

   CTV1 will be an isotropic expansion of the 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 CTV1 by 0.5 cm.

   CTV2 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 below. Inclusion 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 CTV2 by 0.5 cm.

5. **Dose and fractionation:**

   For subjects treated with RT alone:

   i. **Single-Modality De-escalation Arm (SDA) -- RT:** PTV1 will be treated to 50 Gy (2 Gy QD) with radiation alone over 5 consecutive weeks. <u>There will be no PTV2 volume.</u>

   For subjects treated with CRT on the TFHX platform:

   i. **Intermediate De-escalation Arm (IDA):** PTV1 will be treated to 45 Gy (1.5 Gy BID) over the course of 3 cycles. PTV2 will be treated to 30 Gy (1.5 Gy BID) during the first 2 cycles of CRT for low-risk subjects with <50% response. <u>There will be no PTV2 volume for high-risk subjects with ≥50% response.</u> 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 QD fraction of 2 Gy. Accordingly, the final cumulative dose will be slightly less.
   ii. **Regular Dosing Arm (RDA):** 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) during 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 QD fraction of 2 Gy. Accordingly, the final cumulative dose will be slightly less.

For subjects treated with CRT with cisplatin, RT dose, fractionation, and volume delineation will be as follows:

i. **Intermediate De-escalation Arm (IDA):** PTV1 will be treated to 50 Gy (2 Gy QD) over the course of 5 consecutive weeks. PTV2 will be treated to 30 Gy (2 Gy QD) during the first 3 weeks of CRT for low-risk subjects with <50% response. <u>There will be no PTV2 volume for high-risk subjects with ≥50% response.</u>
ii. **Regular Dosing Arm (RDA):** PTV1 will be treated to 70 Gy (2 Gy QD) over the course of 7 consecutive weeks. PTV2 will be treated to 50 Gy (2 Gy QD) during the first 5 weeks of CRT.

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 arrangement will be determined based on the treatment planning techniques employed. All fields must be treated during each treatment session.

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

   Intensity Modulated Radiotherapy: Optimal IMRT planning will depend on the planning system employed. We anticipate the optimal plan will use 7 to 11 gantry positions. Acceptable plans will encompass the PTV with the 95% isodose line. 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 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 Histograms:** 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:** Subjects on the *Regular Dose Arm* treated on the TFHX platform will undergo repeat CT simulation during cycle 3 for adaptive re-planning 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 (T-M) 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 subject set up. In such a situation, 3D conformal treatment techniques may be preferable to IMRT.

5.6.6 Nodal Planning Target Volume Delineation:

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

	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

5.7 Adjuvant Immunotherapy Details and Guidelines

Nivolumab: 480 mg flat dose every 28 days (7 doses total = 6 months adjuvant treatment). The goal is to potentially re-activate a potential antitumor response triggered during the induction phase after immunosuppressive RT or CRT treatment and eradicate micro-metastatic residual disease.

5.8 Supportive Guidelines

- Antiemetics will be ordered at the discretion of the attending physician.

- Use of growth factor support (G-CSF) on days 16/17/18 of induction if counts drop and Physician-recommended.. During the TFHX week-on week-off regimen G-CSF may be used during the off week at the treating physician's discretion.

- A double lumen venous access device (e.g., Port-a-Cath®) is recommended prior to initiation of therapy, although peripheral IV access is acceptable.

- Use of a feeding device is recommended for high-risk subjects. Placement of a feeding device is left to the discretion of the treating physician/investigator. Commonly applied criteria for feeding device placement include:
    i. Loss of > 10% of body weight from the start of therapy
    ii. Dehydration or inability to maintain adequate oral hydration
    iii. Inability to maintain intake of ≥25 kcal/kg of ideal body weight

- During chemoradiotherapy subjects should receive instructions for oral hygiene and prescriptions to include standard of care treatment typical for the care of HNC subjects undergoing radiation or chemoradiation:
    i. Oral nystatin or fluconazole (100mg QD)
    ii. Viscous lidocaine HCl (Xylocaine®) solution) and/or Grade I mouthwash 10 mL QID, swish and spit

Table: Grade I mouthwash

Lidocaine, Viscous (2%)	50 mL
Diphenhydramine elixir (12.5 mg/5 mL)	50 mL
Sodium bicarbonate injection	100 mL
Normal saline irrigation	500 mL
Total volume	700 mL

    iii. Normal saline mouthwash 10ml QID swish and spit

    iv. Natural Care Gel (or similar product) BID during chemoradiotherapy and TID during rest week.

    v. Vigilon (or similar product) to be applied to open wounds during chemoradiotherapy.

    vi. Silvadene cream to open wounds followed by zinc oxide cream and then Telfa dressings BID during rest week (N.B.: discontinue Silvadene and zinc oxide creams 1 day prior to radiotherapy).

vii. Aquaphor (or similar brand) cream to lips PRN.

viii. Adequate analgesia is essential to maintain oral intake and subject comfort. Narcotic analgesics are usually necessary and should be used at the physician/investigator discretion.

ix. Therabite for trismus if appropriate.

x. Replacement for electrolyte imbalances when applicable.

- Prior to discharge of the subjects 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 intravenous home hydration is strongly recommended in subjects with inadequate oral intake: normal saline 1000ml IV QD during rest week (days 6-14).

- If Hgb <10, subjects should generally be transfused an amount sufficient to increase Hgb to ≥10. The Hgb level should be maintained >10 mg/dl for the duration of chemoradiotherapy in all subjects.

- The use of peg-filgrastim is described in section 6 and G-CSF (filgrastim) is described in section 5.8.

- The use of amifostine during chemoradiotherapy is **not** permitted.

5.9 Post-therapy Follow-up

Every subject should be followed clinically until taken off study. Subjects will be seen in clinical evaluation approximately 4 weeks after completing locoregional therapy with repeat imaging of the head and neck at that time. PET-CT at 12 weeks post-completion of locoregional therapy may also be optionally performed for surveillance of indeterminate findings at 6-week imaging. Salvage surgical intervention may be indicated by either 6- or 12-week post-treatment imaging findings (upon review in multidisciplinary tumor board).

Subjects 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. Radiographic assessment should include imaging of the head, neck, and chest. Laboratory evaluation should consist of at least a CBC, serum electrolytes, serum creatinine, liver enzymes (AST, ALT, alkaline phosphatase), 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.

In addition, in an exploratory manner, we will draw blood for cell free circulating tumor DNA extraction and evaluation of HPV titers as an exploratory marker of early detection of potential recurrences. This is a research/exploratory evaluation and will not be used for clinical decision making at this point.

5.10 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).
- Subject decides to withdraw from the study.
- General or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the investigator.

5.11 Late Toxicity Assessment

5.11.1 Late Toxicity Assessment Schedule

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

5.11.2 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 subjects as to whether their voice has returned to normal. Swallowing will be determined by a subject's ability to swallow table food. A formal swallow evaluation will be done on subjects experiencing dysphagia. Additionally, late toxicity will be determined by evaluating presence and degree of xerostomia, dental decay, osteoradionecrosis, as well as the presence of G-tube or tracheotomy dependence.

5.11.3 Performance Measures

The proposed regimen aims to decrease treatment toxicity without compromising outcomes. Thus, QoL 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 subject's experience of treatment effects; evaluate changes in QoL and performance as a function of treatment regimen; determine extensiveness and persistence of QoL and function-related treatment effects; and describe the pattern, timing and extent of recovery of function and QoL.

Performance measures to be used in this protocol include (Appendix F):

- **Performance Status Scale for Head and Neck Cancer Patients (PSS-HN)**
- **Functional Assessment of Cancer Therapy - Head and Neck Version 4 (FACT-H&N)**
- **Selected questions from the McMaster University Head and Neck Radiotherapy Questionnaire Performance Status Scale for Head and Neck Cancer (MRQ)**

The PSS-HN is a clinician 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 subjects.

Functional Assessment of Cancer Therapy-Head and Neck Version 4 (FACT-H&N). The FACT-H&N is a multidimensional, self-report QoL instrument specifically designed for use with head and neck cancer subjects. The core scale (FACT-G) consists of 27 core items assessing subject 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.

McMaster Radiotherapy Questionnaire. This subject self-report instrument (can be clinician administered) quantifies subjects' perception of the frequency and severity (troublesomeness) of radiation related side effects.

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

6 EXPECTED ADVERSE EVENTS, RISKS AND DOSE MODIFICATIONS

6.1 Expected Adverse Events

6.1.1 Nab-Paclitaxel

- Cardiovascular: ECG abnormal (60%; 35% in subjects with a normal baseline). Edema /fluid retention (10%), hypotension (5%), cardiovascular events (grades 3/4: 3%; included chest pain, cardiac arrest, supraventricular tachycardia, thrombosis, pulmonary thromboembolism, pulmonary emboli, and hypertension)

- Dermatologic: Alopecia (90%)

- Gastrointestinal: Nausea (30%; grades 3/4: 3%), diarrhea (27%; grades 3/4: <1%), vomiting (18%; grades 3/4: 4%), mucositis (7%; grades 3/4: <1%)

- Hematologic: Neutropenia (80%; grade 4: 9%), anemia (33%; grades 3/4: 1%), myelosuppression (dose-related), bleeding (2%), neutropenic fever (2%), thrombocytopenia (2%; grades 3/4: <1%)

- Hepatic: AST increased (39%), alkaline phosphatase increased (36%), GGT increased (grades 3/4: 14%), bilirubin increased (7%)

- Neuromuscular & skeletal: Sensory neuropathy (71%; grades 3/4: 10%; dose dependent; cumulative), weakness (47%; severe 8%), myalgia/arthralgia (44%), peripheral neuropathy (grade 3: 10%)

- Ocular: Vision disturbance (13%; severe [keratitis, blurred vision]: 1%)

- Renal: Creatinine increased (11%; severe 1%)

- Respiratory: Dyspnea (12%), cough (7%)

- Miscellaneous: Infection (24%; primarily included oral candidiasis, respiratory tract infection, and pneumonia) Hypersensitivity reaction (4%, includes chest pain, dyspnea, flushing, hypotension; severe: <1%)

6.1.2 Carboplatin

- 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 subjects receiving 400 mg/m^2 as a single agent and 80% in subjects receiving 520 mg/m^2; leukopenia has been reported in 27% to 38% of subjects 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 subjects)
- <1% (Limited to important or life-threatening): Neurotoxicity, urticaria, rash, nephrotoxicity, secondary malignancies, anaphylaxis, malaise, hypertension

6.1.3 5-Fluorouracil

Common toxicities include:

- 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

Less commonly observed toxicities include

- Cardiac – myocardial ischemia, arrhythmias
- Allergic reactions
- Neurologic – acute cerebellar syndrome, disorientation, headache
- Eye – lacrimal duct stenosis, lacrimation, photophobia, and visual changes

5-FU may cause birth defects and should not be used in pregnant women. It is a known radiation sensitizer and may potentiate side effects of radiation.

6.1.4 Paclitaxel (during TFHX concurrent chemoradiation)

Common toxicities include

- Myleosuppression
  - Anemia
  - Alopecia
  - Myalgias and arthralgias
  - Peripheral neuropathy
  - Nausea and vomiting (usually mild)
  - Diarrhea
  - Mucositis
  - Hypersensitivity reaction - fever, facial flushing, chills, shortness of breath, or hives after Taxol is given. The majority of these reactions occur within the first 10 minutes of an infusion. Notify your healthcare provider immediately (premedication regimen has significantly decreased the incidence of this reaction).

Less common side effects

- Peripheral edema
- Abnormal liver function tests

- Hypotension
- Skin reactions/darkening of the skin
- Nail changes/discoloration
- Electrocardiogram (ECG) abnormalities with bradycardia, heart block, bundle branch block, and ventricular tachycardia,

The following are less common side effects (occurring in 10-29%) for subjects receiving Taxol:

- Swelling of the feet or ankles (edema).
- Increases in blood tests measuring liver function. These return to normal once treatment is discontinued. (see liver problems).
- Low blood pressure (occurring during the first 3 hours of infusion).
- Darkening of the skin where previous radiation treatment has been given (radiation recall - see skin reactions).
- Nail changes (discoloration of nail beds - rare) (see skin reactions)

6.1.5 Hydroxyurea

Common side effects include:

- Myelosuppression (mainly leukopenia)
- Nausea, vomiting
- Diarrhea or constipation
- Stomatitis

It may aggravate the inflammation of mucous membranes secondary to irradiation.

Less common side effects include:

- Dysuria or impairment of renal tubular function
- Rare neurologic disturbances, e.g., headaches, dizziness, disorientation, hallucination and convulsion.

6.1.6 Cisplatin

Common side effects include:

- Nausea and vomiting
- Renal toxicity
- Electrolyte wasting (magnesium, calcium, potassium)
- Myelosuppression
- Anemia

Less common side effects include:

- Peripheral neuropathy
- Hearing loss
- Anorexia
- Dysguesia, metallic taste
- Elevated liver function tests
- Alopecia

6.1.7 Filgrastim

Common side effects may include chest pain, elevated white count, fatigue, dizziness, skin rash, elevated LDH, nausea, thrombocytopenia, bone aches, epistaxis, fever

6.1.8 Nivolumab

Immuno-Oncology (I-0) agents such as PD-1 inhibitors (e.g. Nivolumab) are associated with adverse events that can differ in severity and duration than adverse events caused by other therapeutic classes. Nivolumab is considered an immune-oncology agent in this protocol. Early recognition and management of adverse events associated with immune-oncology agents may mitigate severe toxicity. For further details please refer to the nivolumab investigator brochure and tables below. Management guidelines are provided under 6.2.2.

Common side effects include:

- Fatigue
- Nausea
- Anemia
- Diarrhea
- Asthenia
- Endocrinopathies (e.g. hypothyroidism)

Less common side effects include:

- Hepatic (e.g. transaminase elvation)
- Pulmonary (e.g. pneumonitis)
- Renal
- Skin
- Hypersensitivity/Infusion Reactions

6.1.9 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, and fibrosis of soft tissues.

6.2 Dose modifications

This study will utilize the CTCAE (NCI Common Terminology Criteria for Adverse Events) Version 4 for toxicity and Adverse Event reporting. A copy of the CTCAE Version 4.0 can be downloaded from the CTEP home page (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).This section discusses the general dose modifications in the setting of the most commonly observed adverse events with systemic therapy. These are general guidelines to be followed, but deviations from the listed dose modifications are allowed at the discretion of the treating physician.

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6.2.1 Induction Chemotherapy Dose Modifications

No more than two dose modifications should be allowed for any subject. If a subject requires a third dose-reduction study treatment should be discontinued. If such a subject is clinically benefiting from treatment, and, if the physician believes the toxicity will be alleviated sufficiently with dose modification, further treatment will be permitted at the discretion of the Principal Investigator. In no case should the three cycles of induction chemotherapy be given over a period exceeding eleven (11) weeks and treatment with surgery, radiation, or chemoradiation (as appropriate) should be initiated.

Hematologic toxicity

- Subjects should not begin a new cycle of induction therapy unless the ANC is $\geq$ 1500 cells/mm^3 and the platelet count is $\geq$ 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 is <1,500 or platelets <100,000 on day 8 or 15 of each cycle, reduce all subsequent doses of nab-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 and a platelet count of at least 50,000 cells/mm^3 on days 8 or 15 of the cycle. Growth factor support should then be used with subsequent cycles.

Dose Modification Table:

Adverse Drug Reaction	Occurrence	Weekly ABRAXANE Dose (mg/m^2)	Every 3-Week Carboplatin Dose (AUC mg•min/mL)
Neutropenic Fever (ANC less than 500/mm^3 with fever >38°C) OR Delay of next cycle by more than 7 days for ANC less than 1500/mm^3 OR ANC less than 500/mm^3 for more than 7 days	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	
Platelet count less than 100,000/mm3	First	75	4.5
	Second	Discontinue Treatment	

Neurotoxicity (Peripheral)

- Subjects 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 – nab-paclitaxel should be dose reduced according to the table below.
- Withhold albumin-bound paclitaxel for grade 3-4 peripheral neuropathy. Resume albumin-bound paclitaxel at reduced doses (see table) when peripheral neuropathy improves to Grade 1 or completely resolves.

Severe sensory Neuropathy – Grade 3 or 4	First	75	4.5
	Second	50	3
	Third	Discontinue Treatment	

Ototoxicity:

- For grade 3 ototoxicity discontinue carboplatin.

Hypersensitivity:

- Albumin-bound paclitaxel (Nab-paclitaxel):
  - For grade 3 reactions manage the reaction according to institutional guidelines. For subsequent doses, use steroid and anti-histamine pretreatment and increase the infusion time to 60 minutes. For documented grade 4 hypersensitivity reactions, manage the reaction according to institutional guidelines and discontinue nab-paclitaxel.

Liver:

- Albumin-bound paclitaxel (Nab-paclitaxel):
  - Mild impairment (AST or ALT <10 times ULN or bilirubin ≤1.25 times ULN): No adjustment required.
  - Moderate impairment (AST or ALT <10 times ULN or bilirubin 1.26-2 times ULN): Reduce dose to 75 mg/m^2.
  - Severe impairment: AST or ALT <10 times ULN or bilirubin 2.01-5 times ULN: Reduce dose to 50 mg/m^2. May increase up to 75mg/m^2 in subsequent cycles if liver impairment improves to either moderate or mild impairment (based on individual tolerance).
  - AST or ALT >10 times ULN or bilirubin >5 times ULN: Discontinue nab-paclitaxel.

- No dose adjustment required for Carboplatin

Other Toxicities

- For all other grade ≥ 2 toxicities (except alopecia, nausea, vomiting, fatigue and anorexia), reduce carboplatin and albumin-

bound paclitaxel by 25% for all subsequent doses during induction.

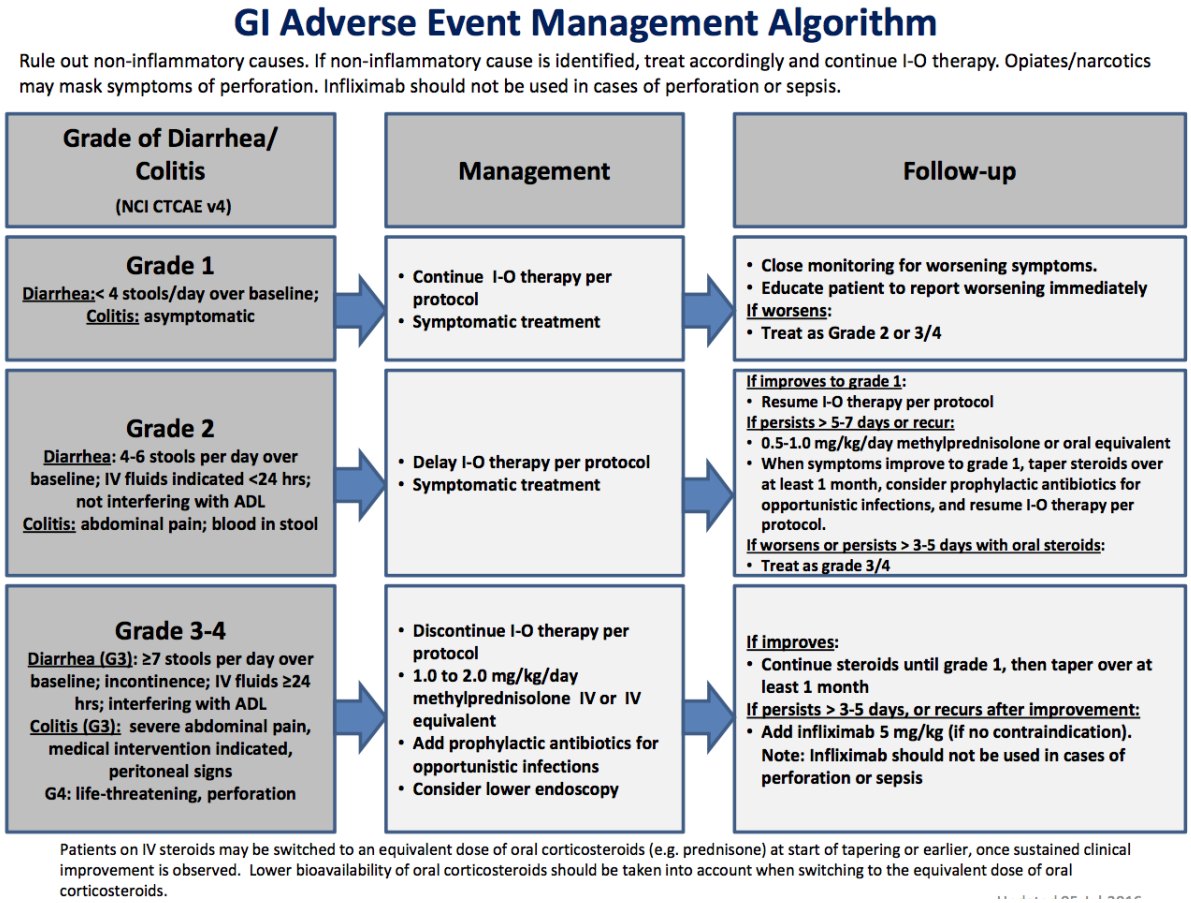
- In the event of recurrent grade 3 or 4 toxicity attributed to chemotherapy (excluding transaminase elevation, nausea, vomiting, and alopecia) reduce carboplatin and nab-Paclitaxel by a further 25% during induction.

6.2.2 Dose Modifications Immunotherapy/Nivolumab during Induction 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 in Tables below (derived from the IB). Detailed guidelines for the management of immune-related adverse reactions are described in the IB).

6.2.3 Adverse Event Management Algorithms for Immunotherapy/Nivolumab



Renal Adverse Event Management Algorithm

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

Grade of Creatinine Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 Creatinine > ULN and > than baseline but ≤ 1.5x baseline	• Continue I-O therapy per protocol • Monitor creatinine weekly	**If returns to baseline:** •Resume routine creatinine monitoring per protocol **If worsens:** •Treat as Grade 2 or 3/4
Grade 2-3 Creatinine > 1.5x baseline to ≤ 6x ULN	• Delay I-O therapy per protocol • Monitor creatinine every 2-3 days • 0.5 to 1.0 mg/kg/day methylprednisolone IV or oral equivalent • Consider renal biopsy with nephrology consult	**If returns to Grade 1:** •Taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy and routine creatinine monitoring per protocol **If elevations persist > 7 days or worsen:** •Treat as Grade 4
Grade 4 Creatinine > 6x ULN	• Discontinue I-O therapy per protocol • Monitor creatinine daily • 1.0-2.0 mg/kg/day methylprednisolone IV or IV equivalent • Consult nephrologist • Consider renal biopsy	**If returns to Grade 1 :** Taper steroids over at least 1 month and add prophylactic antibiotics for opportunistic infections

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.

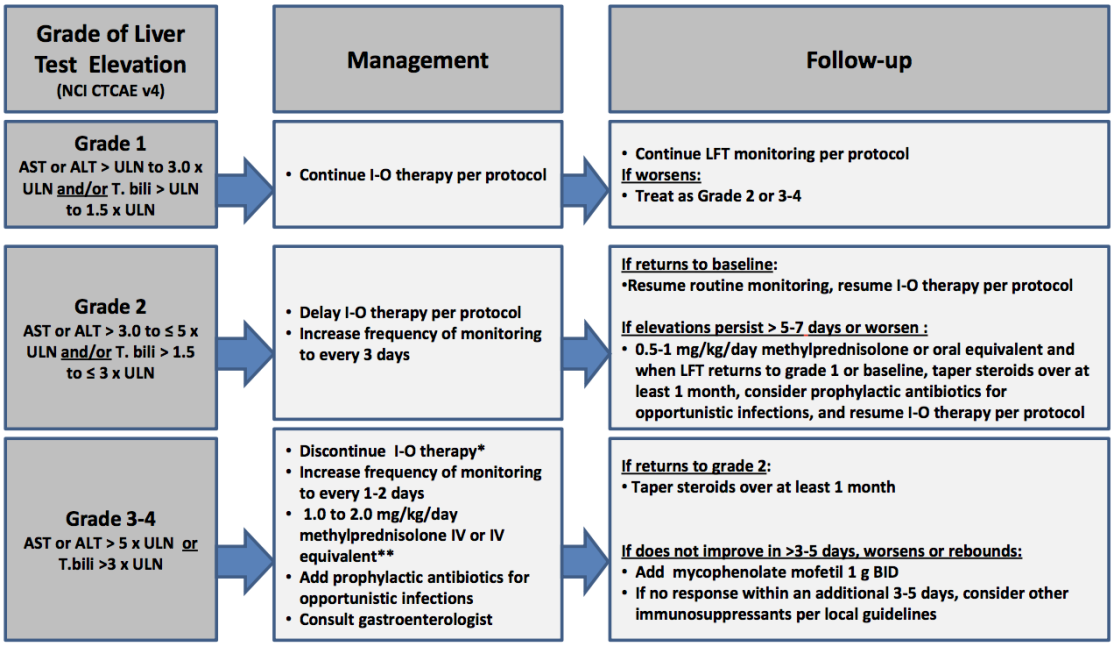
Grade of Pneumonitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Radiographic changes only	• Consider delay of I-O therapy • Monitor for symptoms every 2-3 days • Consider Pulmonary and ID consults	• Re-image at least every 3 weeks **If worsens:** • Treat as Grade 2 or 3-4
Grade 2 Mild to moderate new symptoms	• Delay I-O therapy per protocol • Pulmonary and ID consults • Monitor symptoms daily, consider hospitalization • 1.0 mg/kg/day methyl-prednisolone IV or oral equivalent • Consider bronchoscopy , lung biopsy	• Re-image every 1-3 days **If improves:** • When symptoms return to near baseline, taper steroids over at least 1 month and then resume I-O therapy per protocol and consider prophylactic antibiotics **If not improving after 2 weeks or worsening:** • Treat as Grade 3-4
Grade 3-4 Severe new symptoms; New/worsening hypoxia; Life-threatening	• Discontinue I-O therapy per protocol • Hospitalize • Pulmonary and ID consults • 2-4 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider bronchoscopy, lung biopsy	**If improves to baseline:** • Taper steroids over at least 6 weeks **If not improving after 48 hours or worsening:** • Add additional immunosuppression

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.

Updated 05-Jul-2016

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.



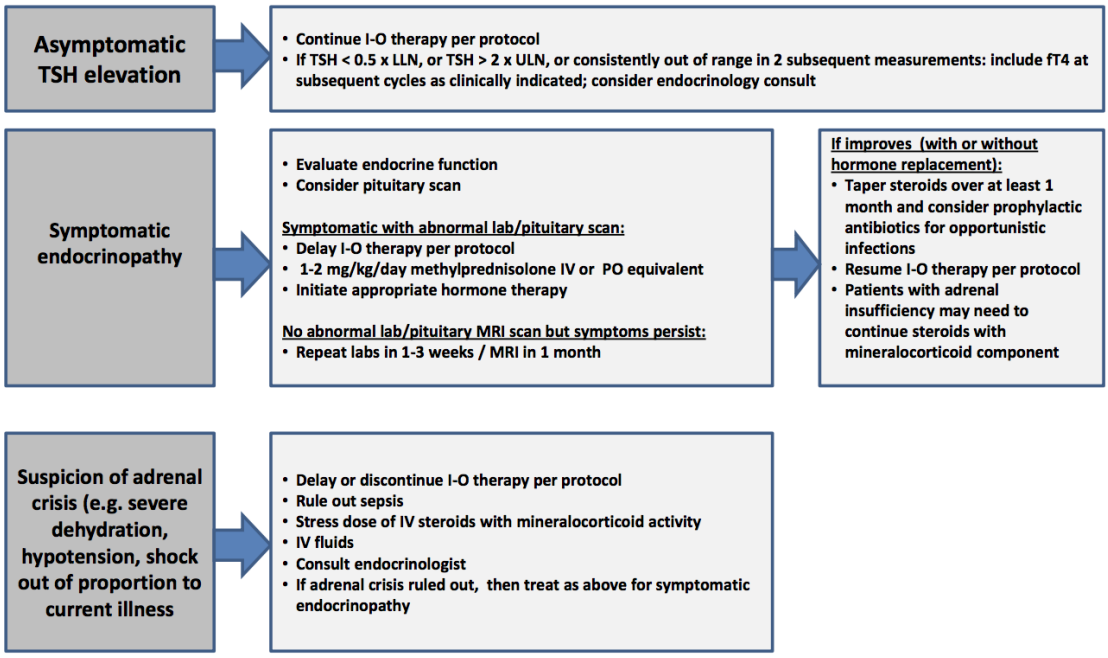
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

***I-O therapy may be delayed rather than discontinued if AST/ALT ≤ 8 x ULN or T.bili ≤ 5 x ULN.**

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

Endocrinopathy Management Algorithm

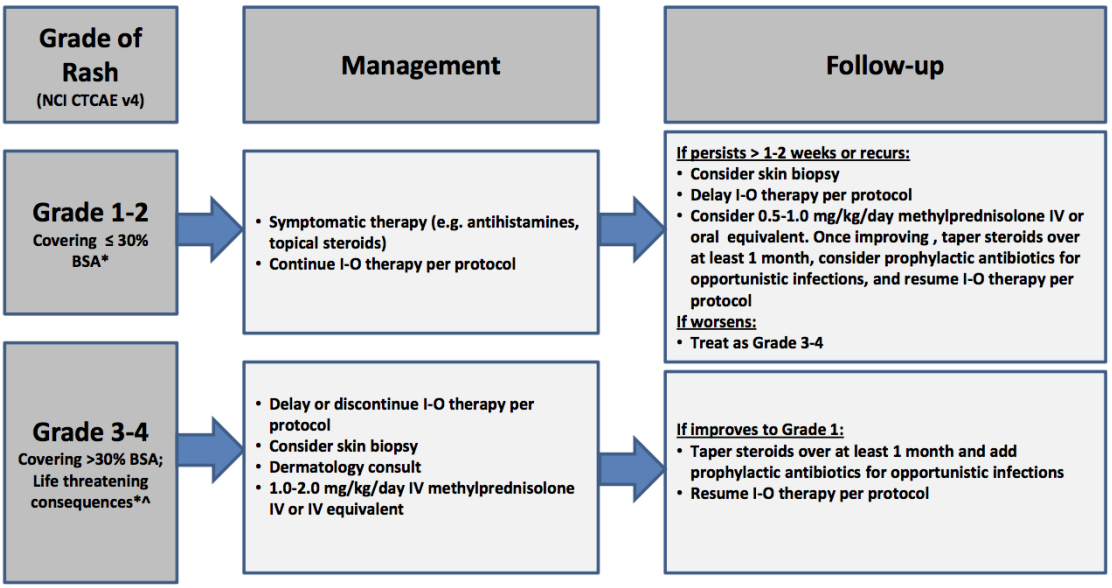
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

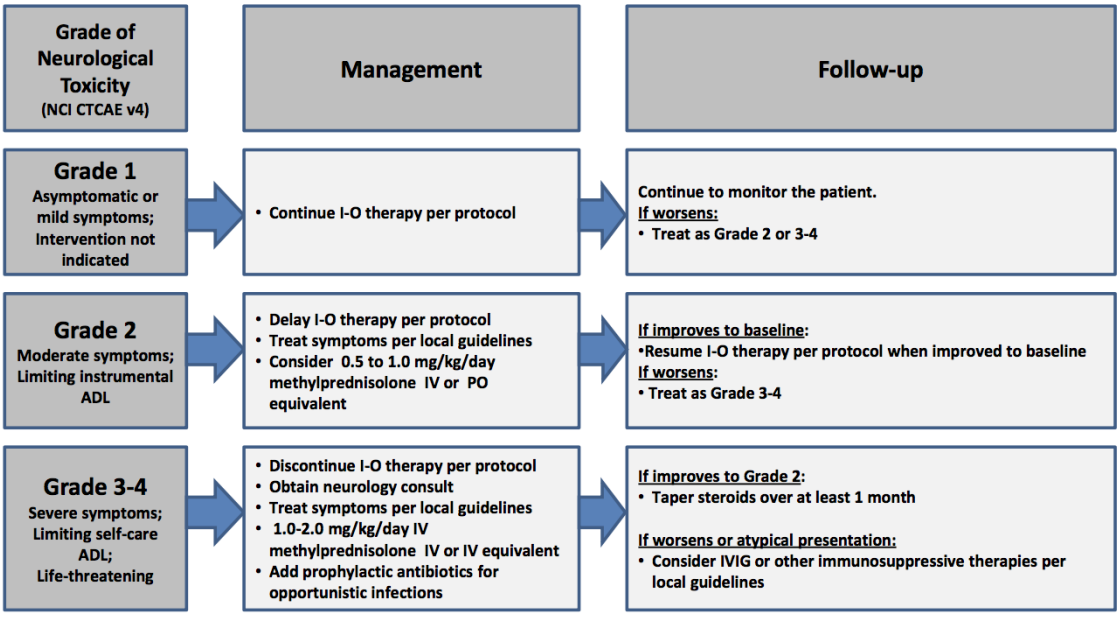
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

Neurological 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.

6.2.3.1 Nivolumab Dose Delay Criteria

Because of the potential for clinically meaningful nivolumab-related AEs requiring early recognition and prompt intervention, management algorithms have been developed for suspected AEs 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 subject 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 nab-paclitaxel while holding nivolumab.

In the event there are adverse events related to carboplatin or nab-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 despite treatment modifications or for inability to reduce corticosteroid dose to 10 mg prednisone or equivalent per day

Table 1:	**Recommended treatment modifications for OPDIVO**	
Immune-related adverse reaction	**Severity**	**Treatment modification**
Immune-related pneumonitis	Grade 2 pneumonitis	Withhold OPDIVO until symptoms resolve, radiographic abnormalities improve, and management with corticosteroids is complete
	Grade 3 or 4 pneumonitis	Permanently discontinue OPDIVO
Immune- related colitis	Grade 2 or 3 diarrhoea or colitis	Withhold OPDIVO until symptoms resolve and management with corticosteroids, if needed, is complete
	Grade 4 diarrhoea or colitis	Permanently discontinue OPDIVO
Immune-related hepatitis	Grade 2 elevation in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin	Withhold OPDIVO until laboratory values return to baseline and management with corticosteroids, if needed, is complete
	Grade 3 or 4 elevation in AST, ALT, or total bilirubin	Permanently discontinue OPDIVO
Immune-related nephritis and renal dysfunction	Grade 2 or 3 creatinine elevation	Withhold OPDIVO until creatinine returns to baseline and management with corticosteroids is complete
	Grade 4 creatinine elevation	Permanently discontinue OPDIVO
Immune-related endocrinopathies	Symptomatic Grade 2 or 3 hypothyroidism, hyperthyroidism, hypophysitis Grade 2 adrenal insufficiency Grade 3 diabetes	Withhold OPDIVO until symptoms resolve and management with corticosteroids (if needed for symptoms of acute inflammation) is complete. OPDIVO should be continued in the presence of hormone replacement therapy[a] as long as no symptoms are present
	Grade 4 hypothyroidism Grade 4 hyperthyroidism Grade 4 hypophysitis Grade 3 or 4 adrenal insufficiency Grade 4 diabetes	Permanently discontinue OPDIVO
Immune-related rash	Grade 3 rash	Withhold dose until symptoms resolve and management with corticosteroids is complete
	Grade 4 rash	Permanently discontinue OPDIVO

Note: Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.0 (NCI-CTCAE v4).

[a] Recommendation for the use of hormone replacement therapy is provided in section 4.4.

6.2.3.2 Treatment of Infusion Reaction

Since Nivolumab contains only human IgG protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reacitons. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash pruritus, athralgias, blood pressure shifts, bronchospasms, or other symptoms. All Grade 3,4, or 5 infusion reacitons should be reported within 24 hours to the primary

investigator and reported as an SAE if criteria are met. Infusion reactions should be graded according to NCI CTCAE v 4.0 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 subject 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 [eg, 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 subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor subject 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 subject 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 subject 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 [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, 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 subject 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. Subject 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 subject until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

6.2.4 Dose Modifications During Concurrent Chemoradiotherapy

Hematologic Toxicity 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 $\leq$ 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 $\leq$ 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.

Hematologic Dose Modifications for Paclitaxel:

Dose Level	Paclitaxel (mg/m^2)
0	100
–1	75
-2	50
-3	Discontinue

Neutropenia and Thrombocytopenia:

For ANC ≤ to 1000 or platelet 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.

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 again on subsequent cycles.

Nephrotoxicity

Grade 2 renal toxicity – administer 50% dose hydroxyurea

Grade 3, 4 renal toxicity – Hold hydroxyurea

Hepatotoxicity on day 0: Grade 3, 4 – Hold hydroxyurea and adjust paclitaxel per package insert

Peripheral neuropathy:

For Grade 2 peripheral neuropathy, decrease paclitaxel by one dose level per CRT dosing schedule (see hematologic toxicity chart).

For Grade 3 or greater peripheral neuropathy, discontinue paclitaxel.

Other Non-hematological Toxicity

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 subjects with myeloproliferative disorders during therapy with hydroxyurea. These vasculitic toxicities were reported most often in subjects with a history of, or currently receiving, interferon therapy. Due to potentially severe clinical outcomes for the cutaneous vasculitic ulcers reported in subjects with myeloproliferative disease, hydroxyurea should be discontinued if cutaneous vasculitic ulcerations develop.

Geriatric Use: Elderly subjects 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 subjects with impaired renal function. Because elderly subjects are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function.

Dose Modifications for Cisplatin:

Cisplatin

Renal Toxicity

CrCl 46-60 – 25% dose reduction

CrCl 31-45 – 50% dose reduction

Myelosuppression

If the absolute neutrophil count (ANC) is < 1000 on day 1 of each cycle, hold cisplatin and when count recover > 1000 ANC, then decrease cisplatin 25%. On subsequent cycles, a reduced starting dose of cisplatin should be used.

Peripheral neuropathy

If Grade 2 neuropathy on day 1 of each cycle, then decrease cisplatin 25%. On subsequent cycles, a reduced starting dose of cisplatin should be used.

If Grade 3 or greater neuropathy on day 1 of each cycle, 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.

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 subject.

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 subject completed the clinical study. If for any subject either study treatment or observations were discontinued the reason will be recorded. Reasons that a subject may discontinue participation in a clinical study are considered to constitute one of the following:

1. adverse event(s)
2. abnormal laboratory value(s)
3. abnormal test procedure result(s)
4. disease progression
5. protocol violation
6. subject withdrew consent
7. lost to follow-up
8. administrative problems
9. death

6.2.5 Dose Modifications Immunotherapy/Nivolumab during Adjuvant Nivolumab Treatment

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 sections/treatment algorithms above for adverse event management during induction for further details (management of adverse events and dose delays will be analogous to the induction phase for immunotherapy with nivolumab).

7 AGENT FORMULATION AND PROCUREMENT

7.1 Nab-paclitaxel

Classification:
Antineoplastic Agent, Antimicrotubular; Natural Source (Plant) Derivative; Taxane Derivative

Mode of Action:
Albumin-bound paclitaxel nanoparticle formulation. Paclitaxel promotes microtubule assembly by enhancing the action of tubulin dimers, stabilizing existing microtubules, and inhibiting their disassembly, interfering with the late G_2 mitotic phase, and inhibiting cell replication. May also distort mitotic spindles, resulting in the breakage of chromosomes. Paclitaxel may also suppress cell proliferation and modulate immune response.

How Supplied:
Injection, powder for reconstitution: Abraxane®: 100 mg [contains albumin (human)]

Storage:
Store in vials in original cartons at room temperature (20oC-25oC; 68oF to 77oF). Retain in the original package to protect from bright light.

Stability:
Unopened vials of nab-paclitaxel are stable until the date indicated on the package when stored at the above temperature in the original package. Reconstituted vials of albumin-bound paclitaxel may be refrigerated at 2oC to 8oC (38oF to 46oF) for a maximum of 8 hours and should be protected from bright light

Dose Specifics:
Albumin-bound paclitaxel 100mg/m2 IV over 30, minutes on day 1, 8, and 15 of each 21-day cycle of induction chemotherapy (total of 3 cycles)

Preparation:
Reconstitute each vial with 20 mL of 0.9% sodium chloride injection, USP injected over at least 1 minute. Direct the NaCl onto the inside wall of the vial, and not directly onto the lyophilized cake, as this will result in foaming. Following reconstitution, allow the vial to sit for a minimum of 5 (five) minutes to ensure proper wetting of the lyophilized cake/powder. Gently swirl and/or invert the vial slowly for at least 2 minutes until complete dissolution of any cake/powder occurs.

Rapid agitation or shaking will result in foaming. If foaming or clumping occurs, stand solution for at least 15 minutes until foam subsides. The reconstituted suspension should appear milky and homogeneous without visible particulates. If unsuspended powder is visible, the vial should be gently inverted again to ensure complete resuspension, prior to

use. Each ml of reconstituted product will contain 5 mg of paclitaxel. Withdraw the desired volume and inject the suspension into an empty sterile PVC container.

Route of Administration
Albumin-bound paclitaxel will be administered as an IV infusion over 30 minutes. On days when carboplatin is given, albumin-bound paclitaxel will be administered first. Filters are not required for preparation or administration of albumin-bound paclitaxel. If filters are used as part of institutional procedures, the pore size must be ≥ 15 micron.

Drug Return and Destruction
Study drug will be disposed of as per the University of Chicago Medical Center Investigational Pharmacy drug destruction policy/procedure. The following information must be recorded on the site's pharmacy drug accountability log:

Quantity of vials destroyed.
Expiration date
Lot number.

The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

a) Supplier

Celgene Corporation
86 Morris Avenue
Summit, NJ 07901

Industry Contact:

Martha Kennedy
Manager, Medical Operations
Celgene Corporation
400 Connell Drive, 7th Floor
Connell Corporate Park
Berkeley Heights, NJ 07922
Mobile: 908-723-6919
Fax: 908-673-2779
Email: Mkennedy@celgene.com

b) Drug Distribution

ABRAXANE® will be distributed by Celgene Corporation. No supplies will be shipped to any site until regulatory approval has been obtained. Investigational sites will be supplied with ABRAXANE® upon identification and screening of a potential trial subject.

Upon identification of a potential subject, sites must fax a completed Drug Request Form to Celgene Corporation. Allow at least 5 working days for drug shipment. There are no shipments on Fridays or holidays.

For re-supply of drug, please complete and fax the Drug Request Form to Celgene Corporation at 908-673-2779.

c) Drug Return and Destruction

If the investigational site does not have a policy, procedure or SOP detailing the process to follow for study drug destruction, the study drug must then be returned to Celgene using the Drug Return Form provided in the package containing the study drug. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials to be returned, expiration date and lot number. A copy of the Drug Return Form and the study drug should be returned to Celgene Clinical Supplies Dept. using the mailing address on the packaging slip that came with the original study drug order. A copy of the Drug Return Form should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

If the investigational site has a policy, procedure or SOP detailing the process to follow for study drug destruction, the pharmacist or designee can choose to destroy the study drug on site. The following information must be recorded on the site's pharmacy drug accountability log: quantity of vials destroyed, expiration date and lot number. The pharmacist must document that the study drug was destroyed in accordance with their institution's drug destruction policy or SOP. A drug destruction memo and the site's drug destruction SOP/policy should be sent to Celgene Medical Operations Dept. A copy of the drug destruction memo should be retained at the clinical site. In the event of study completion or termination, a copy of all pharmacy records (drug dispensing log, drug accountability log and any destruction memos) must be mailed to Celgene Medical Operations.

7.2 Carboplatin

Carboplatin: 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 9.3. 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 n 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 nab-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%).

7.3 Fluorouracil

5-Fluorouracil (Adria, OH): 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 5.6.4. Please refer to the package insert for full prescribing information.

7.4 Hydroxyurea

Hydroxyurea (Bristol-Myers Squibb, Princeton, NY): commercially available as 500 mg capsules. It is stored at room temperature and will be administered orally as described in section 5.6.4. Please refer to the package insert for solution preparation and expected AE. Please refer to the package insert for full prescribing information.

7.5 Paclitaxel

Chemistry: Paclitaxel is a natural product with antitumor activity. The chemical name for paclitaxelis 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 subjects 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 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: Paclitaxel should be given after the subject 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.

7.6 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 15° to 20°C. Do not refrigerate. Protect unopened container from light. The cisplatin remaining in the amber vial following initial entry is stable for 28 days protected from light or for 7 days under fluorescent room light.

Side effects are listed in section 6.1.6. Please refer to the package insert for full prescribing information.

Availability: Cisplatin is commercially available from Bristol Laboratories Oncology Products.

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.

7.7 Filgrastim (Neupogen®) Drug Information

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 10^8 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 46ºF). 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. Subjects 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 Fligrastim clinical trials of cancer subjects receiving myelosuppressive chemotherapy, WBC > 100,000/mm^3 have been reported in less than 5% of subjects, but were not associated with any reported adverse clinical effects.

In cancer subjects 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 subjects 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 subjects with sepsis receiving Filgrastim, and is postulated to be secondary to an influx of neutrophils to sites of inflammation in the lungs. Neutropenic subjects 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 subjects should receive appropriate medical management for this condition.

Allergic-type reactions occurring on initial or subsequent treatment have been reported in < 1 in 4000 subjects 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 subjects 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 subjects who were rechallenged.

Severe sickle cell crisis have been reported in subjects with sickle cell disease (specifically homozygous sickle cell anemia, sickle/hemoglobin C disease, and sickle/□+ 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. Subjects 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.

7.8 Nivolumab

Nivolumab is supplied by BMS.

Nivolumab 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.

Nivolumab Use Time/Stability

Once transferred to IV bags, the solution may be stored for up to 20 hrs in a refrigerator at 2-8 degrees Celsius and used within 8 hours at room temperature and under room light inclusive of administration time. The maximum 8-hour period under room temperature and room light conditions for undiluted and diluted solutions of Nivolumab injection in the IV bag should be inclusive of the product administration period.

Pharmacy supplies required

- Empty IV bags-50mg, 100mL, 200 mL
- 0.9% NaCl bags
- 0.2 or 1.2 micron in line filter and infusion tubing
- Volumetric infusion pumps.

Nivolumab Preparation and Administration:

- Nivolumab injection is to be administered using a volumetric pump with a 0.2/1.2 micron pore size, low protein binding polyethersulfone membrane in-line filter at the protocol-specific doses and infusion times.
- 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 a 1-hour period; infusions will be controlled by a volumetric pump.
- Nivolumab infusins are compatible with polyolefin containers and infusion sets, and glass bottles . I
- Allow the appropriate number of vials of Nivolumab to stand at room temperature for approximately 5 minutes before preparation.
- Ensure that Nivolumab solution is clear, colorless, and essentially free from particulate matter.
- Aseptically withdraw the require volume of Nivolumab into a syringe and dispense into an IV bag.
    - Add the appropriate volume of 0.9% Sodium Chloride injection solution.
    - Mix by gently inverting several times. DO NOT shake.
    - Record the time the Nivolumab was prepared on the IV bag label.
    - Attach the IV bag containing the Nivolumab solution to the infusion set, in-line filter, and infusion pump.

- The infusion rate of the infusion pump should be adjusted to allow for a total infusion time of 30 minutes.
- At the end of the infusion period, flush the line with a sufficient quantity of 0.9% Sodium Chloride injection solution.

8 CORRELATIVE/SPECIAL STUDIES

8.1 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 treatment with nivolumab + chemotherapy using serial samples, and also evaluate potential predictive candidate biomarkers.

We will collect plasma samples to monitor treatment progress using cell free circulating tumor DNA (ctDNA). This will be done by measuring the HPV DNA titer and/or somatic mutations. In addition to providing a marker of treatment efficacy e.g. during induction with nivolumab + chemotherapy, it will also be used to assess subjects after treatment serially to assess any evidence of early recurrence but will not be used for clinical decision making at this point.

8.2 Correlative analysis

8.2.1 Tissue:

Baseline archival (or if not available alternatively fresh) tissue will be collected on all subjects as well as a biopsy at week 2-3 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 subjects with stage IV HNC as enrolled in this trial.

8.2.1.1 Multicolor IF based assessment of immune microenvironment

Using both archival or fresh tumor samples (tissue digest or fresh frozen/OTC tissue) and then the on-treatment paired biopsy during induction (nivolumab+chemotherapy), 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 that will be determined by immunofluorescence. Results will be digitally assessed, and results descriptively compared with results from flow cytometry (cell digest) and mRNA analysis (see below).

8.2.1.2 mRNA analysis / Immune Signatures (Nanostring or similar)

Analysis will be performed using the Nanostring nCounter (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.

8.2.1.3 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 and tumor response. 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.

8.2.1.4 Germline DNA analysis

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

8.2.1.5 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.

8.2.2 Blood:

8.2.2.1 ctDNA analysis

Using cell free circulating DNA (ctDNA) we measure HPV DNA titers and somatic mutations. This will be assessed as a candidate marker of treatment efficacy e.g. during induction with nivolumab + chemotherapy (baseline versus 2-3 weeks into treatment).

Furthermore, it will also be used to assess subjects 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 subjects at risk for recurrence, who may benefit from additional therapy.

8.2.2.2 RNA analysis from blood

Blood samples will be obtained at baseline and after 3 weeks (administration of cycle 2 nivolumab dose). Samples will be processed for RNA extraction (e.g. using the PAXgene RNA kit/tubes). RNA will be analyses by Nanostring (see above) 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.

8.3 Sample and Tissue Procurement

8.3.1 Archival tumor collection

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

8.3.2 Tissue Biopsy

Tumor biopsy will be performed prior to starting therapy or archival tissue will be obtained for all subjects. 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 subject. Furthermore, an on-treatment biopsy during nivolumab induction chemotherapy will be performed at 2-3 weeks post start of treatment as clinically feasible and subject consents to the procedure.

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).

- Write study number, subject 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, subject initials and date filled with RNAlater reagent from Qiagen.
- Freeze over liquid nitrogen vapors or in -80 C freezer.

8.3.3 Blood Isolation

Blood will be obtained from all subjects 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 tubes. Blood should be stored at -80 C 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 store anonymously with a unique barcode at -80 C at the University at Chicago for future genotype analysis.

Subjects will have blood samples for genotyping and plasma analysis collected prior to induction chemotherapy. Samples for serum analysis will be collected prior to radiotherapy initiation, and then after the first week and at the completion of radiotherapy and will be collected at 2 months after radiotherapy.

Plasma will be used for identification of cell free circulating tumor DNA, e.g. for HPV titer and 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.

9 STUDY CALENDAR / FLOWCHART

		Induction therapy									
	Pre-study[1]	C1D1	C1D8	C1D15	C2D1	C2D8	C2D15	C3D1	C3D8	C3D15	Post-Induction
Induction chemotherapy		X	X	X	X	X	X	X	X	X	
RT/CRT											
Adjuvant nivolumab											
Panendoscopy[6]	X										
Biopsy	X[2]			X[3]							
PET/PET-CT[4]	X										
MRI/CT of head and neck, chest [5]	X									X[10]	
Blood for correlatives		X			X			X		X	
Informed consent	X										
Inclusion/Exclusion	X										
Demographics	X										
Medical history	X										
Concurrent meds	X	X	X	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X	X	X	X
Swallowing evaluation	X[6]										
Dental exam	X[8]										
Vital signs	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
Performance status	X	X	X	X	X	X	X	X	X	X	X
TSH	X										
CBC	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[9]	X	X	X	X	X	X	X	X	X	X	X
Adverse event evaluation	X	X	X	X	X	X	X	X	X	X	X
Tumor measurements	X										X
QoL evaluations	X										X
b-hCG [7]	X										
HPV testing	X										

1 Baseline evaluations are to be conducted within 4 weeks prior to start of protocol therapy (excluding biopsy). Screening labs are to be done within 10 days of start of protocol therapy. In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

2 Biopsy should be performed if no adequate archival tissue is available pre-study. A second biopsy for purposes of correlative tissue analysis should be performed during weeks 2-3 of induction chemotherapy.

3 Optional biopsy if patient consented to it.

4 Optional at baseline

5 CT brain is not required but can be done if clinically indicated

6 If clinically indicated.

7 To be done within 24hrs prior to starting therapy

8 Can be done anytime during induction, but before definitive treatment begins.

9 Chemistries should include standard comprehensive metabolic panel

10 Can be delayed up to 3 weeks if a TORS candidate

Subgroup A1: TORS

		adjuvant nivolumab						Long term follow up
	TORS	week 4 post TORS C1D1	week 8 post TORS C2D1	week 12 post TORS C3D1	week 16 post TORS C4D1	week 20 post TORS C5D1	week 24post TORS C6D1	Q6 mos up to 2 years
Adjuvant nivolumab		X	X	X	X	X	X	X
Panendoscopy								
Biopsy			X					
PET/PET-CT				X				
MRI/CT of head and neck, chest [1]		X						X[4]
Blood for correlatives		X	X	X				
Informed consent								
Inclusion/Exclusion								
Demographics								
Medical history								
Concurrent meds	X	X	X	X	X	X	X	X
Physical exam	X	X	X	X	X	X	X	X
Swallowing evaluation		X						
Dental exam								
Vital signs	X	X	X	X	X	X	X	X
Height								
Weight	X	X	X	X	X	X	X	X
Performance status	X	X	X	X	X	X	X	X
TSH[2]								X
CBC	X	X	X	X	X	X	X	X
Serum chemistry[3]	X	X	X	X	X	X	X	X
Adverse event evaluation	X	X	X	X	X	X	X	X
Tumor measurements		X						X
QoL evaluations		X	X	X				

[1] CT brain is not required but can be done if clinically indicated

[2] TSH should be repeated every 2 months while on adjuvant Nivolumab, and annually after that post RT/CRT, and as part of standard of care considered to be continued beyond this protocol

[3] Chemistries should include standard comprehensive metabolic panel

[4] Follow-up Imaging should include evaluation of the head and neck, chest and upper abdomen

Subgroup A2: RT Only

	RT1	RT2	RT3	RT4	RT5	RT6	RT7	adjuvant nivolumab						Long term follow up
								week 4 C1D1	week 8 C2D1	week 12 C3D1	week 16 C4D1	week 20 C5D1	week 24 C6D1	Q6 mos up to 2 years
RT/CRT	X	X	X	X	X	X	X							
Adjuvant nivolumab								X	X	X	X	X	X	X
Panendoscopy														
Biopsy									X					
PET/PET-CT										X				
MRI/CT of head and neck, chest [1]								X						X[4]
Blood for correlatives								X	X	X				
Informed consent														
Inclusion/Exclusion														
Demographics														
Medical history	X	X	X	X	X	X	X							
Concurrent meds		X	X	X	X	X	X	X	X	X	X	X	X	X
Physical exam								X	X	X	X	X	X	X
Swallowing evaluation								X						
Dental exam	X	X	X	X	X	X	X							
Vital signs								X	X	X	X	X	X	X
Height	X	X	X	X	X	X	X							
Weight		X	X	X	X	X	X	X	X	X	X	X	X	X
Performance status								X	X	X	X	X	X	X
TSH[2]	X	X	X	X	X	X	X							X
CBC	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[3]	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event evaluation								X	X	X	X	X	X	X
Tumor measurements								X						X
QoL evaluations								X	X	X				

1 CT brain is not required but can be done if clinically indicated

2 TSH should be repeated every 2 months while on adjuvant Nivolumab, and annually after that post RT/CRT, and as part of standard of care considered to be continued beyond this protocol

3 Chemistries should include standard comprehensive metabolic panel

4 Follow-up imaging should include evaluation of the head and neck, chest, and upper abdomen.

Subgroup B: CRT 3 Cyles

	CRT1	CRT2	CRT3	adjuvant nivolumab						Long term follow up
	RT1	RT2	RT3	week 4 C1D1	week 8 C2D1	week 12 C3D1	week 16 C4D1	week 20 C5D1	week C6D1	Q6 mos up to 2 years
RT/CRT	X*	X*	X*							
Adjuvant nivolumab				X	X	X	X	X	X	X
Panendoscopy										
Biopsy					X					
PET/PET-CT						X				
MRI/CT of head and neck, chest [1]				X						X[4]
Blood for correlatives				X	X	X				
Informed consent										
Inclusion/Exclusion										
Demographics										
Medical history										
Concurrent meds	X	X	X	X	X	X	X	X	X	X
Physical exam		X	X	X	X	X	X	X	X	X
Swallowing evaluation				X						
Dental exam										
Vital signs	X	X	X	X	X	X	X	X	X	X
Height										
Weight	X	X	X	X	X	X	X	X	X	X
Performance status		X	X	X	X	X	X	X	X	X
TSH[2]										X
CBC	X	X	X	X	X	X	X	X	X	X
Serum chemistry[3]	X	X	X	X	X	X	X	X	X	X
Adverse event evaluation	X	X	X	X	X	X	X	X	X	X
Tumor measurements				X						X
QoL evaluations				X	X	X				

1 CT brain is not required but can be done if clinically indicated

2 TSH should be repeated every 2 months while on adjuvant Nivolumab, and annually after that post RT/CRT, and as part of standard of care considered to be continued beyond this protocol

3 Chemistries should include standard comprehensive metabolic panel

4 Follow-up imaging should include evaluation of the head and neck, chest, and upper abdomen.

Subgroup C: CRT 5 Cycles

	CRT1	CRT2	CRT3	CRT4	CRT5	adjuvant nivolumab						Long term follow up
						week 4 C1D1	week 8 C2D1	week 12 C3D1	week 16 C4D1	week 20 C5D1	week 24 C6D1	Q6 mos up to 2 years
RT/CRT	X	X	X	X	X							
Adjuvant nivolumab						X	X	X	X	X	X	X
Panendoscopy												
Biopsy							X					
PET/PET-CT								X				
MRI/CT of head and neck, chest [1]						X						X[4]
Blood for correlatives						X	X	X				
Informed consent												
Inclusion/Exclusion												
Demographics												
Medical history	X	X	X	X	X							
Concurrent meds		X	X	X	X	X	X	X	X	X	X	X
Physical exam						X	X	X	X	X	X	X
Swallowing evaluation						X						
Dental exam	X	X	X	X	X							
Vital signs						X	X	X	X	X	X	X
Height	X	X	X	X	X							
Weight		X	X	X	X	X	X	X	X	X	X	X
Performance status						X	X	X	X	X	X	X
TSH[2]	X	X	X	X	X							X
CBC	X	X	X	X	X	X	X	X	X	X	X	X
Serum chemistry[3]	X	X	X	X	X	X	X	X	X	X	X	X
Adverse event evaluation						X	X	X	X	X	X	X
Tumor measurements						X						X
QoL evaluations						X	X	X				

[1] CT brain is not required but can be done if clinically indicated

[2] TSH should be repeated every 2 months while on adjuvant Nivolumab, and annually after that post RT/CRT, and as part of standard of care considered to be continued beyond this protocol

[3] Chemistries should include standard comprehensive metabolic panel

[4] Follow-up imaging should include evaluation of the head and neck, chest, and upper abdomen.

10 MEASUREMENT OF EFFECT

For the purposes of this study, subjects should have both pre- and post-induction chemotherapy imaging of the head and neck with either CT or MRI for determination of response.

Measurement of target lesions will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST v1.1) Committee.[90]

10.1 Measurement of Target Lesions

Tumor lesions: Must be accurately measured in at least one dimension (*longest* diameter in the plane of measurement is to be recorded) with a *minimum* size of 10 mm by CT scan (CT scan slice thickness no greater than 5 mm).
In cases where based on discussion in tumor board the target lesions cannot be accurately measured by RECIST a volumetric measurement may be used IF agree upon by the tumor board and PI.

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

10.2 Measurement of Response

Target lesion measurements will be summated on pre- and post-induction chemotherapy imaging. The percentage change will be calculated and the response used for treatment stratification as previously described.

10.2.1 Details about diagnostic imaging

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 subjects with this type of cancer. However, CT and FDG-PET often yield false positive or false negative findings for early assessment of treatment response. In particular, increased FDG uptake by activated inflammatory cells occurs in irradiated tissue and can result in false positive results during the early post-treatment period, which limits the utility of 18FDG-PET for the detection of residual tumor prior to 12 weeks (Meng et al). This is beyond the “safe window” for performing surgery in cases of residual tumor that has been described at 4 to 12 weeks following chemoradiation, which is between the period of resolution of acute tissue injury and the onset of chronic tissue injury induced by chemoradiation that results in relatively normal wound healing, and is associated with a reduced incidence of surgical complications.

On the other hand, measurements derived from diffusion weighted imaging perfusion MRI are promising techniques that can serve as potentially accurate imaging biomarkers of early treatment response for head and neck tumors. In particular, ADC, which is a measure of the magnitude of diffusion of water molecules within tissue, and is commonly clinically calculated using MRI with DWI, and K-trans, which is a measure of capillary permeability obtained using dynamic contrast enhanced (DSC) MRI, a perfusion weighted imaging MRI sequence, are potentially useful biomarkers for predicting treatment response.

Indeed, DWI has been one of the most investigated biologic imaging modalities in head and neck cancer, primarily due to its ability to acquire reproducible images in a short sequence that can be incorporated into any head and neck MRI protocol. Studies have demonstrated that changes in ADC and percentage change in tumor volumes between baseline DWI and 3-weeks mid-therapy DWI showed correlation with outcomes, as opposed to percentage change in mean ADC, which did not correlate with tumor control at 6 months. Results from these studies imply that ADC values may be more accurate in detecting changes in tumor architecture, possibly at an earlier stage, compared with conventional measures such as alterations in tumor volume or enhancement. Both baseline ADC and change in ADC during therapy have proved useful as predictors of response in a recent study in which the authors showed that tumors that responded completely to chemoradiation had decreased baseline ADC values compared with tumors that responded only partially; in this study, change in the ADC during therapy served as a better predictor than baseline ADC alone. Ultimately, the true value of ADC in prediction and monitoring of response likely lies in a combination of pre-, intra-, and post-therapy ADC values, which needs to be evaluated in larger samples to establish its utility.

Diffusion-weighted MR imaging (DWI) and dynamic contrast-enhanced perfusion-weighted imaging parameters can potentially serve as biomarkers for predicting treatment response in subjects with head and neck squamous cell carcinomas (Kuang et al, Imanishi et al, Sumi et al, Srinivasan et al, Trojanowska et al, Padhani et al, Surlan-Popovic et al, Galban et al, Cao et al). DWI allows quantification of the diffusion of water molecules in tissues using the apparent diffusion coefficient (ADC), which can reflect tumor cellularity. Previous studies demonstrated that tumors with high ADC values are less likely to respond to chemoradiation, possibly because a high ADC value may reflect the presence of micronecrosis and, consequently, increased resistance to the delivery of cytotoxic drugs as well as oxygen during chemoradiation. DWI has also been used in the prediction of response to chemoradiation in head and neck squamous cell carcinomas.

The subjects in this study will undergo a standardized 3T MRI protocol at baseline before induction chemotherapy and approximately 1 month after immunotherapy. The MRI sequences included in the protocol consist of multiplanar T1, T2, post-contrast T1, diffusion-weighted imaging, and perfusion-weighted imaging, with the same slice thickness, matrix sizes, and echo and repetition times implemented for each subject. The detailed protocol available to the performing technologists is provided in the Appendix.

ADC maps are automatically generated from the DWI sequences and measurement of the ADC values of the tumors will be made by drawing regions of interest at the PACS viewing station in the University of Chicago radiology computers. Post-processing software (Olea) available in the radiology reading room workstations is necessary to derive Ktrans measurement of the tumors from the raw perfusion images.

10.3 Progression-Free and Overall Survival

Progression-Free Survival: From the date of registration to the date of progressive disease or death (whichever is first) or last follow-up if censored.

Overall Survival: From the date of registration to the date of death or date of last follow-up if censored.

Assessment of Local/Distant Failure: If disease progression is documented, subjects should have full assessment of sites of failure (i.e. local and distant). Local failure should be assessed by radiographic imaging and physical examination. Distant failure should be assessed by radiographic imaging. Further assessment of local and distant failure can be performed if warranted by subject symptoms.

Patients should be followed for a minimum of 3 years post completion, but optional follow-up as aligned with clinical care is acceptable.

11 REGULATORY AND REPORTING REQUIREMENTS

11.1 Regulatory Guidelines

11.1.1 Food and Drug Administration (FDA) Approval

This study will be conducted under an IND held by Dr. Tanguy Seiwert 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.

11.2 Expedited Adverse Event Reporting

Adverse events (AEs) will use the descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4. All appropriate treating areas will have access to a copy of the CTCAE version 4. A copy of the CTCAE version 4. A copy of the CTCAE version 4 can be downloaded from the CTEP web site (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf).

11.3 Adverse Event Definitions

11.3.1 Adverse Event

An adverse event is any untoward medical occurrence in a subject or clinical investigation subject 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 subjects should be interviewed in a non-directed manner to elicit potential adverse reactions from the subject. The occurrence of an adverse event will be based on changes in the subject's physical examination, laboratory results, and/or signs and symptoms, and review of the subject's own record of adverse events.

Adverse events will be followed until resolution while the subject remains on-study. Once the subject 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 subject starts a new treatment regimen, or death, whichever comes first. Subjects will be followed for AEs/SAEs for 100 days after their last dose of study drug(s).

11.3.2 Serious Adverse Event (SAE)

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

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

Adverse events must be reported to regulatory authorities according to the definitions and timelines specified in the local laws and regulations.

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 subject 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; blood 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:

- Potential drug induced liver injury (DILI)
- Suspected transmission of an infectious agent (e.g. pathogenic or nonpathogenic) via the study drug
- Pregnancy occurring within the period defined in section 4.1
- Overdose
- Death due to Disease Progression occurring within 100 days of last dose of study drug

11.3.3 Relatedness

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

11.3.4 Adverse Reactions

An adverse event is considered to be an adverse reaction if there 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.

11.4 Adverse Event Reporting

11.4.1 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 <u>also</u> be reported in routine study data submissions.**

All adverse events (except grade 1 and 2 laboratory abnormalities that do not require an intervention), 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 4.0 and their causal relationship.

11.4.2 Serious Adverse Event Reporting

All serious adverse events (as defined in section 11.1.2) occurring on this study require expedited reporting to the University of Chicago Comprehensive Cancer Center (UC CCC). The responsible Research Nurse or Clinical Research Coordinator should report the SAE to the Principal Investigator,CCTO and enter into Velos by the end of the business day when team becomes aware of the event. Events occurring after business hours should be reported to the CCTO by 12pm (noon) the next business day via email to qaccto@bsd.uchicago.edu. Reports in Velos should be made using the 'Serious Event Report' Form.

All unexpected adverse reactions must be reported to the University of Chicago CCTO for FDA reporting. The responsible Research Nurse or Clinical Research Coordinator should provide a complete written report using the FDA MedWatch 3500A form. The completed form should be sent to the CCTO 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.

Clinical staff 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.

11.4.3 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.

Global Pharmacovigilance & Epidemiology
Bristol-Myers Squibb Company
Fax Number: 609-818-3804
Email: Worldwide.safety@bms.com

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.

11.4.4 Serious Adverse Event Reporting to Celgene

Serious adverse events (SAE) are defined above. The investigator must inform Celgene in writing using a Celgene SAE form or MEDWATCH 3500A form of any SAE within 24 hours of being aware of the event. The written report must be completed and supplied to Celgene by facsimile or email within 24 hours/1 business day. The initial report must be as complete as possible, including an assessment of the causal relationship between the event and the investigational product(s), if available. Information not available at the time of the initial report (e.g., an end date for the adverse event or laboratory values received after the report) must be documented on a follow-up report. A final report to document resolution of the SAE is required. The Celgene tracking number (AX-CL-HN-PI-004235) and the institutional protocol number should be included on SAE reports (or on the fax cover letter) sent to Celgene. A copy of the fax transmission confirmation or email of the SAE report to Celgene should be attached to the SAE and retained with the subject records.

Celgene Drug Safety Contact Information:
Celgene Corporation
Global Drug Safety and Risk Management
Connell Corporate Park

300 Connell Dr. Suite 6000
Berkeley Heights, NJ 07922
Fax:(908) 673-9115
E-mail: drugsafety@celgene.com

11.5 Subject registration and data submission

11.5.1 Registration

All patients must be registered with the University of Chicago Head and Neck Clinical Research Coordinator (CRC) prior to the commencement of treatment. PI, Research nurse and CRC will confirm all selection criteria listed in Section 4. Confirmation is documented with signatures and date.

11.5.2 Data management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data.

All required data must be recorded at the completion of each cycle as stated above in section 11.4.2.

11.6 Data and safety monitoring

Data Safety and Monitoring will occur at the weekly University of Chicago Head and Neck Research Program meetings, which are led by senior level medical oncologists. At each meeting, the study will be reviewed for safety and progress toward completion. Toxicities and adverse events will be reviewed at each meeting.

11.7 Auditing

The University of Chicago Comprehensive Cancer Center will perform routine Quality Assurance Audits of investigator-initiated clinical trials as described in the NCI-approved UC CCC 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 subjects enrolled at the University of Chicago in accordance with audit procedures specified in the UC CCC Data and Safety Monitoring plan.

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.

11.8 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 subject consent forms).

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

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

11.9 Obligations of Study Site Investigations

The Study Principal Investigator is responsible for the conduct of the clinical trial in accordance with Title 21 of the Code of Federal Regulations and/or the Declaration of Helsinki. The Principal Investigator is responsible for personally overseeing the treatment of all study subjects. He/she must assure that all study 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 Principal Investigator 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.

12 STATISTICAL CONSIDERATIONS

12.1 Statistical methods

12.1.1 Primary Endpoint: Deep Response Rate (DRR)

Overall Primary Objective: To demonstrate an increased rate of deep responses (deep response rate=DRR) to induction chemotherapy with the addition of nivolumab to the carboplatin/nab-paclitaxel backbone used in the Optima I trial.

- In the predecessor Optima 1 study, deep responses were defined as ≥50% tumor shrinkage by RECIST 1.1 and this is believed to be equivalent to a clinical complete response (CR) as utilized in the ECOG 1308 study (which was the primary outcome for E1308). Hence in this study, deep responses are also defined as ≥50% tumor shrinkage by RECIST 1.1.
- We will employ a superiority test in which the objective is to establish that the response rate to carboplatin/nab-paclitaxel/nivolumab induction chemotherapy is 15% higher than the response rate of 60% in Optima I which utilized a carboplatin/nab-paclitaxel induction regimen.
- We will test: H_0: DRR=60% (based on data from Optima 1 trial) vs H_A: DRR=75% with addition of nivolumab to the carboplatin/nab-paclitaxel induction regimen.
- Using Power Analysis and Sample Size (PASS v11) software, a sample of subjects will provide 87% power to test this hypothesis using a (one-sided) type I error rate of 0.10. Essentially, H_0 will be rejected and nivolumab/carboplatin/nab-paclitaxel based induction regimen declared superior if the lower, one-sided 90% confidence limit for the response rate exceeds 75%. No interim analysis will be conducted.

NB: A minimum of 10 patients will be enrolled on the RT only and also TORS arm to allow for descriptive interpretation of the pathology results in tabular form. The overall trial may overenroll up to 18 patients (N=74) to fulfill this enrollment goal for the RT-only and TORS arms.

12.1.2 Secondary Endpoints

Secondary objectives, respective endpoints, and analyses:

- To determine the tolerability of the nivolumab/carboplatin/nab-paclitaxel induction chemotherapy regimen and its impact on subsequent receipt of definitive chemoradiotherapy.
    - Endpoint will be CTCAE v4.0 adverse events
    - The safety analysis will be performed in all treated subjects. Descriptive statistics of safety will be presented using the National Cancer Institute (NCI)

Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 by treatment arm. All AEs, drug-related AEs, SAEs and drug-related SAEs will be tabulated using the worst grade per NCI CTCAE v 4.0 criteria by system organ class and preferred term. On-study lab parameters including hematology, coagulation, chemistry, liver function and renal function will be summarized using worse grade per NCI CCAE v 4.0 criteria.

- All recorded adverse events will be listed and tabulated by system organ class, preferred term and treatment. Vital signs and clinical laboratory test results will be listed and summarized by treatment. Any significant physical examination findings, and clinical laboratory results will be listed. ECG readings will be evaluated by the investigator and abnormalities, if present, will be listed.

- To determine 2-year progression-free survival (PFS) for the entire cohort and all arms and compare them to the entire cohort and corresponding arms in Optima I.
  - PFS is defined as the time from registration to the date of first documented disease progression, as assessed by the IRC using RECIST 1.1 criteria, or death due to any cause, whichever occurs first. Subjects who died without a reported progression will be considered to have progressed on the date of their death. Subjects who did not progress or die will be censored on the date of their last evaluable tumor assessment. Subjects who did not have any on study tumor assessments and did not die will be censored on the date they were registered. Subjects who started any subsequent anti-cancer therapy, including tumor-directed radiotherapy and tumor-directed surgery, without a prior reported progression will be censored at the last evaluable tumor assessment prior to/on initiation of the subsequent anti-cancer therapy.
  - PFS will be estimated by Kaplan-Meier methodology and comparisons will be made using the log-rank test. PFS analyses will include subjects in the overall cohort and in each of the three arms.
- To determine 2-year overall survival (OS) for the entire cohort and all arms and compare them to the entire cohort and corresponding arms in Optima I.
  - OS is defined as the time between the date of registration and the date of death. For subjects without documentation of death, OS will be censored on the last date the subject was known to be alive.
  - OS will be estimated by Kaplan-Meier methodology and comparisons will be made using the log-rank test. OS analyses will include subjects in the overall cohort and in each of the three arms.
- To determine 2-year rates of locoregional and distant control for the entire cohort and all arms and compare them to the entire cohort and corresponding arms in Optima I.
  - Locoregional failure is defined as the time from registration to the date of first documented disease progression in the head and neck, as assessed by the IRC using RECIST 1.1 criteria.

- Distant failure is defined as the time from registration to the date of first documented disease progression below the clavicles, as assessed by the IRC using RECIST 1.1 criteria.
- Time to locoregional and distant failure rates will be estimated by the Kaplan-Meier methodology and comparisons will be made using the log-rank test. Time to LRF and DF analyses will include subjects in the overall cohort and in each of the three arms.

12.1.3 Exploratory Objectives/Endpoints/Analyses

- To determine rates of acute and late toxicity using CTCAE v4.0 and compare them to rates of acute and late toxicity on the Optima I and RAVD trials.
  - Endpoint will be CTCAE v4.0 adverse events
  - Results will be tabulated and comparisons will be made using the chi-square, Fisher's exact, or t-test as appropriate.
- To determine quality of life scores in subjects and compare them to quality of life scores on the RAVD trial.
  - Endpoints will be overall and domain subset scores on the QOL instruments used.
  - Results will be tabulated and comparisons will be made using the chi-square, Fisher's exact, or t-test as appropriate.
- To determine the comparative efficacy and toxicity profiles of TORS versus RT for management of low risk disease will be exploratory and dependent on number of subjects that are treated.
  - Endpoints for efficacy will include progression-free and overall survival, as calculated above. Comparisons will be made using the log-rank test.
  - Endpoint for toxicity will be CTCAE v4.0 adverse events. Results will be tabulated and comparisons will be made using the chi-square, Fisher's exact, or t-test as appropriate.

12.1.4 Laboratory/Translational Objectives

We will interrogate the immune micro-environment at baseline, and 2-3 weeks into induction therapy with nivolumab and chemotherapy with an optional on-treatment biopsy. This will be exploratory as previously described with descriptive statistical analyses summarized in tabular format.

12.1.5 Visual Aid Objectives

We will administer anonymous and optional subject questionnaires after the

multidisciplinary consultation and prior to allocation to treatment arm. These may be administered during the induction therapy. We will also distribute anonymous and optional questionnaires to providers in surgery, medical oncology, and radiation oncology at Head and Neck Multidisciplinary Tumor Board once subject enrollment is discontinued.

13 REFERENCES:

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APPENDIX A: PERFORMANCE STATUS CRITERIA

ECOG Performance Status Scale		Karnofsky Performance Status scale	
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction	100	Normal. No complaints, no evidence of disease.
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or do active work.
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care.
3	In bed >50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours.	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent.
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair.	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly.
5	Dead	0	Dead

APPENDIX B: RTOG/NRG EARLY TOXICITY GRADING

Tissue	Grade 1	2	3	4
Skin	Follicular, faint or dull erythema / epilation / dry desquamation / decreased sweating	Tender or bright erythema, patchy moist desquamation / moderate edema	Confluent, moist desquamation other than skin folds, pitting edema	Ulceration, hemorrhage, necrosis
Mucous membrane	Injection / may experience mild pain not requiring analgesic	Patchy mucositis that may produce an inflammatory serosanguinous discharge / may experience moderate pain requiring analgesia	Confluent fibrinous mucositis / may include severe pain requiring narcotic	Ulceration, hemorrhage or necrosis
Eye	Mild conjunctivitis w/ or w/o scleral injection / increased tearing	Moderate conjunctivitis w/ or w/o keratitis requiring steroids and/or antibiotics / dry eye requiring artificial tears / iritis with photophobia	Severe keratitis with corneal ulceration / objective decrease in visual acuity or in visual fields / acute glaucoma / panophthalmitis	Loss of vision (uni or bilateral)
Ear	Mild external otitis with erythema, pruritus, secondary to dry desquamation not requiring medication. Audiogram unchanged from baseline	Moderate external otitis requiring topical medication / serous otitis media / hypoacusis on testing only	Severe external otitis with discharge or moist desquamation / symptomatic hypoacusis / tinnitus, not drug related	Deafness
Salivary gland	Mild mouth dryness / slightly thickened saliva / may have slightly altered taste such as metallic taste / these changes not reflected in alteration in baseline feeding behavior, such as increased use of liquids with meals	Moderate to complete dryness / thick, sticky saliva / markedly altered taste	(none)	Acute salivary gland necrosis
Pharynx & esophagus	Mild dysphagia or odynophagia / may require topical anesthetic or non-narcotic analgesics / may require soft diet	Moderate dysphagia or odynophagia / may require narcotic analgesics / may require puree or liquid diet	Severe dysphagia or odynophagia with dehydration or weight loss > 15% from pretreatment baseline requiring NG feeding tube, IV fluids, or hyperalimentation	Complete obstruction, ulceration, perforation, fistula
Larynx	Mild or intermittent hoarseness / cough not requiring antitussive / erythema of mucosa	Persistent hoarseness but able to vocalize / referred ear pain, sore throat, patchy fibrinous exudate	Whispered speech, throat pain or referred ear pain requiring narcotic / confluent fibrinous exudate,	Marked dyspnea, stridor or hemoptysis with tracheostomy or intubation necessary

		or mild arytenoid edema not requiring narcotic / cough requiring antitussive	marked arytenoid edema	
HEME	**1**	**2**	**3**	**4**
WBC	3.0 - < 4.0	2.0 - < 3.0	1.0 - < 2.0	< 1.0
Platelets	75 - < 100	50 - < 75	25 - < 50	<25 or spontaneous bleeding
Neutrophils	1.5 - < 1.9	1.0 - < 1.5	0.5 - < 1.0	< 0.5 or sepsis
Hgb / Hct	11 - 9.5 (28% - < 32%)	< 9.5 - 7.5 (< 28%)	< 7.5 - 5.0 (Packed cell transfusion required)	(none)

APPENDIX C: RTOG LATE TOXICITY GRADING

Tissue	Grade 1	Grade 2	Grade 3	Grade 4
Skin	Slight atrophy; pigmentation change; some hair loss	Patch atrophy; moderate telangiectasia; total hair loss	Marked atrophy; gross telangiectasia	Ulceration
Subcutaneous tissue	Slight induration (fibrosis) and loss of subcutaneous fat	Moderate fibrosis but asymptomatic; slight field contracture; <10% linear reduction	Severe induration and loss of subcutaneous tissue; field contracture > 10% linear measurement	Necrosis
Mucous membrane	Slight atrophy and dryness	Moderate atrophy and telangiectasia; little mucous	Marked atrophy with complete dryness	Ulceration
Salivary glands	Slight dryness of mouth; good response on stimulation	Moderate dryness of mouth; poor response on stimulation	Complete dryness of mouth; no response on stimulation	Fibrosis
Spinal cord	Mild L'Hermitte's syndrome	Severe L'Hermitte's syndrome	Objective neurological findings at or below cord level treated	Mono, para quadraplegia
Brain	Mild headache; slight lethargy	Moderate headache; great lethargy	Severe headache; severe CNS dysfunction (partial loss of power or dyskinesia)	Coma
Eye	Asymptomatic cataract; minor corneal ulceration or keratitis	Symptomatic cataract; moderate corneal ulceration; minor retinopathy or glaucoma	Severe keratitis; severe retinopathy or detachment	Panophthalmitis / blindness
Larynx	Hoarseness; slight arytenoid edema	Moderate arytenoid edema; chondritis	Severe edema; severe chondritis	Necrosis
Esophagus	Mild fibrosis; slight difficulty in swallowing solids; no pain on swallowing	Unable to take solid food normally; swallowing semisolid food; dilatation may be indicated	Severe fibrosis; able to swallow only liquids; may have pain on swallowing; dilatation required	Necrosis / perforation fistula
Bone	Asymptomatic; no growth retardation; reduced bone density	Moderate pain or tenderness; growth retardation; irregular bone sclerosis	Severe pain or tenderness; complete arrest of bone growth; dense bone sclerosis	Necrosis / spontaneous fracture

APPENDIX D: SAMPLE TRANSMISSION FORM AND INSTRUCTIONS

Tissue and Blood Sample Collection Form

Clinician/Research Nurse: Please Fill Out

Tissue Samples

Subject Name: _____ UC MR # (if applicable): _____

Subject Protocol ID #:_____ Date Tissue Obtained: _____

Date of Birth: _____Attending Physician: _____

Site of Biopsy: _____ Institution: _____

Date consent was signed: _____ Diagnosis:_____

Pre/Post Therapy (Please circle) Day started on clinical protocol:_____

Did Surgical Pathology receive tissue for diagnosis? **Yes No**

Contact Person's Phone Number and email Address at Affiliate:

Blood Samples

		date drawn	time	date shipped	
Pre-Therapy, during, and post-therapy	1 Tiger Top for Plasma				
Pre-therapy and 2-3 weeks into induction	1 RNA collection tube				
Pre-therapy	1 lavender top/DNA				

Researcher: Please Fill Out

Date Samples received: _____ Data entered into Database: **Yes**

No

Name of Data Manager informed: _____ Date Informed:_____

Location in –80C freezer **-** _____

Approximate size of tissue: _____

Notes:

SPONSOR: The University of Chicago

Questions or Problems? Please contact:
HTRC, University of Chicago, 5841 S Maryland, MC 3083, Chicago, IL 60637
Phone 773-702-0119*, Pager 773-753-1880-9747*

APPENDIX E: ACCEPTED FORMS OF BIRTH CONTROL

HIGHLY EFFECTIVE METHODS OF CONTRACEPTION

- Hormonal methods of contraception including combined oral contraceptive pills, vaginal ring, injectables, implants and intrauterine devices (IUDs) such as Mirena® by WOCBP subject or male subject's WOCBP partner
- IUDs, such as ParaGard®
- Bilateral Tubal ligation
- Vasectomized partner
- Complete Abstinence*

*Complete abstinence is defined as complete avoidance of heterosexual intercourse and is an acceptable form of contraception for all study drugs. Female subjects must continue to have pregnancy tests. Acceptable alternate methods of highly effective contraception must be discussed in the event that the subject chooses to forego complete abstinence.

Subjects are encouraged to use two methods of contraception, with one method being highly effective and the other method being either highly effective or less effective as listed below:

LESS EFFECTIVE METHODS OF CONTRACEPTION

- 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:

- Vaginal sponge
- Progestin only pills
- Cervical cap with spermicide
- Periodic abstinence (calendar, symptothermal, post-ovulation methods)
- Withdrawal (coitus interruptus)
- Spermicide only
- Lactation amenorrhea method (LAM)
- A male and a female condom must not be used together

APPENDIX F: QUALITY OF LIFE FORMS AND PERFORMANCE MEASURES

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

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

McMaster University Head and Neck Radiotherapy Questionnaire

1. Have you had any pain or soreness in your mouth in the past week?

   1. Yes (Continue to Part b)

   7. No

   Part b: How *troublesome* was this for you?

      1. A Great Deal
      2. A Lot
      3. A Fair Bit
      4. Somewhat
      5. A Little
      6. Hardly Any

2. Have you had dryness of your skin, where it was treated, in the past week?

   1. Yes (Continue to Part b)

   7. No

   Part b: How *troublesome* was this for you?

      1. A Great Deal
      2. A Lot
      3. A Fair Bit
      4. Somewhat
      5. A Little
      6. Hardly Any

• Do not ask the following question if the participant has had a total laryngectomy:

3. Have you had any difficulty swallowing in the past week?

   1. Yes (Continue to Part b)

   7. No

   Part b: How *troublesome* was this for you?

      1. A Great Deal
      2. A Lot
      3. A Fair Bit

4. Somewhat
5. A Little
6. Hardly Any

4. Have you felt low in energy, in the past week?
   1. Yes (Continue to Part b)
   7. No

   Part b: How *often* did you feel this way?
      1. A Great Deal of the time
      2. A Lot of the time
      3. A Fair Bit of the time
      4. Somewhat of the time
      5. A Little of the time
      6. Hardly any of the time

5. In general, have you felt angry, depressed or down in the dumps in the past week?

1. Yes (Continue to Part b)

7. No

Part b: How *often* did you feel this way?

1. A Great Deal of the time
2. A Lot of the time
3. A Fair Bit of the time
4. Somewhat of the time
5. A Little of the time
6. Hardly any of the time

6. Have you felt nauseated, in the past week?

1. Yes (Continue to Part b)

7. No

Part b: How *troublesome* was this for you?

1. A Great Deal
2. A Lot
3. A Fair Bit
4. Somewhat
5. A Little
6. Hardly Any

7. Have you had any itching of the skin, in treated area, in the past week?

1. Yes (Continue to Part b)

7. No

Part b: How *troublesome* was this for you?

1. A Great Deal
2. A Lot
3. A Fair Bit
4. Somewhat
5. A Little
6. Hardly Any

8. Have you had any difficulty getting a good night's sleep, in the past week?

1. Yes (Continue to Part b)

7. No

Part b: How *often* did you feel this way?

1. A Great Deal of the time
2. A Lot of the time
3. A Fair Bit of the time
4. Somewhat of the time
5. A Little of the time
6. Hardly any of the time

9. Have you had any dryness of your mouth in the past week?

   1. Yes (Continue to Part b)

   7. No

   Part b: How *troublesome* was this for you?

      1. A Great Deal
      2. A Lot
      3. A Fair Bit
      4. Somewhat
      5. A Little
      6. Hardly Any

10. Have you felt tired or fatigued, in the past week, such that you are prevented from doing social or recreational activities?

    1. Yes (Continue to Part b)

    7. No

    Part b: How *often* did you feel this way?

       1. A Great Deal of the time
       2. A Lot of the time
       3. A Fair Bit of the time
       4. Somewhat of the time
       5. A Little of the time
       6. Hardly any of the time

• Do not ask the following question if the participant has had a total laryngectomy:

11. Have you had a sore or painful throat in the past week?

    1. Yes (Continue to Part b)

    7. No

    Part b: How *troublesome* was this for you?

        1. A Great Deal

        2. A Lot

        3. A Fair Bit

        4. Somewhat

        5. A Little

        6. Hardly Any

12. Have you had any problems with your stomach in the past week?

    1. Yes (Continue to Part b)

    7. No

    Part b: How *troublesome* was this for you?

        1. A Great Deal

        2. A Lot

        3. A Fair Bit

        4. Somewhat

        5. A Little

        6. Hardly Any

13. Have you found your saliva to be very sticky, in the past week?

    1. Yes (Continue to Part b)

    7. No

    Part b: How *troublesome* was this for you?

        1. A Great Deal
        2. A Lot
        3. A Fair Bit
        4. Somewhat
        5. A Little
        6. Hardly Any

14. Have you had any fatigue or tiredness which interfered with your work or routine daily activities, in the past week?

    1. Yes (Continue to Part b)

    7. No

    Part b: How *often* did you feel this way?

        1. A Great Deal of the time
        2. A Lot of the time
        3. A Fair Bit of the time
        4. Somewhat of the time
        5. A Little of the time
        6. Hardly any of the time

15. Have you had difficulty tasting your food in the past week?

1. Yes (Continue to Part b)

7. No

Part b: How *often* did you feel this way?

1. A Great Deal of the time
2. A Lot of the time
3. A Fair Bit of the time
4. Somewhat of the time
5. A Little of the time
6. Hardly any of the time

16. Have you had difficulty with your appetite in the past week?

1. Yes (Continue to Part b)

7. No

Part b: How *often* did you feel this way?

1. A Great Deal of the time
2. A Lot of the time
3. A Fair Bit of the time
4. Somewhat of the time
5. A Little of the time
6. Hardly any of the time

17. Have you felt good about yourself in the past week?

    1. Yes (Continue to Part b)

    7. No

    Part b: How *often* did you feel this way?

        1. A Great Deal of the time

        2. A Lot of the time

        3. A Fair Bit of the time

        4. Somewhat of the time

        5. A Little of the time

        6. Hardly any of the time

18. Have you had difficulty keeping down foods or liquids, in the past week?

    1. Yes (Continue to Part b)

    7. No

    Part b: How *troublesome* was this for you?

        1. A Great Deal

        2. A Lot

        3. A Fair Bit

        4. Somewhat

        5. A Little

        6. Hardly Any

• Do not ask the following question if the participant has had a total laryngectomy:

19. Have you had a hoarse voice, in the past week?

    1. Yes (Continue to Part b)

    7. No

    Part b: How *troublesome* was this for you?

        1. A Great Deal

        2. A Lot

        3. A Fair Bit

        4. Somewhat

        5. A Little

        6. Hardly Any

20. Have you had any pain or soreness of your skin in the treated area, in the past week?

    1. Yes (Continue to Part b)

    7. No

    Part b: How *troublesome* was this for you?

        1. A Great Deal

        2. A Lot

        3. A Fair Bit

        4. Somewhat

        5. A Little

        6. Hardly Any

21. Have you had any difficulty chewing your food, in the past week?

1. Yes (Continue to Part b)

7. No

Part b: How *troublesome* was this for you?

1. A Great Deal
2. A Lot
3. A Fair Bit
4. Somewhat
5. A Little
6. Hardly Any

22. Do you feel your relationships with your family or friends have been affected because of your treatments, in the past week?

1. Yes (Continue to Part b)

7. No

Part b: How *troublesome* was this for you?

1. A Great Deal
2. A Lot
3. A Fair Bit
4. Somewhat
5. A Little
6. Hardly Any

23. Are you now taking

1. liquids only?
2. liquids and soft foods only?
3. liquids, soft foods and solid foods?