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UMCC 2018.085

PHASE II TRIAL OF RADIOTHERAPY, CARBOPLATIN/PACLITAXEL AND NIVOLUMAB FOR HIGH RISK HPV-RELATED OROPHARYNX CANCER

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NOTE: To effectively manage restrictions put in place during public health or civil emergency or restrictions (i.e. COVID-19 pandemic) changes to protocol-required items are to be made to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to infectious pathogens). These changes are listed in Appendix B of the protocol (Study Management During Public Health or Civil Emergency or Restrictions).

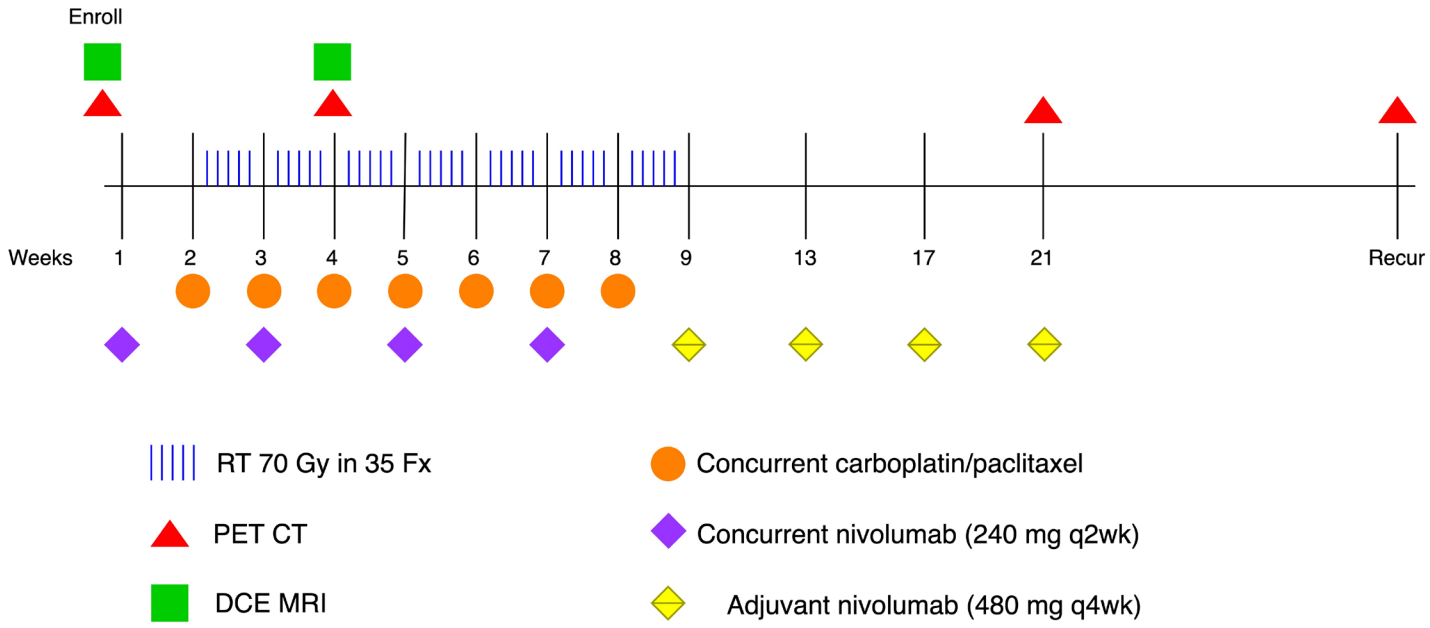
TABLE OF CONTENTS

DEFINITIONS

AIDS: Acquired Immune Deficiency Syndrome
ASTRO: American Society for Therapeutic Radiation Oncology
ANC: Absolute neutrophil count
AUC: Area under the concentration curve (chemotherapy) or area under the curve (statistics)
BED: Biologic equivalent dose
CMR: Complete metabolic response
CR: Complete response
CTSU: Clinical Trials Support Unit
CTV: Clinical target volume
DSMC: Data and Safety Monitoring Committee
ECG or EKG: Electrocardiogram
ED: Effective dose
FDG: 18F-Florodeoxyglucose, a PET/CT imaging agent
GTV: Gross tumor volume
Gy: Gray
HIV: Human immunodeficiency virus
HPV: human papilloma virus
IGRT: Image-guided radiation therapy
IMRT: Intensity modulated radiation therapy
iPET: interval (midtreatment) PET/CT
IV: Intravenous
LRC: Local-regional control
LRR: Local-regional recurrence
LRPF: Freedom from local-regional progression
MTV: Metabolic tumor volume
NRG: NRG Oncology
OARs: Organs at risk
OPSCC: squamous cell carcinoma of the oropharynx
OS: Overall survival
pPET: pre-treatment PET/CT
PD: Progressive disease
PFS: Progression-free survival
PMR: Partial metabolic response
PR: Partial response
PTV: Planning target volume
RT: Radiation therapy or radiation treatment
RTOG: Radiation Therapy Oncology Group
SD: Stable disease
SMD: Stable metabolic disease
SUV: Standardized uptake value
SUVmax: The SUV of the most intense voxel within a tumor
SUVpeak: The average SUV within a 1.2-cm diameter sphere centered on the most metabolically active region of the tumor
3D-CRT: Three dimensional-conformal radiation therapy

SCHEMA

PHASE II TRIAL OF RADIOTHERAPY, CARBOPLATIN/PACLITAXEL AND NIVOLUMAB FOR HGIH RISK HPV-RELATED OROPHARYNX CANCER



Patients will start nivolumab 240 mg IV on day 1, then every 2 weeks (q2wks) for 4 total doses . Carboplatin/paclitaxel and RT will begin on day 8 and carboplatin/paclitaxel will be given weekly (7 doses) during RT. Adjuvantly, starting at week 9, patients will receive nivolumab 480 mg alone IV every 4 weeks (q4weeks) for a total of 4 doses.

STUDY SYNOPSIS

Title	**PHASE II TRIAL OF RADIOTHERAPY, CARBOPLATIN/PACLITAXEL AND NIVOLUMAB FOR HIGH RISK HPV-RELATED OROPHARYNX CANCER**
Phase	II
Methodology	Single arm, open label
Study Duration	5 years (yrs)
Study Center(s)	Single-center
Objectives	**Primary Objective** To determine whether the addition of nivolumab can improve 2 year (yr) PFS (progression free survival) as compared to historical standard of fractionated RT and carboplatin/paclitaxel in patients with high risk HPV-related squamous cell carcinoma of the oropharynx. **2.2 Secondary Objectives** 1. To characterize patterns of failure (loco-regional relapse versus distant) PFS and overall survival; 2. To characterize acute toxicity profiles (during radiation therapy and at 3 and 6 months) and late toxicity profiles at 1 and 2 years; 3. To correlate metabolic image uptake data on mid-treatment FDG-PET scans performed between fractions 8-12 with standard 12 week post-treatment PET-CT.
Number of Subjects	40
Inclusion Criteria	1. Histologically or cytologically proven squamous cell carcinoma of the oropharynx (tonsil, base of tongue, oropharyngeal wall, soft palate) that is p16 positive by immunohistochemistry or HPV positive by in situ hybridization 2. Clinical stage: stage III AJCC 8th edition staging (cT4 or cN3) OR "matted lymph nodes (LNs)" (defined as 3 LNs abutting one another with loss of intervening fat plane that is replaced with evidence of extracapsular spread) OR radiographic extracapsular extension (defined as overt loss of fat plane surrounding a LN) OR radiographically positive retropharyngeal LN >7mm in size 3. Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup: • History/physical examination, including documentation of weight within 2 weeks prior to registration; • FDG-PET/CT scan for staging and RT plan within 4 weeks prior to registration; • Zubrod Performance Status 0-1 within 2 weeks prior to registration; • Age ≥ 18; 4. CBC/differential obtained within 2 weeks prior to registration

	on study, with adequate bone marrow function defined as follows: • Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3; • Platelets ≥ 75,000 cells/mm^3; • Hemoglobin ≥ 9.0 g/dL • AST/ALT ≤ 3x ULN • Total Bilirubin ≤1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level ≤ 3 x ULN) 5. Serum creatinine within normal institutional limits or a creatinine clearance ≥ 45 mL/min within 2 weeks prior to registration; 6. Women of childbearing potential must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study and for five months after the last treatment. A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause. Men receiving nivolumab who are sexually active with WOCBP must agree to use effective contraception throughout their participation in the treatment phase of the study and for seven months after the last treatment. 7. Due to the potential for serious adverse reactions in breastfed infants, women are advised not to breast-feed during treatment with the study drugs. 8. The patient must provide study-specific informed consent prior to study entry.
Exclusion Criteria	1. Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible); 2. Any prior therapy for the study cancer; note that prior chemotherapy for a different cancer is allowable if > 3 years prior to study; 3. Any history of active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. 4. Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields; 5. Severe, active co-morbidity, including but not limited to the

	following: • Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months; • Uncontrolled diarrhea; • Uncontrolled adrenal insufficiency; • Transmural myocardial infarction within the last 3 months; • Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration; • Chronic Obstructive Pulmonary Disease (COPD) exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration; • Acquired Immune Deficiency Syndrome (AIDS) based with CD4+ count < 350 cells per microL; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. 6. Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use contraception; 7. Women who are breastfeeding and are not willing to discontinue breastfeeding during the trial and for 2 months following protocol therapy 8. Poorly controlled diabetes (defined as fasting glucose level > 200 mg/dL) despite 2 attempts to improve glucose control by fasting duration and adjustment of medications. Patients with diabetes will preferably be scheduled in the morning and instructions for fasting and use of medications will be provided in consultation with the patients' primary physicians 9. Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Short bursts of steroids of 5-7 days (for COPD exacerbation or other similar indication) are allowed. 10. Known history of, or any evidence of active, non-infectious pneumonitis. 11. Known history of active TB (Bacillus Tuberculosis). 12. Known hypersensitivity to nivolumab, carboplatin, or paclitaxel, or any of their formulation excipients. Known hypersensitivity to polyoxyl 35 castor oil (Cremophor® EL) (a diluent of paclitaxel and other drugs). 13. Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected). 14. Received a live vaccine within 30 days of planned start of study therapy. 15. Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements

Study Product(s), Dose, Route, Regimen	Nivolumab IV 240mg q2wks x 4 doses before and during radiotherapy, then 480mg q4wks x 4 doses after completion of radiotherapy
Duration of Administration	Total duration of nivolumab is 21 wks
Reference Therapy	Concurrent standard of care therapies are RT/platinum chemotherapy
Statistical Methodology	The primary study endpoint is PFS 2 years after treatment which will be also be estimated using the Kaplan-Meier (KM) method. A log-log transformation of the survival function will be used to calculate a lower 90% confidence limit. Estimated PFS at 2 years was 68% in 125 similar (stage III) historical control patients treated with standard therapy at the University of Michigan (UM) between the years of 2010-2015. If the true PFS at 2 years for this treatment combination in this patient population is 85%, then a sample size of 40 enrolled patients provides at least 80% power to rule out 2 year PFS values of 70% or less. This calculation assumes 10% of patients will be lost to follow-up by the 2 year assessment point and that other patients will either be assessed for progression at 2 years or will have progressed or died prior to 2 years.

1.0 BACKGROUND AND RATIONALE

1.1 Disease Background Oropharyngeal Carcinoma

Over the past three decades, there has been an increase in the incidence of HPV-related oropharyngeal squamous cell carcinoma (OPSCC) with good overall prognosis and high rates of loco-regional control (LRC) *(d'souza 2007, Gillison, 2000, Fahkry, 2008, Ang 2010).* Current standard of care therapy includes definitive chemoradiation as well as resection followed by adjuvant radiation or chemoradiation. Due to the good prognosis and relatively good health of most patients with HPV-related OPSCC, there has been widespread interest in treatment adaptive radiotherapy strategies including decreased doses of radiotherapy and chemotherapy. Ideally, pre- or mid-treatment biomarkers of response would be used to adapt therapy. However, no proven clinical or radiographic biomarkers exist to monitor response during therapy.

In the UM experience with treatment of 515 patients with HPV+ oropharyngeal cancer using concurrent RT with weekly carboplatin (AUC=1) and paclitaxel (30mg/m2), AJCC 8th edition, stage 1 and 2 patients had 90-95 % LRC at 2 years and 2 yr progression free survival (PFS) of 85%. Figure 1 below shows that a subset analysis of patients with stage 3 (cT4 and cN3) disease had 2 yr LRC of 85% with 2 yr PFS of 67%, with a large proportion of those patients developing distant metastases (30%) (Hawkins, 2018).

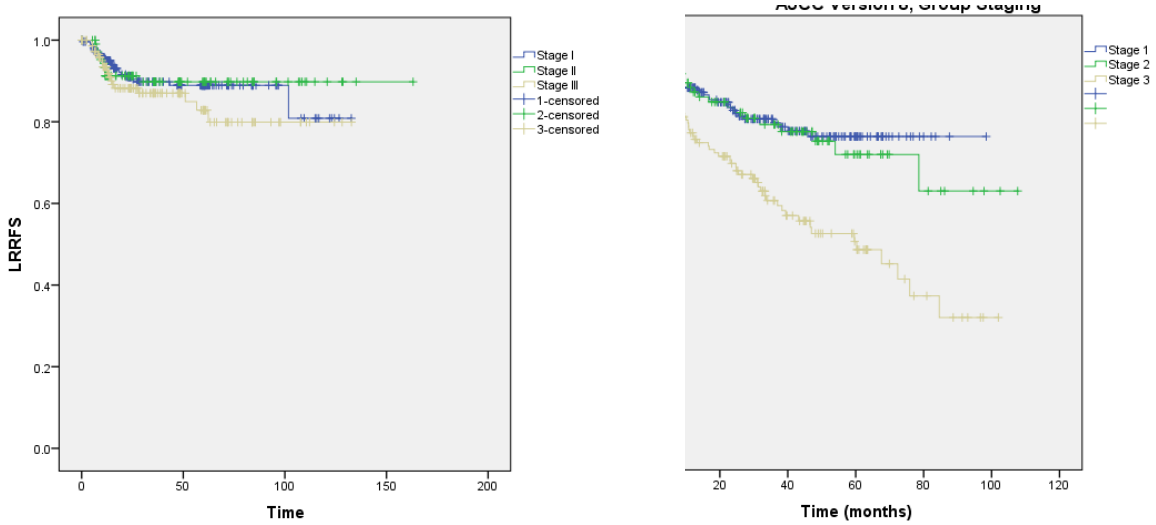


Figure 1. SCC OP HPV+ patients treated with chemoradiation according to 8th edition AJCC stage. 1A (left) Loco-regional relapse free survival Kaplan-Meier estimates. 2A (right) progression-free survival Kaplan-Meier estimates.

We previously published our UM experience with "matted lymph node" patients defined as 3 lymph nodes (LNs) abutting one another with loss of intervening fat plane that is replaced with evidence of extracapsular spread (*Spector, 2016*). This analysis also revealed that patients with "matted nodes" had relatively high rates of LRC, but are at higher risk for distant metastases (Figure 2) and thus have significantly lower DSS (disease specific survival) than HPV+ oropharynx patients without matted nodes.

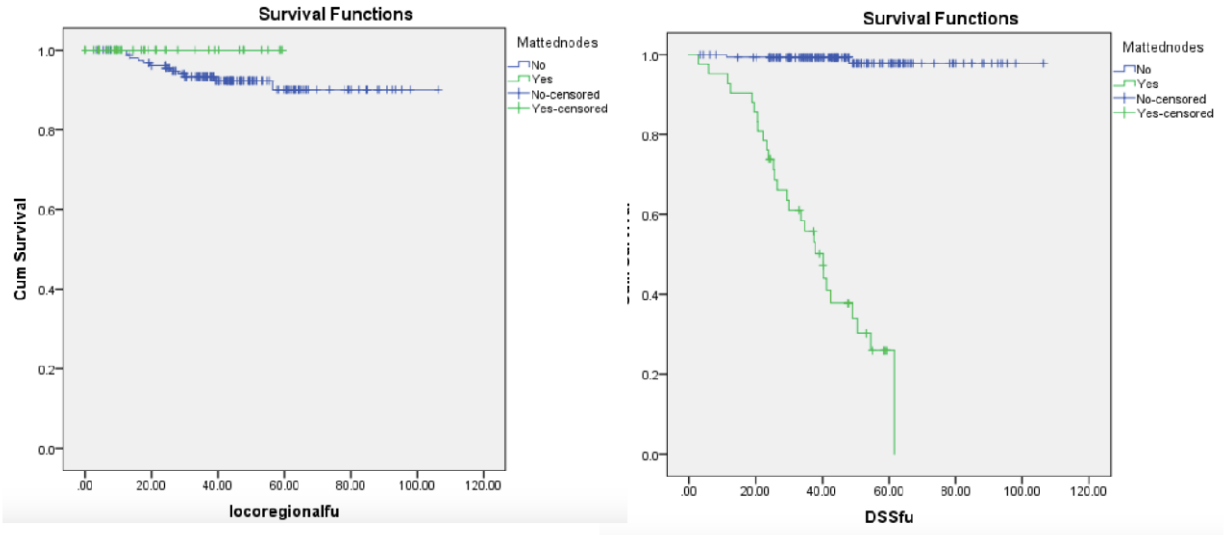
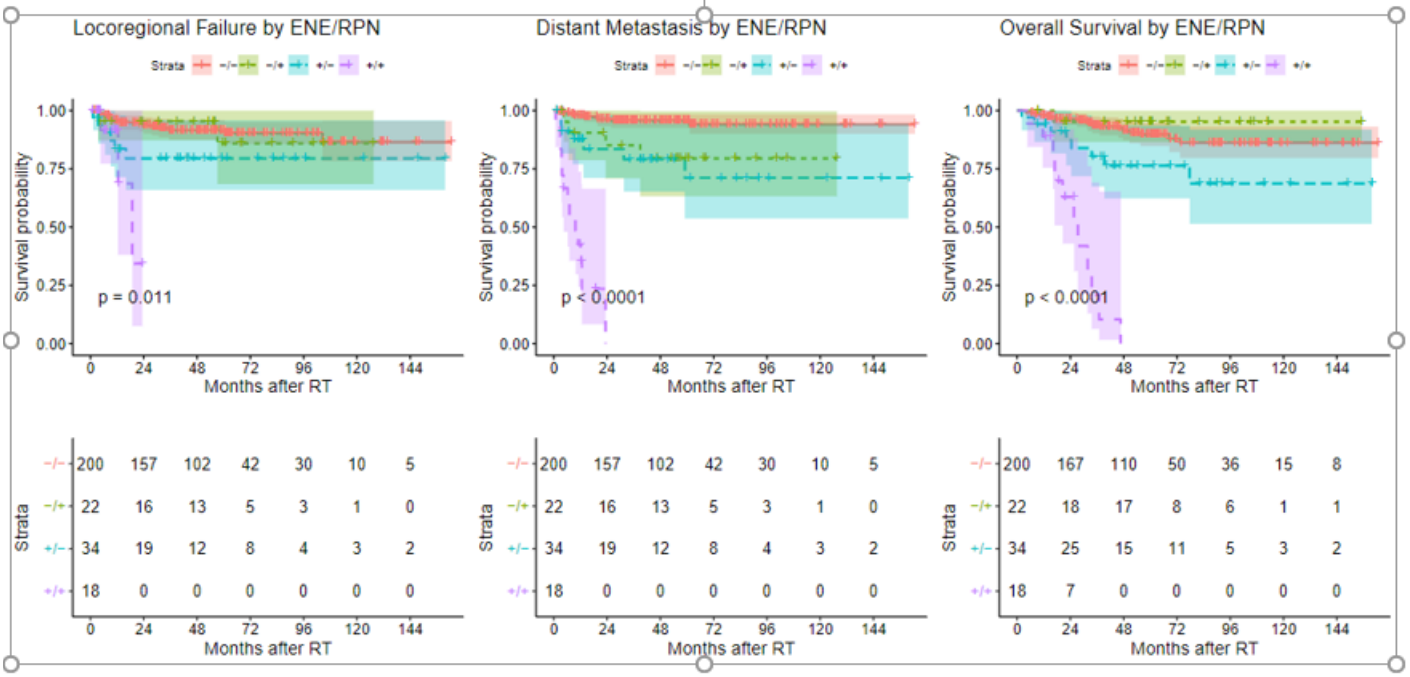


Figure 2. "Matted lymph node" patients. 2A (left) Kaplan-Meier LRC curve. 2B (right) Kaplan-Meier DSS curve.

ECOG 1308 attempted to utilize response to neoadjuvant chemotherapy as a biomarker for HPV+ oropharynx cancer patients who may be candidates for radiation de-escalation (Marur 2017). In this trial, they found an overall correlation between complete clinical response to neoadjuvant cisplatin/cetuximab/Taxol and loco-regional control after 54Gy de-escalated

radiotherapy. However, they found a high rate of loco-regional failure after RT de-escalation among cT4, cN2c and patients with significant smoking history where 2 yr LRC was 70%.

Furthermore, our recent data (submitted for publication) in 282 p16+ OPSCC patients with both pretreatment CT and PET-CT shows that radiographic extranodal extension (rENE), positive retropharyngeal nodes (RPN+), and T-stage were significant on MVA for DMFS: C-index=0.86 (p<0.001).



(C)

Figure 3. Locoregional failure free survival, distant metastatic failure free survival and overall survival by (A) AJCC 8th edition group stage, (B) total MTV and (C) presence of radiographic extranodal extension (rENE), and/or positive retropharyngeal lymph nodes (RPN+).

Thus, this study seeks to study the population of HPV-related oropharynx cancer patients that appear to be at highest risk for distant metastases and loco-regional failure include cT4, cN3 those with "matted nodes", radiographic ECE (extracapsular extension) and radiographically positive retropharyngeal lymph nodes

1.2 Study Agents and Associated Known Toxicities: Nivolumab

Nivolumab is a fully humanized IgG4 anti-PD1 monoclonal antibody. In metastatic platinum-refractory squamous cell carcinoma of the head and neck, nivolumab has been shown to improve survival from 5.1 months to 7.5 months in a randomized trial p=0.01 (*Ferris, 2016*). In combination with concurrent RT and cisplatin in the upfront treatment of intermediate and high risk loco-regionally advanced Head and Neck Squamous Cell Carcinoma (HNSCC), nivolumab has been shown to be safe and feasible to administer (*Gillison, 2018*). Here, we propose to study combination carboplatin/paclitaxel, nivolumab and radiotherapy in HPV-related oropharynx cancer including cT4, cN3 and those with "matted nodes". We hypothesize that this combination can improve progression-free survival (PFS). Our institutional experience in HPV-related oropharynx cancer treated with RT and concurrent carboplatin (AUC=1) and paclitaxel (30mg/m2) has been extremely favorable (*Feng 2010*). Furthermore, in comparison with concurrent cisplatin, the UM experience has shown that oncologic outcomes are similar with concurrent carboplatin/paclitaxel with decreased ≥ grade 3 toxicity and need for late feeding tube

(*Worden, 2008, Dobrosotskaya, 2013*).

This study will run concurrently at UM with a sister study in AJCC 8th ed stage I and II HPV+ oropharyngeal cancer patients where carboplatin/paclitaxel alone is given with FDG-PET adapted de-escalated radiotherapy (UMCC 2017.113).

At UM, we have found a LRC at 2 yrs of 95% for HPV+ AJCC 8th ed stage 1 and 2 patients and a slightly lower rate of 85% for stage 3 (cT4, cN3). Interestingly, our data further suggest that cT4 and cN3 tumors (AJCC 8th edition staging) have high rates of distant metastases (unpublished data).

Experience with Nivolumab in Squamous cell carcinoma of the head and neck

Nivolumab monotherapy has demonstrated clinical benefit in subjects with squamous cell carcinoma of the head and neck (SCCHN) who have progressed on or after a platinum-based therapy, and has been approved for use in the US.

In locally advanced squamous cell carcinoma of the head and neck, nivolumab has been evaluated with concurrent cisplatin and radiotherapy on RTOG 3504, showing safety and feasibility of administration (*Gillison 2018).* Cisplatin was discontinued early in 3 pts due to AEs unrelated to nivolumab. No DLT was observed. SAEs included anaphylaxis to cisplatin (cis) (n=1), cholecystitis (1), but none attributable to nivolumab. Grade >3 toxicities attributable to nivo included fatigue (n=1),anorexia (1), WBC decrease (2), neutrophil count decrease (1), mucositis (1), lipase elevation (n=2).

1.3 Mid-Treatment PET-CT

Post-treatment PET-CT obtained 12 weeks after therapy has been shown to be a reliable predictor of treatment response and has been widely adopted. A recently published prospective, randomized control trial studying PET surveillance at 12 weeks post-treatment found PET-CT surveillance was not inferior to planned neck dissection for advanced (N2/N3) SCC of the head and neck *(Mehenna, 2016).* While PET-CT surveillance at this interval was non-inferior in terms of survival benefit, this group resulted in fewer neck dissections overall, no difference in complication rate, and similar 2-year survival rate. Furthermore, PET-CT was more cost effective, saving about $2000 per patient over the trial duration in decreased number of operations *(Mehenna, 2016)*.

Prospective trials have demonstrated value of pre- treatment PET-CT (pPET) and mid-treatment interval PET-CT (iPET) as a potential radiographic biomarker to predict loco-regional control (LRC), disease-free survival (DFS) and distant metastasis free survival (DMFS). For example, Pollom, et al. studied iPET at median radiation dose of 33.5Gy in OPSCC where 88% of patients were p16 positive and 40% were "smokers" (*Pollom, 2016).* They found that pre-treatment $MTV_{50\%}$ and iPET $MTV_{2.0}$ were correlated with PFS (p=0.015), where MTV_x was defined as the metabolic tumor volume above a threshold "x". Additionally, they found that nodal total lesion glycolysis (TLG) of > 5% per week correlated with PFS (p=0.03).

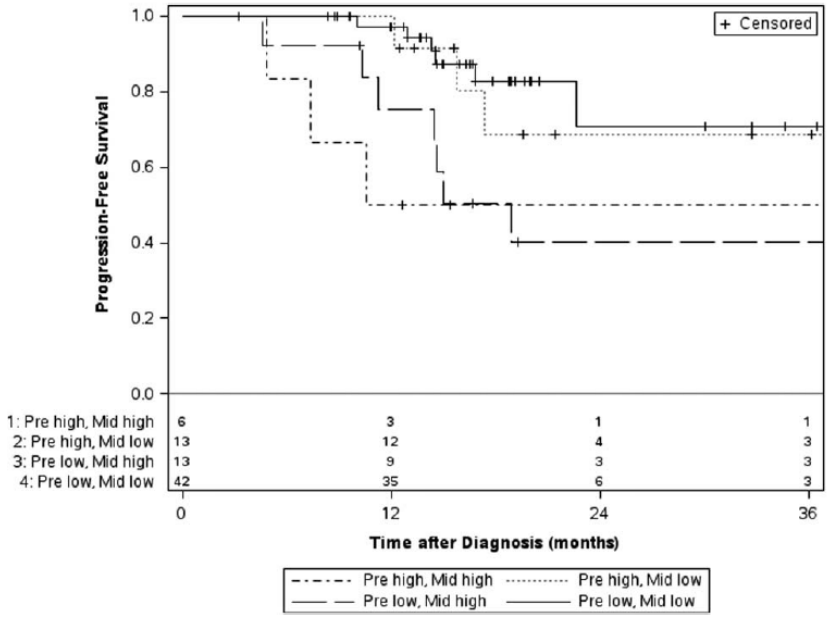


Figure 3. PFS according to MTV parameters.

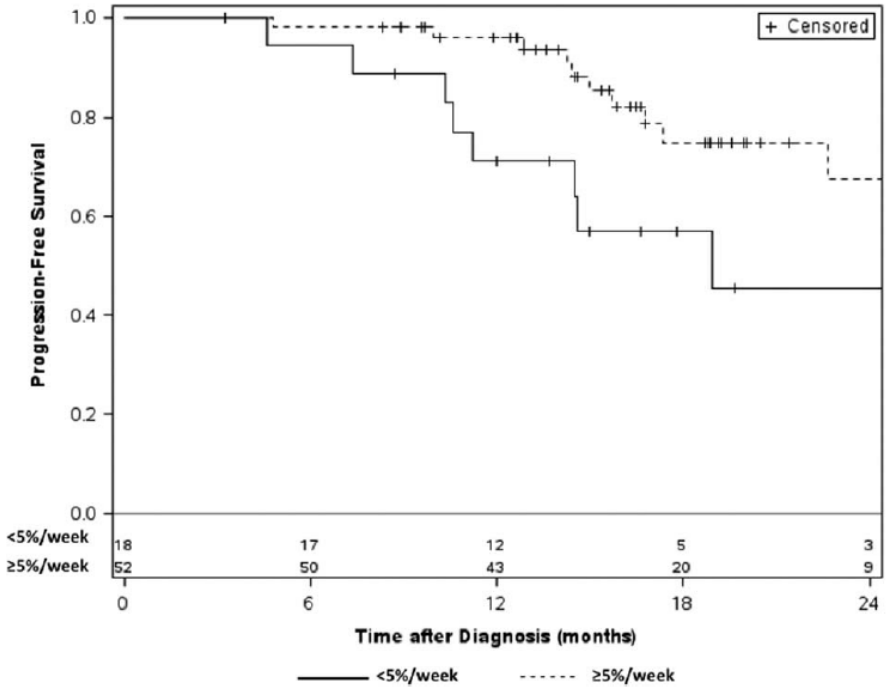


Figure 4. PFS according to velocity of TLG decrease.

Schwartz, et al. performed a retrospective analysis of pPET in 74 patients treated on RTOG 0522 patients

(*Schwartz, 2016)*. They found that the SUV_{max} and SUV_{mean} were non-prognostic, but that a $MTV_{40\%}$ of the primary tumor, as well as the total MTV (primary tumor + involved lymph nodes) higher than cohort mean, correlated with worse PFS (HR 2.34, 95% CI [1.02, 5.37], p=0.05) and LRC (HP 4.01, CI [1.28,12.52], p=0.02). Primary MTV remained prognostic in the 56 patients of this study who had p16+ OPSCC.

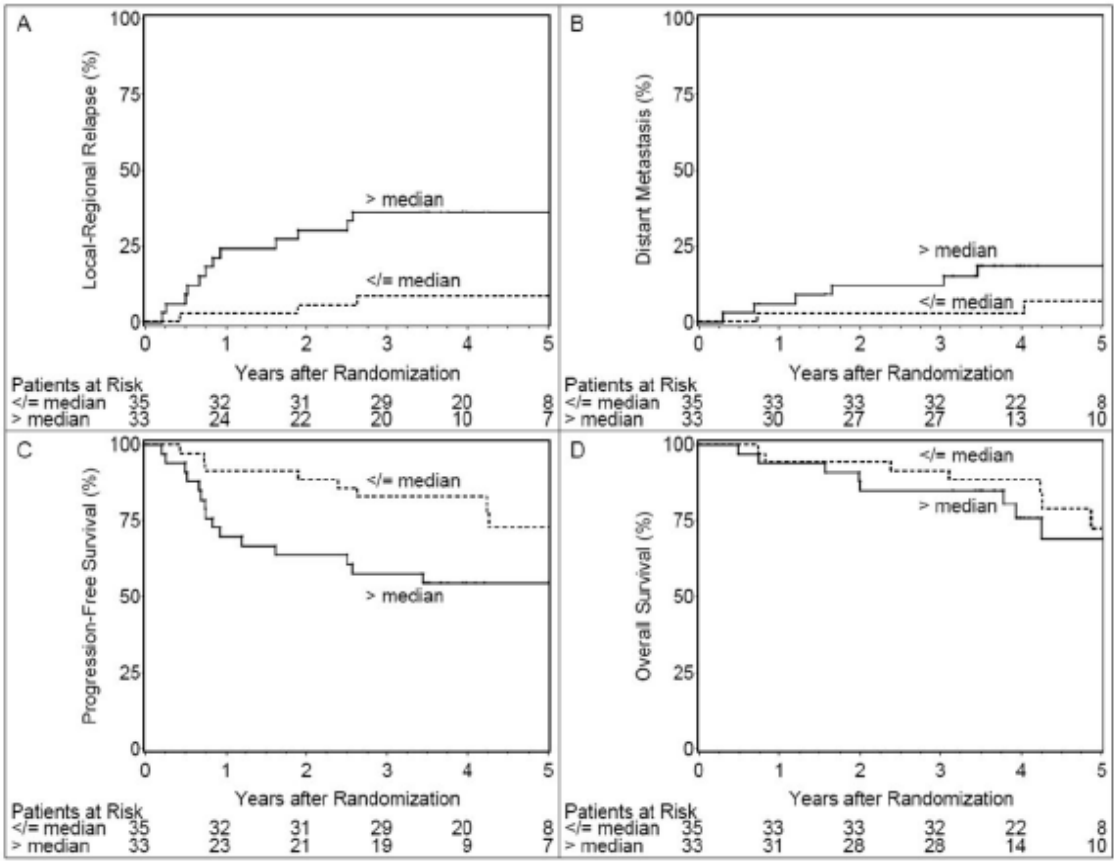


Figure 5. Schwartz, et al. Cumulative incidence estimates of local-regional relapse (Panel A) and distant metastasis (Panel B) and Kaplan-Meier estimates of progression-free survival (Panel C) and OS (Panel D) for patients with baseline primary MTV ≤ median or > median. Two-year local-regional relapse rates were 5.7% (95% CI: 0, 13.5) for patients with MTV ≤ median and 30.3% (95% CI: 14.3, 46.3) for patients with MTV > median. Two-year distant metastases rates were 2.9% (95% CI: 0, 8.5) for patients with MTV ≤ median and 12.1% (95% CI: 0.8, 23.4) for patients with MTV > median. Two-year progression-free survival rates were 88.6% (95% CI: 78.0, 99.1) for patients with MTV ≤ median and 63.6% (95% CI: 47.2, 80.0) for patients with MTV > median. Two-year overall survival rates were 94.3% (95% CI: 86.6, 100) for patients with MTV ≤ median and 84.9% (95% CI: 72.6, 97.1) for patients with MTV > median.

An Australian study of pPET and iPET in 75 patients by Lin, et al. evaluated all head and neck mucosal sites of cancer *(Lin, 2015*). They performed iPET at a mean of 18.5 days from the start of RT, and evaluated SUV_{max}, SUV_{mean}, MTV and TLG in both primary tumor and lymph nodes. They found that the pPET parameters were not predictive of treatment response. However, multi-variate analysis demonstrated iPET reduction of total node MTV by 50% from baseline to correlate with loco-regional failure -free survival (FFS), DFS and OS (p=0.026, 0.003, and 0.014, respectively). iPET reduction of nodal TLG by > 50% from baseline was predictive of FFS, DFS and OS in multi-variate analysis (p=0.01, 0.01, 0.014).

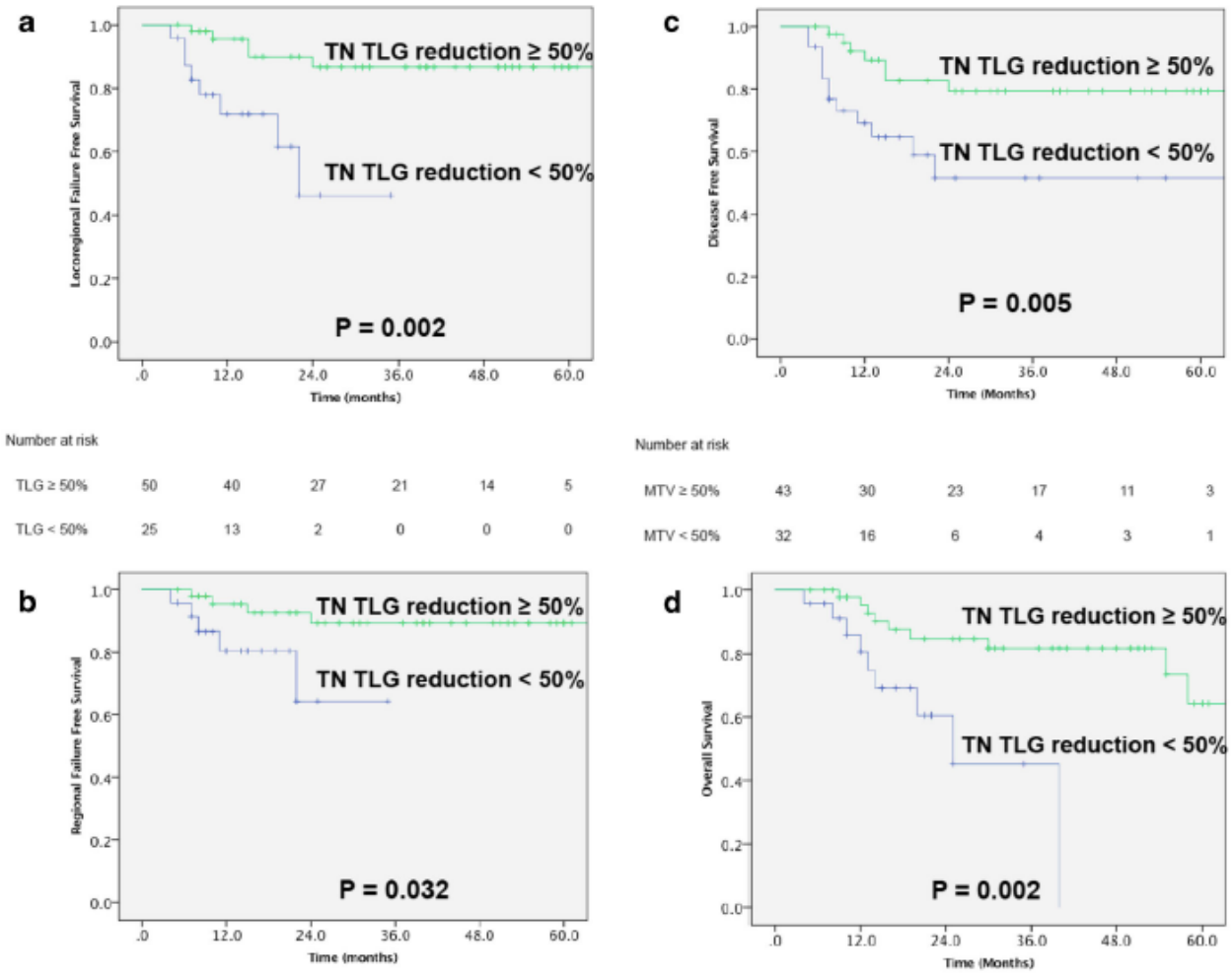


Figure 6. Kaplan-Meier survival rates in relation to the optimum total node TLG cut-off value of 50 % on iPET for locoregional failure-free survival (LRFFS), b regional failure-free survival (RFFS), c disease-free survival (DFS) and d overall survival (OS).

In non-small cell lung cancer (NSCLC), the University of Michigan has conducted 2 consecutive prospective dose escalation trials to test a hypothesis that radiation dose can be escalated safely above 74 Gy when the radiation dose prescription is individualized at the beginning (UMCC 2003.073) and adapted to the reduced MTV on during-RT FDG-PET/CT (UMCC 2007.123) (*Kong 2005, 2006, 2007, 2017*). The prescription dose of the first trial was individually set to correspond to a 15% risk of RT-induced lung toxicity (RILT) according to a NTCP model at the baseline. RT dose was further escalated in the second trial by adapting dose individually to the residual metabolic volume on FDG-PET/CT obtained during RT, so the residual metabolic volume would receive the maximal dose that would maintain a tolerable risk of RILT while the pre-RT CTV on CT was not compromised (would receive at least 60 Gy). On the first trial, patients treated to a higher dose had significantly better survival (p=0.02). The median survival on the second trial has not yet been reached.

This prospective study aims to collect pre- and mid-treatment PET-CT to investigate changes in FDG-PET after administration of nivolumab. Early timing of mid-treatment PET-CT between fractions 8-12 has been planned to minimize risk of mucositis induced false positivity.

1.4 Correlative Studies

Circulating tumor DNA (ctDNA)

An additional exploratory aim of this study is to study circulating tumor DNA in the patients undergoing therapy on this study. Based on review of our previous experience at UM, we estimate the 2 year LRC of our study population to be 85%. Furthermore, 15-30% of HPV-related oropharynx cancer patients will go on to develop distant metastases. We hypothesize that additional biomarkers will aid in personalized care with potential selective treatment de-intensification for our patients.

One promising non-invasive biomarker is quantification of circulating tumor DNA (ctDNA). It is known that tumor cell division and death causes release of cell free fragmented DNA into circulation. ctDNA is composed of small fragments of nucleic acid that are not associated with cells. ctDNA is currently being explored in many cancers in early stage and metastatic settings to evaluate response. Circulating tumor DNA has been detected in 70-100% at diagnosis in a cohort of 640 patients with multiple types of advanced stage cancers (Bettegowda 2014). This study included 14 head and neck cancer patients of all stages and found 73% were positive for detectable ctDNA.

The concept of ctDNA is not new to head and neck cancer. In EBV (Ebstein Barr virus)-related endemic nasopharynx cancer, multiple publications have demonstrated detectable serum EBV DNA in > 80% patients with pre-treatment levels correlated to tumor stage (Le 2013, Chan 2012). Furthermore, clearance of EBV DNA after definitive chemoradiation is associated with improved PFS (Wang 2012, Lin 2004).

Serum detection of ctDNA is now being explored in other head and neck cancers. Gupta, et al. have have explored serum detection of HPV DNA during de-escalated chemoradiation for oropharynx cancer showing that 80% patients had detectable HPV16 data and that clearance by 4th week of RT is associated with improved prognosis (Gupta 2018). Emerging data in HPV+ recurrent or metastatic OPSCC shows that serum levels correlate with total disease burden[i] and studies are ongoing to assess correlation with treatment response (Hanna 2018). To date, no group has attempted to detect ctDNA in head and neck cancer through somatic mutations. Dr. Brenner's lab at the University of Michigan has the technical ability to detect HPV DNA as well as the capability to detect the most commonly mutated oropharynx cancer genes through a next generation sequencing approach to ctDNA cell fragments. In this trial, we plan to collect 6ml of EDTA blood at several time points correlated with clinical blood draw times in order to explore correlation with ctDNA and treatment response as well and potential early detection of recurrence.

Flow cytometry for analysis of serum immune biomarkers

Optimal serum biomarkers have not been developed for identifying the subset of patients who best respond to immune checkpoint blockade. The measurement of peripheral blood immune cell subsets as a biomarker for immune activation or inhibition may be an important, noninvasive method to predict treatment response. Patients with high risk HPV+ OPSCC are at risk for treatment failure, thus careful monitoring during treatment and in the post-treatment period is of extreme importance. As an exploratory aim, we will plan to perform flow cytometry analysis pre-treatment, weekly during treatment and post-treatment.

DCE-MRI

Several physiological and metabolic imaging modalities, most in isolation, have been investigated for prediction of treatment failure in head and neck cancer. Fludeoxyglucose (FDG) positron emission tomography (PET), a marker for glucose metabolism, has shown high FDG uptake associated with poorer prognosis, whereas rapid metabolic response on PET/CT has been associated with high LRC. Hypoxic PET, and perfusion CT/MRI and diffusion MRI have shown to be biomarkers for outcomes in HNSCC. Persisting poorly perfused tumors during the early course of RT is associated with high risk for local and regional failure. Diffusion imaging, a measure of water mobility in tissue and sensitive to cellularity, has shown that an increase in apparent diffusion coefficient (ADC) of the HNSCC during RT is associated with positive therapy response. Most clinical trials currently underway use a single imaging modality to guide radiation escalation or de-escalation and single imaging modalities are limited to image only one aspect of tumor biology. The spatial relationship between imaging risk-factor parameters in HNSCC are largely unknown.

One exploratory aim of this study is to investigate whether FDG uptake, low blood volume, and low diffusion coefficient in HPV-related oropharynx cancer have any spatial correspondence and their early responses to RT to determine the implication of this overlap or lack thereof for adaptive boosting strategy.

1.5 Rationale

Above, we have identified a group of HPV+ oropharynx cancer patients at highest risk for metastatic disease and loco-regional failure including the cT4,cN3 and "matted nodes" patients. To date, only multi-agent induction chemotherapy have been shown to improve distant metastases in head and neck cancer, but these regimens have not improved loco-regional control or overall survival. We hypothesize that the addition of nivolumab to definitive chemoradiation will improve loco-regional control and distant metastasis rate in these patients.

2.0 Study Objectives

2.1 Primary Objective

2.1.1 To determine whether the addition of nivolumab can improve 2 yr PFS (progression free survival) as compared to historical standard of fractionated RT and carboplatin/paclitaxel in patients with high risk HPV-related squamous cell carcinoma of the oropharynx.

2.2 Secondary Objectives

2.2.1 To characterize patterns of failure (loco-regional relapse versus distant) PFS and overall survival;

2.2.2 To characterize acute toxicity profiles (during radiation therapy and at 3 and 6 months) and late toxicity profiles at 1 and 2 years;

2.2.3 To correlate metabolic image uptake data on mid-treatment FDG-PET scans performed between fractions 8-12 with standard 12 week post-treatment PET-CT.

2.3 Exploratory Correlative Science Objectives

2.3.1 To quantify circulating tumor HPV DNA in the blood pre-, mid- and post-treatment.

2.3.2 To perform integrative targeted sequencing of primary HPV+ tumor specimens to identify the distribution of lesions co-incident with commonly deregulated genes (as well as the transcriptional programs deregulated in these tumors and assess overall mutational burden).

2.3.3 To describe the serum immune cell profile pre-treatment, weekly during RT and post-treatment by flow cytometry and correlate with clinical outcomes

2.3.4 To correlate pre-treatment tumor immune phenotype with clinical outcomes

2.3.5 To determine patient-reported quality of life at 3, 6 months and 1 year using FACTHN, U Washington QOL, CTCAE PRO as well as xerostomia questionnaire;

2.3.6 To determine swallowing outcomes using barium swallow pre-treatment as well as 3- and 12- months post treatment

2.3.7 To descriptively assess FDG-PET after nivolumab is administered.

2.3.8 To quantify the low blood volume and apparent diffusion coefficient in DCE-MRI of HPV-related oropharynx cancer in patients treated with anti-PD1 therapy

2.4 Endpoints

The primary study endpoint is the PFS at 2 years which will be estimated using the Kaplan-Meier method. Secondary aims include estimation of toxicity, patterns of failure, freedom from local and distant progression and overall survival. To characterize patterns of failure we will summarize at fixed timepoints, the proportion of patients who progressed in any location and whether the first progression was local, regional, distant or in multiple locations. Overall survival will be estimated using the Kaplan-Meier methods with associated 90% confidence intervals. Freedom from local/regional or distant progression will be estimated using cumulative incidence functions with death prior to progression as a competing risk. Toxicity outcomes will be estimated as proportions for patients with available toxicity data at 3, 6 12 and 24 months. They will also be estimated as the proportion of all treated patients through cumulative incidence estimates with death or disease progression treated as competing risks and censoring for patients lost to FU. Quality of Life (QOL) outcomes and swallowing study results will be summarized descriptively by timepoint. If there is substantial missing data points in the QOL outcomes we will assess for informative missing data points by comparing earlier QOL scores and change in earlier QOL scores between patients missing QOL at later timepoints (e.g. 1 or 2 years). Another secondary aim is to correlate metabolic image uptake data on mid-treatment FDG-PET scan with standard 12 week post-treatment PET-CT. This will be done both at the patient level for summary measures and also spatially within a patient.

3.0 PATIENT ELIGIBILITY

3.1 **Inclusion Criteria**

3.1.1 Histologically or cytologically proven squamous cell carcinoma of the oropharynx (tonsil, base of tongue, oropharyngeal wall, soft palate) that is p16 positive by immunohistochemistry or HPV positive by in situ hybridization

3.1.2 Clinical stage: stage III AJCC 8th edition staging (cT4 or cN3) OR “matted lymph nodes” (defined as 3 LNs abutting one another with loss of intervening fat plane that is replaced with evidence of extracapsular spread) OR radiographic extracapsular extension (defined as overt loss of fat plane surrounding a LN) OR radiographically positive retropharyngeal LN >7mm in size

3.1.3 Appropriate stage for protocol entry, including no distant metastases, based upon the following minimum diagnostic workup:

History/physical examination, including documentation of weight within 2 weeks prior to registration;

FDG-PET/CT scan for staging and RT plan within 4 weeks prior to registration;

Zubrod Performance Status 0-1 within 2 weeks prior to registration;

Age ≥ 18;

3.1.4 CBC/differential obtained within 2 weeks prior to registration on study, with adequate bone marrow function defined as follows:

Absolute neutrophil count (ANC) ≥ 1,000 cells/mm^3; Platelets ≥ 75,000 cells/mm^3; Hemoglobin ≥ 9.0 g/dL

AST/ALT ≤3 x ULN
Total Bilirubin ≤1.5 x ULN (except subjects with Gilbert Syndrome who must have a total bilirubin level ≤ 3 x ULN)

3.1.5 Serum creatinine within normal institutional limits or a creatinine clearance ≥ 45 mL/min within 2 weeks prior to registration;

3.1.6 Women of childbearing potential must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study and for five months after the last treatment. A woman of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) and is not postmenopausal. Menopause is defined as 12 months of amenorrhea in a woman over age 45 years in the absence of other biological or physiological causes. In addition, females under the age of 55 years must have a serum follicle stimulating hormone (FSH) level > 40 mIU/mL to confirm menopause. Men receiving nivolumab who are sexually active with WOCBP must agree to use effective contraception throughout their participation in the treatment phase of the study and for seven months after the last treatment.

3.1.7 Due to the potential for serious adverse reactions in breastfed infants from carboplatin/paclitaxel and nivolumab, women are advised not to breast-feed during treatment with carboplatin/paclitaxel or nivolumab

3.1.8 The patient must provide study-specific informed consent prior to study entry.

3.2 Exclusion Criteria

3.2.1 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 3 years (For example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

3.2.2 Any prior therapy for the study cancer; note that prior chemotherapy for a different cancer is allowable if > 3 years prior to study;

3.2.3 Any history of active autoimmune disease that has required systemic treatment in the past 2 years (i.e., with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment.

3.2.4 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.5 Severe, active co-morbidity, defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months;
- Uncontrolled diarrhea;
- Uncontrolled adrenal insufficiency;
- Transmural myocardial infarction within the last 3 months;
- Acute bacterial or fungal infection requiring systemic antibiotics at the time of registration;
- Chronic Obstructive Pulmonary Disease (COPD) exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;
- Acquired Immune Deficiency Syndrome (AIDS) with CD4+ count < 350 cells per microL; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive.

3.2.6 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.7 Women who are breastfeeding and are not willing to discontinue breastfeeding during the trial

3.2.8 Poorly controlled diabetes (defined as fasting glucose level > 200 mg/dL) despite 2 attempts to improve glucose control by fasting duration and adjustment of medications. Patients with diabetes will preferably be scheduled in the morning and instructions for fasting and use of medications will be provided in consultation with the patients' primary physicians

3.2.9 Diagnosis of immunodeficiency or is receiving systemic steroid therapy or any other form of immunosuppressive therapy within 7 days prior to the first dose of trial treatment. Short bursts of steroids of 5-7 days (for COPD exacerbation or other similar indication) are allowed.

3.2.10 Known history of, or any evidence of active, non-infectious pneumonitis.

3.2.11 Known history of active TB (Bacillus Tuberculosis).

3.2.12 Hypersensitivity to nivolumab or any of its excipients or known hypersensitivity to carboplatin/paclitaxel.

3.2.13 Known active Hepatitis B (e.g., HBsAg reactive) or Hepatitis C (e.g., HCV RNA [qualitative] is detected).

3.2.14 Received a live vaccine within 30 days of planned start of study therapy.

3.2.15 Have any condition that, in the opinion of the investigator, would compromise the well-being of the subject or the study or prevent the subject from meeting or performing study requirements

4.0 SUBJECT SCREENING AND REGISTRATION PROCEDURES

Patient registration The University of Michigan Rogel Cancer Center as described below:

A potential study subject who has been screened for the trial and who has signed the Informed Consent document will be initially documented by the Screening and Enrollment Log.

The UM CTSU Coordinator, who acts as the registrar, will review the submitted documents and process the registration. After informed consent is obtained and PRIOR to the initiation of protocol therapy all patients satisfying the inclusion/exclusion criteria must have eligibility confirmed by the Clinical Trials Support Unit. The patient will not be considered registered and enrolled in the study until all information is confirmed by the Clinical Trials Support Unit Data Manager. To enroll a patient, call 734-936-4300 Monday through Friday, 9:00AM-5:00PM.

Patients found to be ineligible for participation after being consented will be considered screen failures, and documented as such in the Screening and Enrollment Log. These patients will not have study identification number assigned to them, and will not receive study treatment.

5.0 TREATMENT PLAN

5.1 Treatment dosage and Administration

Protocol treatment must start within 30 days of enrollment. Nivolumab (240mg) will be administered on Day 1 and then continued q2wk throughout RT. On day 8, RT as well as carboplatin (AUC=1) and paclitaxel (30mg/m^2) will be administered with paclitaxel infusion first, followed directly by carboplatin infusion. RT (70Gy in 35 daily fractions on business days) will begin within 24 hours of chemotherapy infusion. Carboplatin/paclitaxel will be administered weekly during RT. Patients will receive a total of 7 concurrent carboplatin/paclitaxel doses and 4 concurrent nivolumab doses. Starting in week 9, after completion of RT, adjuvant nivolumab (480mg) will be given q4weeks for a total of 4 doses. Premedications and supportive care will be administered per institution guidelines. On carboplatin/paclitaxel days, premedications will include antiemetics, histamine H1 and H2 antagonists, and dexamethasone according to the institution standards.

5.1.1 Nivolumab

Nivolumab (investigational product) will be supplied by Bristol Myers Squibb.

Patients will start nivolumab 240 mg IV prior to chemotherapy and radiation. Then, nivolumab will continue at 240 mg IV for 4 total doses q 2wks concurrent with RT. Adjuvantly, patients will receive nivolumab 480 mg alone IV q 4weeks for a total of 4 doses.

Drug Product Description, Preparation and Administration (nivolumab Investigator's Brochure)

Nivolumab is provided as a 10mg/mL solution in single-use vials. The drug product is sterile, non-pyrogenic, single-use, isotonic aqueous solution for IV infusion.

Vials of nivolumab injection must be stored at 2°C to 8°C (36°F to 46°F) and protected from light and freezing. The unopened vials can be stored at room temperature (up to 25°C, 77°F) and room light for up to 48 hours.

Preparation
Refer to the latest Investigator's Brochure for drug preparation information.

Nivolumab is a clear to opalescent, colorless to pale-yellow liquid, which may contain light (few) particulates.

- When the dose is fixed (eg, 240 mg, 360 mg, or 480 mg flat dose), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL.
- If diluted, dilute nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a protein concentration as low as 0.35mg/mL. The total volume of infusion must not exceed 160 mL.
- For patients with body weights less than 40 kg, the total volume of infusion must not exceed 4 mL/kg of body weight.
- During drug product preparation and handling, vigorous mixing or shaking is to be avoided. Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of nivolumab.

Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

Storage of Infusion
The product does not contain a preservative.
The administration of nivolumab infusion must be completed within 24 hours of preparation. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°C to 8°C, 36°F to 46°F) for up to 24 hours, and a maximum of 8 hours of the total 24 hours can be at room temperature (up to 25°C, 77°F) and room light. The maximum of 8 hours under room temperature and room light conditions includes the product administration period.

Administration
Administer the infusion over 30 minutes (study allows +/- 5 minutes window) through an intravenous line containing a sterile, non-pyrogenic, low protein binding (polyethyersulfone membrane) in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). It is not to be administered as an IV push or bolus injection.

Do not coadminister other drugs through the same intravenous line. Flush the intravenous line at end of infusion.

5.1.2 Carboplatin

Chemistry: Carboplatin is a hydrophilic platinum-containing compound and is an analog of cisplatin, producing intrastrand DNA cross- links.

Human Toxicology: Side effects of carboplatin include: myelosuppression, nausea, vomiting, abdominal pain, diarrhea, and constipation. Other toxicities include: allergic reactions (including hypersensitivity, i.e. rash, urticaria, erythema, pruritis, bronchospasm, and profound hypotension), peripheral neuropathy, paresthesias, loss of hair, hearing loss, visual disturbances, and change in taste. Serum creatinine elevations and blood urea elevations have occurred as well as abnormal liver function tests and decreased serum electrolyte values. Although rare, pain asthenia, cardiovascular, respiratory, genitourinary, and mucosal side effects have occurred in some patients. Cancer-associated hemolytic uremic syndrome has been reported. Rarely carboplatin may cause fetal harm; therefore, women of childbearing potential should be advised to avoid becoming pregnant. The renal effects of nephrotoxic compounds may be potentiated by carboplatin. Carboplatin is contraindicated in patients with a history of severe allergic reactions to cisplatin or to other platinum-containing compounds or mannitol. This drug should not be used in patients with severe bone marrow depression or significant bleeding. The occurrence of acute leukemia has been reported rarely in patients treated with anthracycline/alkylator combination chemotherapy. For a completed list of adverse effect see the current drug label.

Pharmaceutical Data
Pharmacokinetics:
Distribution: V_d: 16 L (based on a dose of 300 to 500 mg/m^2); into liver, kidney, skin, and tumor tissue
Protein binding: Carboplatin: 0%; Platinum (from carboplatin): Irreversibly binds to plasma proteins
Metabolism: Minimally hepatic to aquated and hydroxylated compounds
Half-life elimination: CrCl >60 mL/minute: Carboplatin: 2.6 to 5.9 hours (based on a dose of 300 to 500 mg/m^2); Platinum (from carboplatin): ≥5 days
Excretion: Urine (~70% as carboplatin within 24 hours; 3% to 5% as platinum within 1 to 4 days)

Formulation and Preparation:
Carboplatin Injection is supplied as a sterile, pyrogen-free, aqueous solution available in 50 mg/5 mL, 150 mg/15 mL, 450 mg/45 mL or 600 mg/60 mL multi-dose vials containing 10 mg/mL of carboplatin for administration by intravenous infusion. Each mL contains 10 mg carboplatin and Water for Injection.

Carboplatin can be further diluted to concentrations as low as 0.5 mg/mL with 5% Dextrose in Water or 0.9% Sodium Chloride injection, USP.

Storage and Stability: Unopened vials of carboplatin for injection are stable for the life indicated on the package when stored at 25°C (77°F); excursion permitted to storage at controlled room temperature (15-30°C; 59-86°F), and protected from light. When reconstituted as directed, the solution of carboplatin exhibits no decomposition for eight hours at room temperature (25°C). Like cisplatin, this drug should not be given through aluminum needles or intravenous administration sets. Caution: The single-use lyophilized dosage form contains no antibacterial preservatives. Therefore, it is advised that the reconstituted product be discarded eight hours after dilution.

Administration: Infuse intravenously at a rate per institution standard.

Supplier: Carboplatin is commercially available and should be from commercial sources and billed to patients or their insurers.

5.1.13 Paclitaxel

Chemistry: Paclitaxel is a semi-synthetic antimicrotubule agent that promotes the assembly of microtubules from tubulin dimers and stabilizes microtubules by preventing depolymerization hence producing abnormal bundles of microtubules throughout the cell cycle. As a result, paclitaxel inhibits interphase and cellular function.

Human Toxicology: Side effects of paclitaxel include: hypersensitivity reaction, myelosuppression, alopecia, peripheral neuropathy, nausea/vomiting, mucositis, alkaline phosphatase elevation, abnormal EKG, myalgia/arthlagia, asthenia, and hypotension. The development of severe hypersensitivity reactions is rare and documented in 1% of patients overall. For a completed list of adverse effects see the current drug label.

Pharmaceutical Data

Pharmacokinetics:

Distribution (V_{dss}): 24-hour infusion: 227 to 688 L/m^2; biphasic with initial rapid distribution to the peripheral compartment; later phase is a slow efflux of paclitaxel from the peripheral compartment; widely distributed into body fluids and tissues; affected by dose and duration of infusion

Protein binding: 89% to 98%

Metabolism: Hepatic via CYP2C8 and 3A4; forms metabolites (primarily 6α-hydroxypaclitaxel)

Half-life elimination:

Adults:

3-hour infusion: Mean (terminal): ~13 to 20 hours

24-hour infusion: Mean (terminal): ~16 to 53 hours

Excretion: Feces (~71%; ~5% as unchanged drug); urine (~14%)

Potential drug interactions: It has been demonstrated that paclitaxel is metabolized primarily by CYP450 2C8 and to a lesser extent 3A4. As a result, the pharmacokinetics of paclitaxel may be altered in vivo as a result of interactions with compounds that are substrates, inducers, or inhibitors of CYP2C8 and/or CYP3A4

Formulation and Preparation:
Paclitaxel is a clear, colorless slightly yellow viscous solution intended for dilution prior to intravenous infusion. Each mL of sterile non-pyrogenic solution contains 6 mg paclitaxel, Polyoxyl 35 Castor Oil (Cremophor® EL), dehydrated alcohol, and may contain possible citric acid. Paclitaxel is available in 30 mg (5 mL), 100 mg (16.7 mL), 150mg (25mL) and 300 mg (50 mL) vials.
Paclitaxel must be diluted prior to infusion. Paclitaxel should be diluted in 0.9% Sodium Chloride Injection, USP; 5% Dextrose Injection, USP; 5% Dextrose and 0.9% Sodium Chloride Injection, USP or 5% Dextrose in Ringer's Injection to a final concentration of 0.3 to 1.2 mg/mL. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration whenever solution and container permit.
Upon preparation, solutions may show haziness, which is attributed to the formulation vehicle. No significant losses in potency have been noted following simulated delivery of the solution through intravenous tubing containing an in-line (0.22 micron) filter. Data collected for the presence of the extractable plasticizer DEHP [di-(2-ethylhexyl) phthalate] show that levels increase with time and concentration when dilutions are prepared in PVC containers. Therefore, the use of plasticized PVC containers and administration sets is not recommended. Paclitaxel solutions should be prepared and stored in glass, polypropylene, or polyolefin containers.

Storage and Stability: Unopened vials of paclitaxel for injection are stable until the date indicated on the package when stored at controlled room temperature (20-25°C; 68° to 77°F), and protected from light. Neither freezing nor refrigeration adversely affects the stability of the product. When diluted as directed, the solution of paclitaxel is physically and chemically stable for up to 27 hours at ambient temperature (approximately 25°C).

Administration: Infuse paclitaxel intravenously at a rate per institution standards. Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Non-PVC containing administration sets, such as those which are polyethylene-lined, should be used.

Supplier: Paclitaxel is commercially available and should be purchased from commercial sources and billed to patients or their insurers.

5.2 Toxicities and Dosing Delays/Dose Modifications

5.2.1 Nivolumab

Suggested supportive care measures for the management of adverse events with potential immunologic etiology are outlined below. Where appropriate and at the discretion of treating physicians, these guidelines include the use of oral or intravenous treatment with corticosteroids as well as additional anti-inflammatory agents if symptoms do not improve with administration of corticosteroids. Note that several courses of steroid tapering may be necessary as symptoms may worsen when the steroid dose is decreased. For each disorder, attempts should be made to rule out other causes such as metastatic disease or bacterial or viral infection, which might require additional supportive care. The treatment

guidelines are intended to be applied when the investigator determines the events to be related to nivolumab.

Treatment delay is up to 6 weeks for nivolumab are allowable. It is permissible in cases of a dose held due to AE to skip the dose in the cycle in order to bring the patient back on track with the next Cycle visit.

Tumor assessments for all subjects should continue as per protocol even if dosing is delayed.

Nivolumab should be delayed for the following:

Grade 2 non-skin, drug-related AE, with the exception of fatigue

Grade 2 drug-related creatinine, AST, ALT and/or Total Bilirubin abnormalities

Grade 3 skin, drug-related AE

Grade 3 drug-related laboratory abnormality, with the following exceptions:

Grade $\geq$3 lymphopenia or asymptomatic amylase or lipase does not require dose delay

Grade $\geq$3 AST, ALT, Total Bilirubin will require dose discontinuation

All grade 1 or higher ocular AEs should be evaluated within 48 hours of occurrence by Radiation Oncology (Radonc) MD.

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Subjects who require delay of nivolumab should be re-evaluated weekly or more frequently if clinically indicated and resume nivolumab dosing when re-treatment criteria are met.

For nivolumab: A dose given more than 3 days after the intended dose date will be considered a dose delay

There will be no dose reductions for nivolumab.

Criteria to Resume Nivolumab Dosing

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade $\leq$ 1 or baseline, with the following exceptions:

Subjects may resume treatment in the presence of Grade 2 fatigue.

Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.

For participants with Grade 2 AST, ALT and/or Total Bilirubin Abnormalities, dosing may resume when laboratory values return to baseline and management with corticosteroids, if needed, is complete.

Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the BMS Medical Monitor.

Participants with drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment after consultation with the UM principal investigator (PI) (or

designee). Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

Treatment Discontinuation Criteria

For all subjects, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time will be captured on the health outcomes questionnaires. Tumor assessments for subjects who discontinue study treatment without radiographic progression, should continue as per protocol until radiographic progression is determined.

Nivolumab Dose Discontinuation

Treatment with nivolumab should be permanently discontinued for any of the following:

Any Grade 2 drug-related uveitis, eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment

Any Grade 3 non-skin, drug-related AE lasting > 7 days, or recurs with the following exceptions for laboratory abnormalities, diarrhea, colitis, neurologic toxicity, drug-related uveitis, pneumonitis, bronchospasm, hypersensitivity reactions, infusion reactions, and endocrinopathies. This excludes grade 3 mucositis as grade 3 mucositis including the need for placement of feeding tube is anticipated in 25% of patients with standard of care chemoradiation. For any patient where nivolumab is held during RT for grade 3 mucositis or feeding tube placement, patient should be re-evaluated within 4 weeks of the completion of RT. If feeding tube has been removed and/or mucositis has improved to $\leq$ Grade 2, adjuvant nivolumab should be restarted.

Grade 3 drug-related diarrhea, colitis, neurologic toxicity, uveitis, pneumonitis, bronchospasm, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation

Grade 3 drug-related endocrinopathies, adequately controlled with only physiologic hormone replacement do not require discontinuation. Adrenal insufficiency requires discontinuation regardless of control with hormone replacement.

Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:

Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation

Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation:

- Grade 3 drug-related AST, ALT or Total Bilirubin requires discontinuation*
- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2x ULN

* In most cases of Grade 3 AST or ALT elevation, study treatment will be permanently discontinued. If the investigator determines a possible favorable benefit/risk ratio that warrants continuation of study treatment, a discussion with the UM-PI must occur.

Any Grade 4 drug-related adverse event or laboratory abnormality (including but not limited to creatinine, AST, ALT, or Total Bilirubin), except for the following events which do not require discontinuation:

- Grade 4 neutropenia < 7 days
- Grade 4 lymphopenia or leukopenia or amylase or lipase < 7 days
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical

sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset

- Grade 4 drug-related endocrinopathy adverse events, such as, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose-controlling agents, respectively, may not require discontinuation after discussion with and approval from the BMS Medical Monitor.

Any event that leads to delay in dosing lasting > 6 weeks from the previous dose requires discontinuation, with the following exceptions:

- Dosing delays to allow for prolonged steroid tapers to manage drug-related adverse events are allowed.
- Dosing delays lasting > 6 weeks from the previous dose that occur for non-drug-related reasons may be allowed if approved by the BMS Medical Monitor (or designee).

Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the participant with continued nivolumab dosing.

Prior to re-initiating treatment in a participant with a dosing delay lasting > 6 weeks, the UM PI (or designee) must be consulted. Tumor assessments should continue as per protocol even if dosing is delayed. Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

Algorithms for management of nivolumab toxicity can be found in Appendix A. These algorithms are to be used in conjunction with treating physician discretion possibly in addition to other medications.

5.2.2 Carboplatin/paclitaxel

Toxicity	Action Taken
• **AST and/or ALT is > 2.5 x ULN** • **Alkaline phosphatase ≥ 2.5 x ULN *and* AST and ALT is > 1.5 x ULN**	**Step 1: Interrupt paclitaxel treatment until the toxicity has resolved, up to 2 weeks (14 days).** **Paclitaxel should be reduced by 15 mg/m^2 when restarted.** **Monitor as clinically indicated.**
If CrCl < 30, hold carboplatin. When CrCl returns to ≥ 30, initiate/resume carboplatin at previous dose.	
Hematologic Toxicity	
• **Neutrophil count is < 1000 cells/ mm3** • **Platelet count is < 75,000 cells/mm3**	**Step 1: Interrupt treatment (carboplatin and paclitaxel) until the toxicity has resolved to ≤ Grade 1 or pre-therapy baseline, up to 2 weeks (14 days).** **Step 2: Restart treatment monitor as clinically indicated.**

• **Grade 4 neutropenia (< 500 cells/mm3) lasting 7 days or more** • **Grade 3 or 4 neutropenia with an oral temperature of at least 38.5°C**	**Step 1: Interrupt treatment with carboplatin/paclitaxel until resolved to ≤ Grade 1, up to 2 weeks (14 days).** **Step 2: Restart treatment with carboplatin by tat AUC 1 Monitor as clinically indicated.**
Other Toxicities	
• Any Grade 4 or at the discretion of treating Medical Oncologist	**Discontinuation of treatment with chemotherapy and follow-up per protocol.**

5.3 Concomitant Medications/Treatments

5.3.1 Steroids or other immunosuppressive medications are prohibited for treatment of toxicities during protocol therapy, and used only if these medications are deemed medically necessary after thoughtful review. Premedications for chemotherapy are allowed.

5.3.2 The metabolism of paclitaxel is catalyzed by cytochrome P450 isoenzymes CYP2C8 and CYP3A4. In the absence of formal clinical drug interaction studies, caution should be exercised when administering paclitaxel concomitantly with known substrates or inhibitors of the cytochrome P450 isoenzymes CYP2C8 and CYP3A4. Caution should be exercised when paclitaxel is concomitantly administered with known substrates (eg, midazolam, buspirone, felodipine, lovastatin, eletriptan, sildenafil, simvastatin, and triazolam), inhibitors (eg, atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, and telithromycin), and inducers (eg, rifampin and carbamazepine) of CYP3A4. Caution should also be exercised when paclitaxel is concomitantly administered with known substrates (eg, repaglinide and rosiglitazone), inhibitors (eg, gemfibrozil), and inducers (eg, rifampin) of CYP2C8.

Due to potential drug interactions, the complete patient medication list, including paclitaxel, should be screened prior to initiation of and during treatment with paclitaxel and patients on potential interacting drugs monitored.

Since these lists of potentially interacting drugs are not complete, it is important to regularly consult frequently-updated drug information resources.

5.4 Other Modalities

5.4.1 Radiation Therapy

Simulation and Treatment Planning

Patients should undergo simulation to include 5-point aquaplast masking and CT scan with IV contrast unless contraindicated in the Department of Radiation Oncology at the University of Michigan. The treatment planning CT scan should be obtained in the immobilization device and in the treatment position with a slice thickness of 3 mm or less.

Dose Specifications

-GTVp is gross primary tumor volume. GTVn is gross nodal tumor volume.
-CTV1 is gross clinical volume with tight (typically 0.5 cm) margins around the GTV.
-CTV2 includes areas containing sub-clinical at-risk around the gross disease and at areas at risk of lymph node metastases.
-PTV1 and PTV2 consist of uniform 3 mm expansions of the CTV1 and 2 respectively.

Patients will initially receive a single prescription of 70 Gy to PTV1 in 35 fractions with RT given once daily, 5 days a week along with weekly carboplatin/paclitaxel (standard therapy). All fields must be treated daily. On days when chemotherapy is given, it will be administered prior to RT. Prescription to high risk PTV will be 70Gy in 35 fractions and to PTV2 will be 56Gy in 35 fractions.

Optimization goals:

The primary PTV dose will be 99% +/- 7% of the prescribed dose and to sub- clinical PTVs within +/- 5% of the prescribed dose. The maximal "hot spot" within a PTV will be <115% of the prescribed dose to that target delivered to a volume of at least 0.5 cc. The maximal dose outside the targets will be <105% of the prescribed dose delivered to at least 0.5 cc. volume. The maximal dose to the spinal cord, expanded by 0.5 cm, will be < 50 Gy, to the non-expanded cord < 45 Gy, and where applicable, to the optic pathways < 50 Gy and to the brainstem <54 Gy. Other normal tissue optimization are per institutional standards.

5.5 Duration of Therapy

Therapy will continue for 21 weeks total. This includes 4 doses of of nivolumab (240mg/m2) before and concurrent with RT/carboplatin/paclitaxel and 4 adjuvant nivolumab doses (480mg/m2) after the end of RT unless one of the following apply:

- Disease progression as defined in Section 7.0
- Inter-current illness that prevents further administration of treatment
- Unacceptable adverse event
- Patient voluntarily withdraws from treatment
- General or specific changes in the patient's condition render the patient unacceptable for further treatment

5.6 Off Treatment Criteria

Patients will be removed from protocol therapy when any of the criteria listed in Section 5.5 apply. The reason for ending protocol therapy and the date will be documented in the source. All patients who discontinue therapy should comply with protocol specific follow-up procedures as outlined in Section 5.7. The only exception to this requirement is when a subject withdraws consent for all study procedures or loses the ability to consent freely.

5.7 Duration of Follow-up

Patients will be followed for 2 years after completion of or removal from treatment or death, whichever comes first. Patient removed from treatment for unacceptable adverse events will be followed until resolution or stabilization of adverse event and not followed further. Clinical examinations will be performed as comparable to clinical practice: at 1 month after the completion of therapy and then approximately every 3 months for 2 years (+/- 2 months). This follow up schedule will adhere to standard of care clinical follow up. Therefore, missed visits and visits that diverge from this regimen will not be considered protocol deviations.

5.8 Off Study Criteria

5.8.1 Patient withdraws consent (termination of treatment and follow-up);
5.8.2 Loss of ability to freely provide consent through imprisonment or involuntary incarceration for treatment;
5.8.3 Patient is unable to comply with protocol requirements;
5.8.4 Treating physician judges continuation on the study would not be in the patient's best interest;
5.8.5 Patient becomes pregnant or female partner of male patients (pregnancy to be reported along same timelines as a serious adverse event);
5.8.6 Development of second malignancy (except for basal cell carcinoma or squamous cell carcinoma of the skin) that requires treatment, which would interfere with this study;
5.8.7 If a research subject cannot be located to document survival after a period of 2 years, the subject may be considered "lost to follow-up." All attempts to contact the subject during the two years must be documented;
5.8.8 Termination of the study by The University of Michigan or other regulatory bodies;
5.8.9 Patient completes protocol treatment and follow-up criteria

6.0 STUDY PROCEDURES

6.1 Screening/Baseline Procedures NOTE: This section lists required baseline evaluations needed before the initiation of protocol treatment.

6.1.2 Screening procedures include: Comprehensive metabolic panel, CBC with diff, Magnesium, TSH and cortisol within 2 weeks prior to enrollment, Radonc evaluation including nutritional assessment within 4 wks of enrollment, pretreatment imaging to assess staging including CT neck and chest (may be done as part of head and neck protocol PET-CT) within 4 wks of enrollment
6.1.3 Quantification of patients smoking history including number of pack years (# packs per day x # years) and whether they have smoked more than 100 cigarettes within last 365 days
6.1.4 Pre-treatment blood draw for ctDNA/exosomes/immune flow cytometry (optional per the subject)
6.1.5 Pre-treatment patient reported quality of life questionnaire
6.1.6 Pre-treatment barium swallow videofluoroscopy examination
6.1.7 Pre-treatment MRI in Radiation Oncology is planned. Will not be completed if patient has a contraindication to MRI. Please note that patients with a contraindication to MRI or who refuse MRI will continue with trial as otherwise planned
6.1.8 Tumor biopsy specimen is required for sequencing analysis. Archival tissue is acceptable if available. If archival tissue is not available, subjects will be asked to undergo a fresh tissue biopsy.

6.2 Procedures During Treatment

6.2.2 Day 1. Nivolumab Administration
6.2.3 Day 8. Carboplatin/paclitaxel as well as start of radiotherapy (all to occur within a 24 hour period).

6.2.4 Weekly CBC, CMP (incluing Mg), LFTs, TSH, cortisol
6.2.5 Weekly Radonc MD evaluation with toxicity evaluation
6.2.6 Weekly PRO (CTCAE PRO)
6.2.7 Between RT fractions 8-12, mid-treatment MRI and FDG-PET-CT
6.2.8 Weekly blood for ctDNA and exosomes (optional per the subject)
6.2.9 Weekly carboplatin/paclitaxel administration , with nivolumab administration every 2 weeks.

6.3 Follow-up Procedures- patients will be followed at 3,6,12, and 24 months post RT
6.3.2 FDG-PET-CT at 3mo (+/- 2 wks) after completion of RT
6.3.3 Q3mo (+/- 1 month) clinical followup with multi-disciplinary head and neck cancer team (Oto, Radonc, MedOnc)
6.3.4 Barium swallow evaluation 3mo and 12 mo post RT
6.3.5 Q3 mo QOL evaluation (FACT HN, U Washington and Xerostomia questionnaires). Financial toxicity survey collected a 3 mo post RT only
6.3.6 Q3mo toxicity and nutritional evaluation
6.3.7 Blood for correlatives at 3,6,12,24 months post RT (optional per the subject)
6.3.8 In the event of recurrence- FDG-PET-CT and biopsy confirmation are required

6.4 Schedule of Events

	Screening	Pre-Therapy	Day 1	Pre-RT	Between fractions 8-12	Weekly during CRT	+ 1 Month[6]	+ 3 month[6]	+ 6 month[6]	+ 12 month[6]	+ 24 month[6]	Recurrence
Rad Onc eval[6]	X	X				X	X	X	X	X	X	X
CBC with diff, CMP, Mg, LFTs, TSH, cortisol[7]	X	X				X[10]	X[10]	X[10]	X	X		
Pregnancy test	X[12]											
MRI		X[11]			X[11]							
PET/CT[3]	X	X			X			X				X
Toxicity & nutritional Evaluation[4]		X		X		X	X	X	X	X	X	
QOL Questionnaire[5]		X		X		X	X	X	X	X		
Videofluoroscopy[1]		X						X		X		
Dental Evaluation[2]				X								
Carboplatin/paclitaxel						X						
Nivolumab			X			X[8]	X[9]					
Blood for correlatives[13]		X				X	X	X	X	X	X	X
Primary tumor specimen for correlatives required		X[14]										X[13]

1 videofluoroscopy to be completed at baseline, 3 mo post RT and 12 mo post-RT per standard of care. Baseline can occur prior to the initiation of Nivolumab, during the first week of therapy (between the first dose of Nivolumab and radiation) or during the first week of radiation.

2 Pre-RT dental evaluation is encouraged but not required for all patients due to insurance issues

3 PET-CT to be completed at baseline within 4 wks of registration, mid-treatment (fx 8-12) and 3 mo post-RT (+/- 3 weeks)

4 toxicity evaluation per CTCAE v 5.0

5 QOL Suggested but not required. Financial toxicity will only be given at one time point 3 months post RT. All other questionnaires given at baseline and all follow-ups through 1 year. The CTCAE PRO will be given weekly during RT (this will be the only questionnaire administered during RT. *As patients can be seen in a variety of clinics, and occasionally do not follow a standard clinic schedule, missed QOLs will not be reported as a protocol deviation.* Nutritional assessment to be completed within 6 wks of start of therapy

6 Radonc exam will include med hx and physical as well as pregnancy test if applicable. Follow Up: Examinations will be performed as comparable to clinical practice: at 1 month (+/- 2 weeks) after the completion of therapy and then approximately every 3 months (+/- 1 month) for 2 years (+/- 2 months). This follow up schedule will adhere to standard of care clinical follow up. Therefore, missed visits and visits that diverge from this regimen will not *be considered protocol deviations. RadOnc evaluation must be completed at baseline, but follow-up visits may be completed by RadOnc, Oto, or MedOnc.* Baseline Radonc eval will include smoking history as per "pretreatment evaluation" section. Minimum follow-up is 3 mo after completion of protocol therapy.

7 Baseline within 2 weeks of registration

8 Nivolumab will be started on day 1 and given as follows: 240 mg IV q2 wks for 4 doses concurrent with RT.

9 Adjuvantly, patients will receive nivolumab 480 mg alone IV q 4weeks for a total of 4 doses.

10 Labs during RT, and in follow up 1-mo through 3-mo will occur with each chemotherapy dose

11 MRI is encouraged but not required- patients with a contraindication to MRI or who are unable to tolerate MRI will continue on the study as otherwise planned

12 Pregnancy test should also be performed as part of pre-RT workup in women of child bearing potential

13 Collection and banking of blood samples for correlative studies (genetic testing) is optional per the subject.

14 Tumor biopsy specimen is required for sequencing analysis. Archival tissue is acceptable if available. If archival tissue is not available subjects will be asked to undergo a fresh tissue biopsy.

7.0 MEASUREMENT OF EFFECT

7.1 Antitumor Effect

Efficacy on imaging will be determined by imaging and clinical exam. . Initial staging imaging will be obtained at registration; then routine PET-CT imaging will be obtained at 3 months (+/- 1 month) from completion of definitive therapy as per standard of care. After 3 mo post-RT PET scan, patients will be followed by head and neck clinical exam. Further imaging will be ordered based on clinical symptoms or findings as per standard of care.

Response and progression will be evaluated in this study and will be scored as no evidence of disease, local progression, regional progression, and distant progression. This will assessed based upon imaging and clinical exam.

7.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with study drug.

Evaluable for objective response. All patients who complete the entire course of radiation therapy and who complete standard of care 3 mo post-therapy PET-CT scan will be evaluable for response.

Disease Parameters

Measurable disease. Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter in the plane of measurement is to be recorded) with a minimum size of:

- 10mm by CT scan (irrespective of scanner type) for studies with a slice thickness of ≤5mm or twice the slice thickness or MRI
- 10mm caliper measurement by clinical exam (lesions which cannot be accurately measured with calipers should be recorded as non-measurable). All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Malignant lymph nodes: To be considered pathologically enlarged and measurable, a lymph node must be ≥15mm 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.

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable, and the conditions under which such lesions should be considered may be defined in the protocol when appropriate.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <20 mm with conventional techniques or <10 mm using CT scan), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

Guidelines for Evaluation of Measurable Disease

All measurements should be recorded in metric notation, using calipers if clinically assessed. All baseline evaluations should be performed as close as possible to the treatment start and never more than 4 weeks before the beginning of the treatment.

The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging based evaluation should always be done rather than clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial and >10mm diameter as assessed using calipers (e.g. skin nodules). For the case of skin lesions, documentation by color photography including a ruler to estimate the size of the lesion is suggested. As noted above, when lesions can be evaluated by both clinical exam and imaging, imaging evaluation should be undertaken since it is more objective and may also be reviewed at the end of the study.

Chest X-ray: Chest CT is preferred over chest X-ray, particularly when progression is an important endpoint, since CT is more sensitive than X-ray, particularly in identifying new lesions. However, lesions on chest X-ray may be considered measurable if they are clearly defined and surrounded by aerated lung.

CT, MRI: CT is the best currently available and reproducible method to measure lesions selected for response assessment. This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5mm or less. When CT scans have slice thickness greater than 5 mm, the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (e.g. for body scans).

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, laparoscopy: The utilization of these techniques for objective tumor evaluation is

not advised. However, they can be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess objective tumor response. If markers are initially above the upper normal limit, however, they must normalize for a patient to be considered in complete response. Because tumor markers are disease specific, instructions for their measurement should be incorporated into protocols on a disease specific basis. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer), have been published. In addition, the Gynecologic Cancer Intergroup has developed CA125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer.

Cytology, Histology: These techniques can be used to differentiate between PR and CR in rare cases if required by protocol (for example, residual lesions in tumor types such as germ cell tumors, where known residual benign tumors can remain). When effusions are known to be a potential adverse effect of treatment (e.g. with certain taxane compounds or angiogenesis inhibitors), the cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment can be considered if the measurable tumor has met criteria for response or stable disease in order to differentiate between response (or stable disease) and progressive disease.

Response Criteria

Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions, determined by two separate observations conducted not less than 4 weeks apart. There can be no appearance of new lesions.

Partial Response (PR): At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD. There can be no appearance of new lesions.

Progressive Disease (PD): At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started, or the appearance of one or more new lesions.

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.

Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Response for this Category Also Requires:
CR	CR	No	CR	≥4 wks. confirmation
CR	Non-CR/SD	No	PR	≥4 wks. confirmation
PR	Non-PD	No	PR	
SD	Non-PD	No	SD	documented at least once ≥4 wks. from baseline
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD*	Yes or No	PD	
Any	Any	Yes	PD	

* In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.

Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration"*. Every effort should be made to document the objective progression even after discontinuation of treatment.

Note: If subjects respond to treatment and are able to have their disease resected, the patient's response will be assessed prior to the surgery.

Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that recurrent disease is objectively documented.

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started.

Progression-Free Survival

Progression-free survival (PFS) is defined as the duration of time from start of treatment to time of progression.

8.0 ADVERSE EVENTS

8.1 Experimental Therapy

For the most recent safety update, please refer to the current Investigator's Brochure.

8.2 Adverse Event Reporting Requirements

Data on adverse events will be collected from the time of the initial study drug administration through 100 days after the last dose of nivolumab. Any serious adverse event that occurs more than 100 days after the last study nivolumab dose and is considered related to the study must also be reported. Serious Adverse Events (SAEs) will continue to be followed until:

- Resolution or the symptoms or signs that constitute the serious adverse event return to baseline;
- There is satisfactory explanation other than the study agent nivolumab for the changes observed; or
- Death.

The investigator is responsible for the detection, documentation, grading and assignment of attribution of events meeting the criteria and definition of an AE or SAE. The definitions of AEs and SAEs are given below. It is the responsibility of the principal investigator to ensure that all staff involved in the trial is familiar with the content of this section.

Any medical condition or laboratory abnormality with an onset date before initial study nivolumab dose is considered to be pre-existing in nature. Any known pre-existing conditions that are ongoing at time of study entry should be considered medical history.

All events meeting the criteria and definition of an AE or SAE, as defined in Section 8.3, occurring from the initial nivolumab dose through 100 days following the last dose of nivolumab must be recorded as an adverse event in the patient's source documents and on the CRF regardless of frequency, severity (grade) or assessed relationship to the study treatment.

In addition to new events, any increase in the frequency or severity (i.e., toxicity grade) of a pre-existing condition that occurs after the patient begins study [treatment or intervention] is also considered an adverse event.

8.3 Definitions

8.3.1 Adverse Event

An adverse event (AE) is any untoward medical occurrence in a patient receiving study treatment and which does not necessarily have a causal relationship with this treatment. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an experimental intervention, whether or not related to the intervention.

Diagnostic and therapeutic non-invasive and invasive (i.e., surgical) procedures will not be reported as adverse events. However, the medical condition for which the procedure was performed must be reported if it meets the definition of an adverse event unless it is a pre-existing (prior to protocol treatment) condition.

- *Symptoms of the original or targeted disease are not to be considered adverse events for this study. The following symptoms are indicative of underlying oropharynx cancer and will not be reported as adverse events (unless the event is considered serious):*
    - *Pain, dysphagia, otalgia, odynophagia in the setting of clinical evidence of disease progression*

- *Abnormal laboratory values or test results constitute adverse events if they induce clinical signs or symptoms or require therapy. They are to be captured under the signs, symptoms or diagnoses associated with them.*

8.3.2 Serious Adverse Event

An adverse event is considered "serious" if, in the view of either the investigator [sponsor (UNIVERSITY OF MICHIGAN)"], it results in any of the following outcomes:

- Death
  If death results from (progression of) the disease, the disease should be reported as event (SAE) itself.

- A life-threatening adverse event
  An adverse even is considered 'life-threatening' if, in the view of either the investigator [or sponsor], its occurrence places the patient or subject at immediate risk of death. It does not include an adverse event that, had it occurred in a more severe form, might have caused death.

- Inpatient hospitalization or prolongation of existing hospitalization for $\geq$ 24 hours.

- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions

- A congenital anomaly/birth defect

- Important medical event
  Any event that may not result in death, be life-threatening, or require hospitalization may be considered serious when, based upon appropriate medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in this definition of "Serious Adverse Event". Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home; convulsions that do not result in inpatient hospitalization or the development of drug dependency or drug abuse.

Previously planned (prior to signing the informed consent form) surgeries should not be reported as SAEs unless the underlying medical condition has worsened during the course of the study. Preplanned hospitalizations or procedures for preexisting conditions that are already recorded in the patient's medical history at the time of study enrollment should not be considered SAEs. Hospitalization or prolongation of hospitalization without a precipitating clinical AE (for example, for the administration of study therapy or other protocol-required procedure) should not be considered SAEs. However, if the preexisting condition worsened

during the course of the study, it should be reported as an SAE.

8.3.3 Expected Adverse Events

An adverse event (AE) is considered "expected" if:

- For approved and marketed drugs or devices, those adverse events are described in the approved Package Insert (Label).
- For investigational new drugs or devices, those adverse events are described in the FDA Investigator's Brochure.
- In clinical research studies, information on expected adverse events is also summarized in the protocol and in the consent document. See section 9.1 for the list of expected adverse events related to the drug under study.

8.3.4 Unexpected Adverse Event

An adverse event (AE) is considered "unexpected" if it is not described in the Package Insert, Investigator's Brochure, in published medical literature, in the protocol, or in the informed consent document.

8.4 Adverse Event Characteristics

8.4.1 CTCAE Term

AE description and grade: The descriptions and grading scales found in the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be down loaded from the CTEP web site. (http://ctep.cancer.gov)

8.4.2 Attribution of the AE

The investigator or co-investigator is responsible for assignment of attribution.
Definite – The AE *is clearly related* to the study [treatment/intervention].
Probable – The AE *is likely related* to the study [treatment/intervention].
Possible – The AE *may be related* to the study [treatment/intervention].
Unlikely – The AE *is doubtfully related* to the study [treatment/intervention].
Unrelated – The AE *is clearly NOT related* to the study [treatment/intervention].

8.5 Serious Adverse Event Reporting Guidelines

8.5.1 The Principal Investigator must be notified within 2 business day of study team's knowledge of any event meeting the criteria and definition of a serious adverse event, regardless of

attribution, occurring during the study or within 100 days of the last administration of the study related [treatment/intervention].

8.5.2 The investigator must report all events meeting the criteria and definition of a serious adverse event to the local IRB per current institutional guidelines. When applicable, the CTSU Serious Adverse Event form will be used.

- Contact information for study PI: Michelle Mierzwa, 734-936-4300 phone, mmierzwa@med.umich.edu.
- For IND/IDE trials: The study sponsor will be responsible for notifying the Food and Drug Administration (FDA) of any unexpected fatal or life-threatening suspected adverse reaction as soon as possible, but in no case later than 7 calendar days after the sponsor's initial receipt of the information. Unexpected suspected serious adverse reactions that are not fatal or life threatening need to be reported to the FDA as soon as possible, but in no case later than 15 calendar days after the sponsor's initial receipt of the information. In addition, the sponsor must notify FDA and all participating investigators in an Investigational New Drug (IND) safety report of potential serious risks, from clinical trials or any other source, as soon as possible, but in no case later than 15 calendar days after the sponsor determines that the information qualifies for reporting.

8.6 Routine Reporting

All other adverse events- such as those that are expected, or are unlikely or definitely not related to the study participation- are to be reported annually as part of regular data submission.

8.7 Reporting of Unanticipated Problems

There are types of incidents, experiences and outcomes that occur during the conduct of human subjects research that represent unanticipated problems but are not considered adverse events. For example, some unanticipated problems involve social or economic harm instead of the physical or psychological harm associated with adverse events. In other cases, unanticipated problems place subjects or others at increased risk of harm, but no harm occurs.

Upon becoming aware of any incident, experience, or outcome (not related to an adverse event) that may represent an unanticipated problem, the investigator should assess whether the incident, experience, or outcome represents an unanticipated problem. The incident, experience or outcomes is considered unanticipated if it meets all of the following criteria:

1. Unexpected (in terms of nature, severity, or frequency);
2. Related or possibly related to participation in the research;
3. Suggests that the research places subjects or others at a greater risk of harm than was previously known or recognized.

If the investigator determines that the incident, experience, or outcome represents an unanticipated problem, the investigator must report it to the IRB -per current institutional guidelines.

8.8 AE and SAE reporting to Bristol-Myers Squibb (in addition to institutional requirements)

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- 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.

Medwatch SAE form should be used to report SAEs to BMS as well as UM.as to the UM IRB and the FDA.

- The MedWatch form is available at: MedWatch 3500 Form.
- Worldwide.Safety@bms.com
- Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
- In addition to the Sponsor Investigator's responsibility to report events to their local IRB, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours \ 1 Business Day of becoming aware of the event. SAEs must be recorded on MedWatch.

Pregnancies must be reported and submitted to BMS on any of the following form(s):
1. MedWatch or, CIOMS or
2. BMS Pregnancy Surveillance Form or,
3. Approved site SAE form

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

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 \ 1 Business Day to BMS using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

9.0 Drug Information: Nivolumab

Nivolumab (also referred to as BMS-936558, MDX1106, or ONO-4538) is a human monoclonal antibody (HuMAb; immunoglobulin G4 [IgG4]-S228P) that targets the programmed death-1 (PD-1) cluster of differentiation 279 (CD279) cell surface membrane receptor. PD-1 is a negative regulatory molecule expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligands 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens. Nivolumab is expressed in Chinese hamster ovary (CHO) cells and is produced using standard mammalian cell cultivation and chromatographic purification technologies. The clinical study product is a sterile solution for parenteral administration.

Pharmacokinetics (adapted from Nivolumab IB Version 17.0, 6/27/2018)

The PK of nivolumab was studied in subjects with cancer over a dose range of 0.1 to 20 mg/kg administered as a single dose or as multiple doses of nivolumab every 2 or 3 weeks. Nivolumab clearance (CL) decreases over time, with a mean maximal reduction (% coefficient of variation [CV%]) from baseline values of approximately 24.5% (47.6%) resulting in a geometric mean steady state clearance (CLss) (CV%) of 8.2 mL/h (53.9%); the decrease in CLss is not considered clinically relevant. The geometric mean volume of distribution at steady state (Vss) was 6.8 L (27.3%), and geometric mean elimination half-life (t1/2) was 25 days (77.5%). Steady-state concentrations of nivolumab were reached by 12 weeks when administered at 3 mg/kg Q2W, and systemic accumulation was approximately 3.7-fold. The exposure to nivolumab increased dose proportionally over the dose range of 0.1 to 10 mg/kg administered every 2 weeks. Additionally, nivolumab has a low potential for drug-drug interactions. The clearance of nivolumab increased with increasing body weight. The PPK analysis suggested that the following factors had no clinically important effect on the CL of nivolumab: age (29 to 87 years), gender, race, baseline LDH, PD-L1 status, solid tumor type, baseline tumor size, and hepatic impairment.

Although ECOG status, baseline glomerular filtration rate (GFR), albumin, and body weight had an effect on nivolumab CL, the effect was not clinically meaningful. PPK analysis suggest that nivolumab CL in subjects with cHL was approximately 32% lower relative to subjects with NSCLC; however, the lower CL in cHL subjects was not considered to be clinically relevant as nivolumab exposure was not a significant predictor for safety risks for these patients.

PPK and exposure response analyses have been performed to support use of nivolumab 240 mg Q2W, 360 mg Q3W, and 480 mg Q4W dosing regimens in subjects with cancer in addition to the 3 mg/kg Q2W regimen. A flat dose of nivolumab 240 mg Q2W was selected since it is identical to a dose of 3 mg/kg for subjects weighing 80 kg, the observed median body weight in nivolumab- treated cancer patients, while the nivolumab 360 mg Q3W and 480 mg Q4W regimens allow flexibility of dosing with less frequent visits and in combination with other agents using alternative dosing schedules to Q2W. Using a PPK model, the overall distributions of nivolumab exposures (Cavgss, Cminss, Cmaxss, and Cmin1) are comparable after treatment with either nivolumab 3 mg/kg or 240 mg Q2W. Following nivolumab 360 mg Q3W and 480 mg Q4W, Cavgss are expected to be similar to those

following nivolumab 3 mg/kg or 240 mg Q2W, while Cminss are predicted to be 6% and ~16% lower, respectively, and are not considered to be clinically relevant. Following nivolumab 360 mg Q3W and 480 mg Q4W, Cmaxss are predicted to be approximately ~23% and ~43% greater, respectively, relative to that following nivolumab 3 mg/kg Q2W dosing. However, the range of nivolumab exposures (median and 90% prediction intervals) following administration of 240 mg flat Q2W, 360 mg Q3W, and 480 mg Q4W regimens across the 35 to 160 kg weight range are predicted to be maintained well below the corresponding exposures observed with the well tolerated 10 mg/kg nivolumab Q2W dosing regimen.

The PK of single-dose nivolumab monotherapy in subjects with sepsis is under evaluation; however, no data are currently available.

Drug Accountability

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the inventory and disposition of the investigational drug nivolumab. The drug accountability records will capture drug receipt, drug dispensing, drug return and final disposition.

Return/Retention of Drug
All drug destruction will be performed on site per UM institutional guidelines.

10.0 Correlative Studies

Collection and banking of blood samples for correlative studies (genetic testing) is optional per the subject.

10.1 Circulating tumor DNA (ctDNA) and tumor exosomes

Hypothesis 1*:* Recurrent cancer in HPV positive OPSCC can be detected in serum biospecimens collected at routine interval time points and will identify tumor recurrence earlier than clinical exam.

Correlative Justification

Patients with high risk HPV+ OPSCC are at risk for treatment failure, thus careful monitoring during treatment and in the post-treatment period is of extreme importance. The measurement of serum circulating free (cf)DNA and antitumor antibodies as a biomarker for recurrence may be an important, noninvasive method to detect treatment failures. We have previously examined serum antitumor antibodies (E6 and E7) in a longitudinal sample of patients who were treated under UMCC 2002-0221. Our preliminary data indicate that patients who have decreased clearance of E6/E7 antibody from their baseline measurement are at risk for disease recurrence. Finally, we have funding to perform targeted next generation sequencing on the primary tumor specimens from all patients enrolling in this trial, which can be used to prioritize evaluable somatic mutations in cfDNA from both the blood of each patient for targeted sequencing studies (Hypothesis 1). Therefore, our goal is to collect longitudinal samples of serum as a part of our trial to determine if serum biomarkers can predict recurrence in HPV+ OPSCC. Our hypothesis is that *serum biospecimens collected at routine interval time points will identify tumor recurrence earlier than clinical exam.*

ctDNA/Exosome/ImmuneSample Collection

We plan to collect and bank serial serum samples until 24 months from diagnosis. These samples are obtained at baseline, weekly during chemoradiation and at 3, 6, 12, 24 months post-therapy (see Schedule of events). Samples will be banked for planned analysis in the Brenner/Walline/Zhou labs.

Blood Samples

Patient's blood will be drawn at baseline, weekly during treatment, and at 4 wks, 3 mo, 6mo, and 12 months post-therapy as part of their routine follow up appointments. At baseline, two heparinized green top 6 mL tubes and two Paxgene blood collection tubes will be drawn. At each subsequent time points, only two Paxgene tubes will be drawn. Sample tubes will be provided by Brenner Lab. We will extract measure cfDNA from serum samples using the QIAamp Circulating Nucleic Acid Kit according to manufacturer instructions, cfDNA will be sequenced according to standard protocol in the Brenner lab. We will perform functional immunophenotyping by flow cytometry to assess the consequence of therapy on the circulating hematopoietic compartment

Sample Transportation

Whenever as specimen has been obtained (i.e. after a blood draw), the designee will transport the sample directly to the Brenner laboratory.

Tumor exosome analysis

Tumor extracellular vesicles (TEV) will be isolated from pre-treatment serum samples using an optimized spin column method and verified using TEM. For each sample isolation, DNA, RNA, and microRNA (miRNA) will be extracted from tumor EV fractions and fluorometrically quantitated. DNA will be assessed for presence and type of high-risk HPV using a highly sensitive multiplex PCR-MassArray strategy. MiRNA will be reverse-transcribed and expression of cancer relevant miRNAs will be measured using a validated qRT-PCR miRNA array customized for HNSCC. The miRNA panel includes biomarkers reported to have changes in expression associated with prognosis, radiation response, and survival. We will serially assess tumor-associated DNA and miRNA from tumor EVs in post-treatment patient liquid biopsies for the duration of patient follow-up to identify changes associated with response to treatment, cancer progression, or tumor free survival**.**

10.2 Serum Immunophenotyping

Hypothesis 2: Functional immunophenotyping during therapy will identify prognostic and predictive biomarkers in HPV positive OPSCC for response to immune checkpoint blockade in conjunction with chemoradiation.

Correlative Justification

Optimal serum biomarkers have not been developed for identifying the subset of patients who best respond to immune checkpoint blockade. The measurement of peripheral blood immune cell subsets as a biomarker for immune activation or inhibition may be an important, noninvasive prognostic biomarkers for patients who respond well to nivolumab. Patients with high risk HPV+ OPSCC are at risk for treatment failure, thus careful monitoring during treatment and in the post-treatment period is of extreme importance. Other groups have identified the ratio of T-cell invigoration to tumor burden has been associated with response to anti-PD-1 response in metastatic melanoma patients, highlighting the potential use of peripheral blood flow cytometry as a predictive biomarker for immune checkpoint blockade in other disease sites.

Functional Immunophenotyping

Peripheral Blood Mononuclear Cells (PBMCs) will be isolated from pre-treatment and mid-treatment whole blood samples using centrifugation to analyze the changes of different immune cell sub populations. Samples will be labeled with a panel of fluorescently labeled antibodies and stimulated with a leukocyte activation cocktail. Multiparametric flow cytometry analysis will include enumeration and functional evaluation of antigen presenting cell subsets, innate lymphoid cell subsets, myeloid derived suppressor cells, and T cell subsets (including NKT cells, CD8+ effector cells, and CD4+ helper cells). Cytokine secretion, proliferation, immunoinhibitory ligand expression, and transcription factor profile will be quantified by flow cytometry in T cell subsets.

10.3 DCE-MRI

Hypothesis: Changes in BV and apparent ADC seen on DCE-MRI between pre-treatment and mid-therapy will be significantly inversely correlated with changes in the metabolic tumor volume (MTV).

Methods:
The MRI scan will be performed in the exact patient position used for the simulation CT, including the same head rest and mask used for simulation. The MRI scanner installed recently at the UM Department of Radiation Oncology will be used for imaging. It has a large bore which facilitates imaging using these devices. Images will include FLAIR T2-weighted imaging, pre contrast T1-weighted imaging, diffusion weighted imaging, T1-weighted dynamic contrast enhancement imaging with single-bolus intravenous injection of Gd-DTPA, and post Gd-DTPA T1-weighted imaging. All images will be obtained with multiple-slices or 3D to cover the whole tumor volume. The scan time will be estimated to be one hour.

Identification of Subvolumes of the Tumor
Global-initiated regularized local fuzzy clustering (GIRLFC) is a method that is designed to first globally initiate training to identify fuzzy clusters of the physiological imaging parameters in the feature space, and then classify each tumor volume with local regularization to subvolumes according to the global feature clusters. This method is designed not only to identify the subvolumes of individual tumors based upon the heterogeneous distributions of physiological imaging parameters but also to be able to compare the classified subvolumes of the tumors across patients and over multiple time points. The fuzzy clustering method, specifically fuzzy C- means clustering (FCM), chosen in the GIRLFC method aims to deal with (1) intrinsic variations of the physiological parameters in the tumors, (2) partial volume effects due to the limited resolution of imaging sources, and (3) uncertainty due to noise.

Fuzzy C-Means clustering is a method of unsupervised learning to assign a set of observations to belong to subsets (clusters) with probability memberships. To partition a set of observations [x_k], e.g., image voxels, into c clusters, an objective function with local spatial regularization is to be minimized.

$$(1) \quad J_m = \sum_{i=1}^{c}\sum_{k=1}^{N} u_{ik}^{m}\left\|x_k - v_i\right\|^2 + \alpha\sum_{i=1}^{c}\sum_{k=1}^{N} u_{ik}^{m}\left\|\bar{x}_k - v_i\right\|^2$$

In Eq [1], the first term is a standard FCM cost function and the second term provides a spatial constraint to overcome the effect of image noise and to improve spatial connectivity. Here u_{ik} is a probabilistic (fuzzy) membership of observation x_k belonging to class i v_i is a prototype vector of class i, x_k is a mean or median value of neighbors of voxel k, m defines fuzziness of the membership, and α is a weighting factor of spatial constraints. A 2D or 3D kennel, depending upon image resolution, can be used to define neighbors of each voxel for spatial constraint. Solutions that minimize the

$$u_{ik} = \frac{\left(\left\|x_k - v_i\right\|^2 + \alpha\left\|\bar{x}_k - v_i\right\|^2\right)^{-\frac{1}{(m-1)}}}{\sum_{j=1}^{c}\left(\left\|x_k - v_j\right\|^2 + \alpha\left\|\bar{x}_k - v_j\right\|^2\right)^{-\frac{1}{(m-1)}}} \quad \text{and} \quad v_i = \frac{\sum_{k=1}^{n} u_{ik}^{m}(x_k + \alpha\bar{x}_k)}{(1+\alpha)\sum_{k=1}^{n} u_{ik}^{m}} \qquad (2)$$

objective function of Eq [1] are given by:

which are solved iteratively until reaching a stopping criterion. The values for m and α are usually determined empirically. The analysis can be applied to either single- or multiple- component parameters.

In order to evaluate longitudinal changes in physiological imaging parameters of interest in the tumor, first a set of data is used as training data to determine definitions of clusters (prototype vectors and relationships between fuzzy memberships and observations), and then the remaining sets of data are partitioned according to the class definitions of training data. To avoid a bias from large tumors in training data, each of the tumor volumes is up-sampled or down-sampled to have an equal number of voxels contributing to the training data while maintaining the initial distribution of the physiological imaging parameters from the original into the re-sampled tumor. To do so, a histogram of the physiological imaging parameters of each tumor is generated, and re-sampled to create a new tumor volume with the same size. The re- created tumor volume, while preserving the original distribution (histogram) of the imaging parameters, cannot maintain the original spatial relationship between voxels, which is not critical for training data to determine prototype vectors of global clusters. To partition individual tumors in the second data set, fuzzy membership of each voxel of each tumor is classified using the prototype vectors found in analysis of the training data by Eq [2], where spatial constraint is used to improve spatial continuity. Finally, the highest probability of fuzzy membership of each voxel is used to assign the voxel to a discreet class. As a result, the tumor is partitioned into spatial subvolumes based upon the similarity of the physiological parameters of interest. The

temporal changes in partitioned subvolumes of the tumor are evaluated for their association with outcomes.

To evaluate this method to identify significant subvolumes of the tumor related to outcomes, we will apply the method to BV and BF images derived from DCE MRI of patients with advanced head and neck cancer.

Diffusion-weighted MRI

A diffusion weighted, single shot, spin-echo, echo planar imaging (EPI) series with diffusion sensitization will be constructed along three orthogonal directions, with the diffusion-weighted images (DWI) contributing approximately two minutes of scan time to the MRI. The product of the three orthogonal DW images exhibits strong sensitivity to diffusion but without sensitivity to the structural directionality of the tissues. This isotropic feature is crucial to follow serial changes in water diffusion without confounding effects due to tissue orientation. ADC maps will be calculated

$$ADC = \ln\left[\frac{S_{b_0}}{S_{b_1}}\right] \Big/ (b_1 - b_0) \qquad (1)$$

from the DW images as follows:
where S is the DW image at b-values of b_0=0 and b_1=800 s/mm^2.

Subsequent to image registration, contours will be manually drawn over tumors as delineated on T_2-weighted, T_1-weighted or contrast-enhanced images. From the volume-of-interest (VOI) tumor volume and mean ADC will be assessed pre- and 2 weeks post-treatment initiation. Subsequent to contouring the tumors, a geometric warping interpolant, i.e. thin plate spline, algorithm will be used to map (warp) the tumor volumes from interval exams onto the tumor volumes from pre-therapy b_0 DW images (reference dataset). The Parametric Response Map of ADC (PRM_{ADC}) will be determined by first calculating the difference between the ADC values (ΔADC = mid-treatment ADC – pre-treatment ADC) for each voxel within the tumor pre- treatment and at week 2 post-treatment initiation. Voxels yielding ΔADC greater than a predetermined threshold set to 25 ADC units [= x 10^{-5} mm^2/s] will be designated as significantly increased. Voxels whose ADC values significantly decreased by more than 25 x 10^{-5} mm^2/s (i.e. ΔADC < -25 x 10^{-5} mm^2/s) will be designated as significantly increased, and the rest of the voxels as non-changed. The volume fractions within the tumor as determined by PRM_{ADC} will be denoted by PRM_{ADC+} (increased ADC), PRM_{ADC-} (decreased ADC), and PRM_{ADC0} (unchanged ADC). PRM thresholds of significant change will be empirically assessed over a range of ΔADCs (0 to 70). PRM_{ADC+} with a threshold of ±25 ADC units provided the best correlation with tumor control in our previous study (Galban et al) and will be tested in the current study.

Risks in MRI

Our MRI protocol has risks and discomforts similar to clinical MRI with intravenous injection of a

contrast agent. Subjects run the risk of claustrophobia when they are lying inside the MRI scanner. They may also feel uncomfortable because of the loud noises made by the machines and the physical sensations they may feel during the process. Subjects are also exposed to some risk because of the injected contrast agent, gadolinium-DTPA, which may cause headache, nausea, and local burning. Because of the use of the contract agent, all female subjects of child- bearing potential will be required to use adequate birth control. Patients who have implanted or internalized metallic objects cannot participate in this research. Recent FDA guideline indicates there is an association between exposure to gadolinium and the development of Nephrogenic Fibrosing Dermopathy (NFD) (also known as Nephrogenic Systemic Fibrosis (NSF)) in 3-5% of the patients with advanced renal failure. We will follow the Institutional Standard Practice guidelines, which is based upon the FDA guideline, to screen the patients with renal disease, dysfunction, and dialysis for this study.

10.4 FDG-PET/CT Imaging

All PET exams should contain 3 trans-axial whole body series, attenuated and non-attenuated, corrected PET and CT images;
The emission PET scan will begin 60 +/- 10 minutes after injection;
The patient will empty his/her bladder immediately before the acquisition of images;
The patient will be positioned on the flat table imaging couch in treatment planning position.
The transmission scan should be a low-dose CT scan without IV contrast (oral contrast is permitted per institutional procedure) for the PET/CT, done before the emission imaging. The transmission scan type, length, etc., should exactly match that used in the calibration and qualification procedure.
An emission scan from the skull base to thighs will be performed. The number of bed positions will be determined by the patient's height. The acquisition time per bed position will be 2 minutes. Typical parameters are 6-8 bed positions, leading to an emission scan time of 12-16 minutes.

Expected Adverse Events Related to FDG-PET Imaging

Adverse events (AEs) from FDG-PET/CT are exceedingly rare. If an AE from functional imaging is to occur, it would most likely be related to the intravenous catheter infusion site, consisting of erythema and discomfort from the IV. An allergic reaction to the FDG is possible as well. The most expected AEs from a PET scan include discomfort and claustrophobia.

Expected Adverse Events from the FDG Injection:

- Bruising;
- Bleeding;
- Phlebitis;
- Infection at the site of injection;
- Allergic-type or other adverse reaction to FDG.

Expected Adverse Events from the PET Scan:

- Discomfort;
- Claustrophobia.

Expected Adverse Events from the CT Scan:

- Discomfort;

- Claustrophobia;
- Malfunction of implanted electronic medical devices, e.g., pacemakers, neurostimulators, insulin pumps.

Estimation of Radiation Doses Due to FDG-PET/CT

Reports of radiation doses from PET/CT scanning have varied in the literature. These differences can be attributed to different methods of attenuation correction, the timing of the scan, the area of the body being evaluated, and the radiopharmaceutical being investigated. This research study involves radiation exposure from 1 research FDG-PET/CT scan for patients. The radiation exposure from each FDG-PET/CT scan is equal to a uniform whole-body exposure of approximately 14 mSv, with approximately 11 mSv from the injected radioactive FDG and 3 mSv from the CT component.

11.0 Statistical Considerations and Justification of Sample Size

11.1 Description and Justification of Design

The sample size of 40 patients is justified with respect to the primary aim of detecting improved PFS. We will estimate PFS over time using the Kaplan-Meier (KM) method. The primary study endpoint is PFS 2 years after treatment which will be also be estimated using the KM method. A log-log transformation of the survival function will be used to calculate a lower 90% confidence limit. Estimated PFS at 2 years was 68% in 125 similar (stage III) historical control patients treated with standard therapy at UM between the years of 2010-2015. If the true PFS at 2 years for this treatment combination in this patient population is 85%, then a sample size of 40 enrolled patients provides at least 80% power to rule out 2 year PFS values of 70% or less. This calculation assumes 10% of patients will be lost to follow-up by the 2 year assessment point and that other patients will either be assessed for progression at 2 years or will have progressed or died prior to 2 years. We note that the power from a log-rank test comparing the PFS curve for these patients to that of the historical control actual patient level data is only slightly higher (~85% depending on assumptions regarding survival distribution and follow-up). UM retrospective data also demonstrates 10% risk of death within 1 year of RT completion and 0% deaths due to toxicity.

Based on previous experience, 30 eligible patients per year will be seen in Radiation Oncology at UM. Assuming successful enrollment of 1/2 of these patients we expect to enroll 40 patients in approximately 2.5-3 years. The primary analysis will be based on an Intent to treat population and all enrolled subjects who begin protocol treatment will be included in the primary analysis including those who may have discontinued treatment due to toxicity or early disease progression.

11.2 Analysis Plan

The primary study endpoint is the PFS at 2 years which will be estimated using the KM method. To test the null hypothesis that the true rate is less than or equal to 70% we will compare the lower bound of a 1-sided 90% confidence limit to 70%. The confidence limits for the KM estimates will be calculated using a log-log transformation. Patients with no observed progression or death will be censored at the last date they were assessed for loco-regional or distant progression. We note that we also have access to patient level data for historical control patients treated without Nivolumab. These data will allow us

to perform secondary analyses directly comparing a range of outcomes between protocol patients and historical control patients with for example, propensity score matching.

Secondary aims include estimation of toxicity, patterns of failure, freedom from local and distant progression and overall survival. To characterize patterns of failure we will summarize at fixed timepoints, the proportion of patients who progressed in any location and whether the first progression was local, regional, distant or in multiple locations. Overall survival will be estimated using the Kaplan-Meier methods with associated 90% confidence intervals. Freedom from local/regional or distant progression will be estimated using cumulative incidence functions with death prior to progression as a competing risk. Toxicity outcomes will be estimated as proportions for patients with available toxicity data at 3, 6 12 and 24 months. They will also be estimated as the proportion of all treated patients through cumulative incidence estimates with death or disease progression treated as competing risks and censoring for patients lost to FU. Quality of Life (QOL) outcomes and swallowing study results will be summarized descriptively by timepoint. If there is substantial missingness in the QOL outcomes we will assess for informative missingness by comparing earlier QOL scores and change in earlier QOL scores between patients missing QOL at later timepoints (e.g. 1 or 2 years). Another secondary aim is to correlate metabolic image uptake data on mid-treatment FDG-PET scan with standard 12 week post-treatment PET-CT. This will be done both at the patient level for summary measures and also spatially within a patient.

Exploratory endpoints include cell free DNA (cfDNA) characterization, tumor exosome characterization and serum immune phenotype characterization by flow cytometry pre-treatment, weekly during treatment, post-treatment and at recurrence. Exploratory analyses primarily involve summarizing these endpoints which will be done using frequency tables for categorical endpoints and summary statistics such as mean, standard deviation and various percentiles for continuously distributed endpoints. A few of the exploratory aims involve assessing the relationship between the exploratory endpoints and clinical outcomes. These will be done both descriptively using the appropriate correlation metric, graphically and also in the context of a regression model for the clinical outcome (e.g. Cox model for survival type outcomes) with the exploratory endpoint included as a covariate.

11.3 Stopping Rules

With standard treatment, fewer than 10% of patients are expected to experience delays or dose reductions for RT or chemo. An interim analysis will be performed after 20 patients have been enrolled. We will monitor the number of patients for whom this occurs to assess for the possibility that the addition of nivolumab significantly increases this proportion, the table below provides the specific stopping boundaries. For example, if 2 or more of the first 5 patients experience either delays or dose reductions in chemo or RT, enrollment will be halted to allow thorough review of the data.

Enrollment will be halted to allow thorough review as per the following:

Number with dose delay / reduction	Number treated
2	3
2	4
2	5

3	6
3	7
4	8
4	9
4	10
4	11
5	12
5	13
6	14

Enrollment will be halted to allow thorough review of safety data if at any time prior to the planned interim safety analysis >5 patients experience dose delays or reductions in chemotherapy or RT due to toxicity.

12.0 Data and Safety Monitoring

This study will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan.

The study team will provide continuous review of the data and patient safety and meet monthly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness. At these regular meetings, the protocol specific Data and Safety Monitoring Report form will be completed and signed by the Principal Investigator or by one of the co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Rogel Cancer Center Data and Safety Monitoring Committee (DSMC) on a monthly basis for independent review.

13.0 Clinical Monitoring Procedure

Clinical Monitoring Plan
This trial will be monitored in accordance with the NCI approved University of Michigan Rogel Cancer Center Data and Safety Monitoring Plan by the Oncology Clinical Trial Support Unit (O-CTSU).

Record Retention

To enable evaluations and/or audits from regulatory authorities, the investigator agrees to keep records, including the identity of all participating subjects (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent forms, copies of all CRFs, serious adverse event forms, source documents, and detailed records of treatment disposition. The records should be retained by the investigator according to Standard Practice Guidelines.

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15.0 Appendix A

GI Adverse Event Management Algorithm

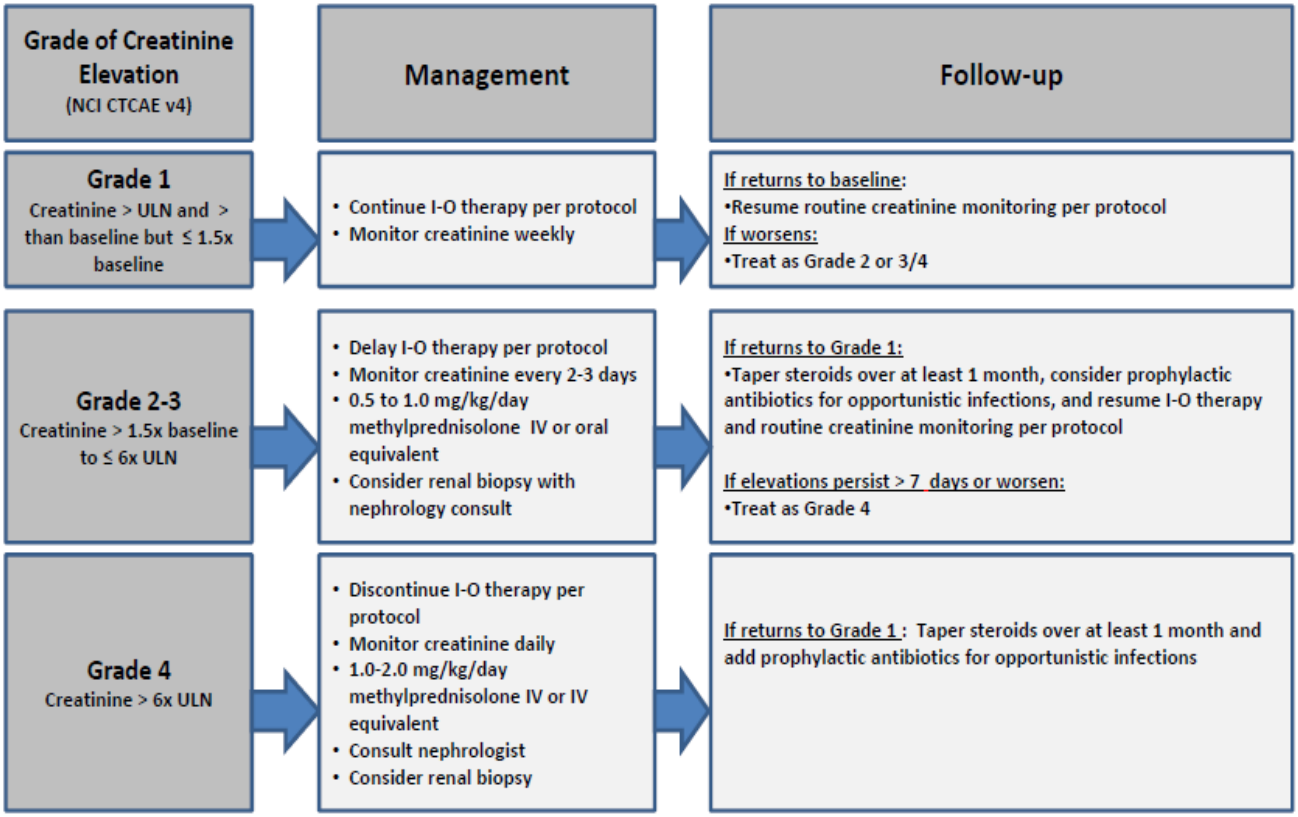
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.

Grade of Diarrhea/ Colitis (NCI CTCAE v4)	Management	Follow-up
Grade 1 Diarrhea:< 4 stools/day over baseline; Colitis: asymptomatic	• Continue I-O therapy per protocol • Symptomatic treatment	• Close monitoring for worsening symptoms. • Educate patient to report worsening immediately If worsens: • Treat as Grade 2 or 3/4
Grade 2 Diarrhea: 4-6 stools per day over baseline; IV fluids indicated <24 hrs; not interfering with ADL Colitis: abdominal pain; blood in stool	• Delay I-O therapy per protocol • Symptomatic treatment	If improves to grade 1: • Resume I-O therapy per protocol If persists > 5-7 days or recur: • 0.5-1.0 mg/kg/day methylprednisolone or oral equivalent • When symptoms improve to grade 1, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol. If worsens or persists > 3-5 days with oral steroids: • Treat as grade 3/4
Grade 3-4 Diarrhea (G3): ≥7 stools per day over baseline; incontinence; IV fluids ≥24 hrs; interfering with ADL Colitis (G3): severe abdominal pain, medical intervention indicated, peritoneal signs G4: life-threatening, perforation	• Discontinue I-O therapy per protocol • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections • Consider lower endoscopy	If improves: • Continue steroids until grade 1, then taper over at least 1 month If persists > 3-5 days, or recurs after improvement: • Add infliximab 5 mg/kg (if no contraindication). Note: Infliximab should not be used in cases of perforation or sepsis

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.

Renal Adverse Event Management Algorithm

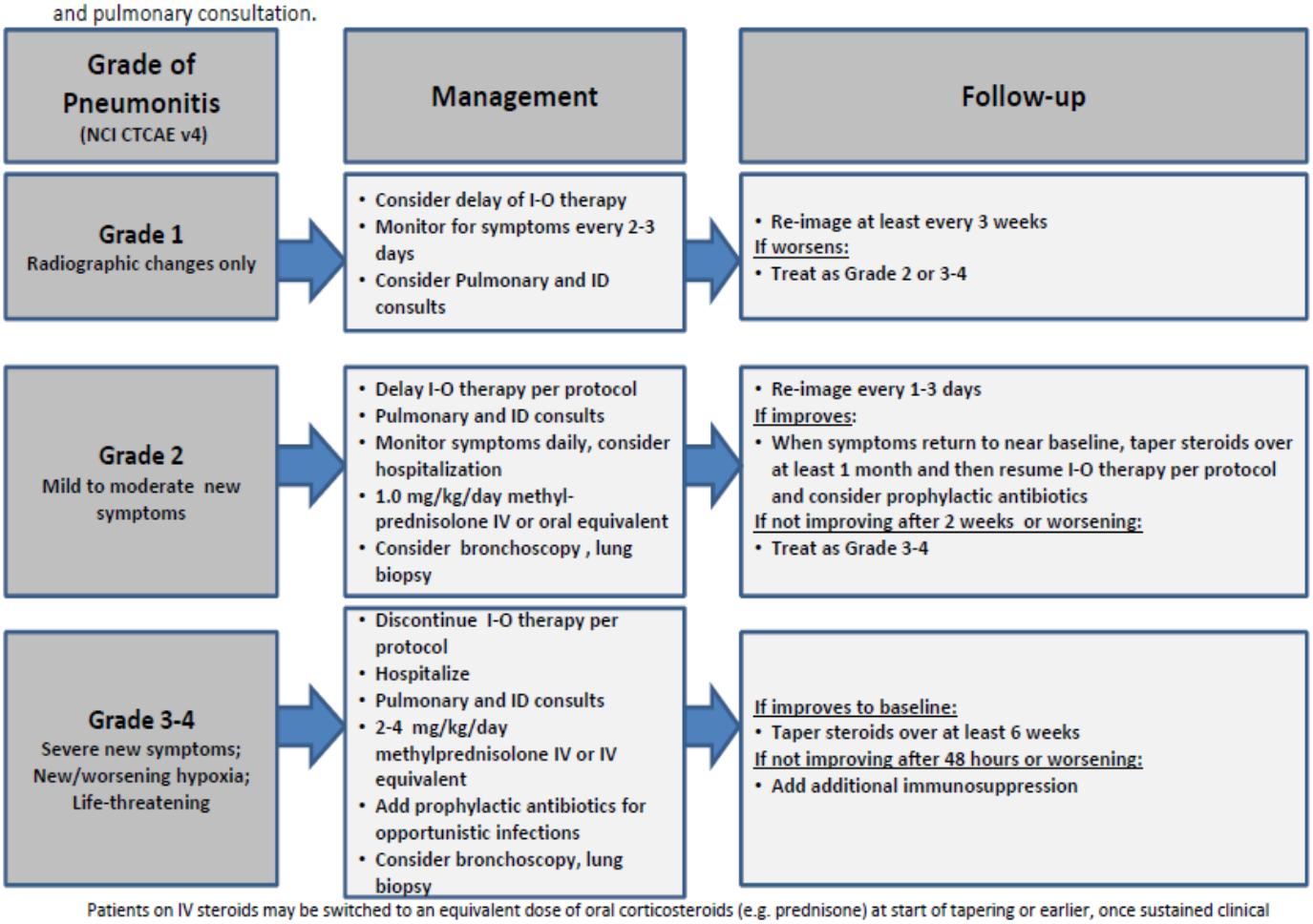
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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

Pulmonary Adverse Event Management Algorithm

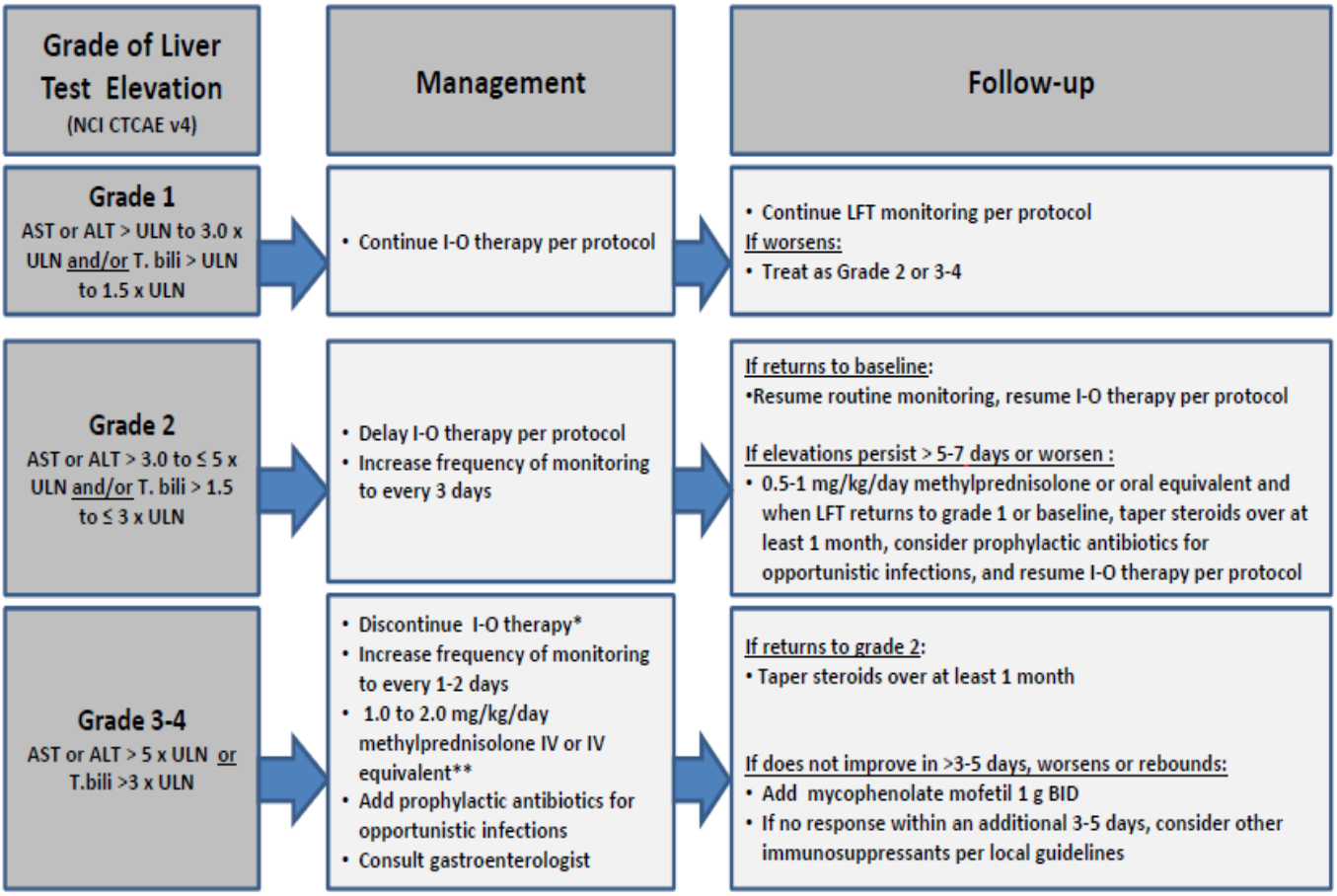
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Evaluate with imaging and pulmonary consultation.



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

Hepatic Adverse Event Management Algorithm

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



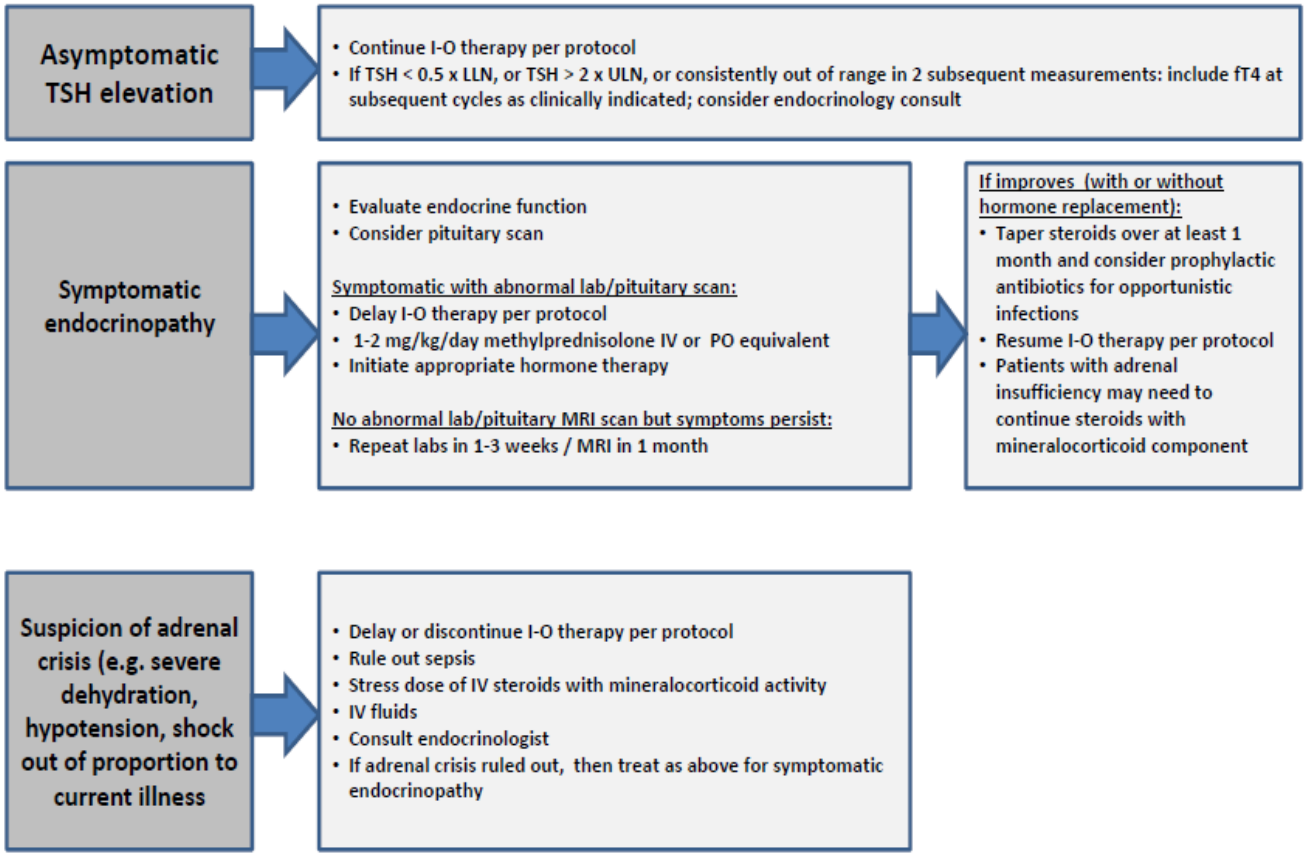
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

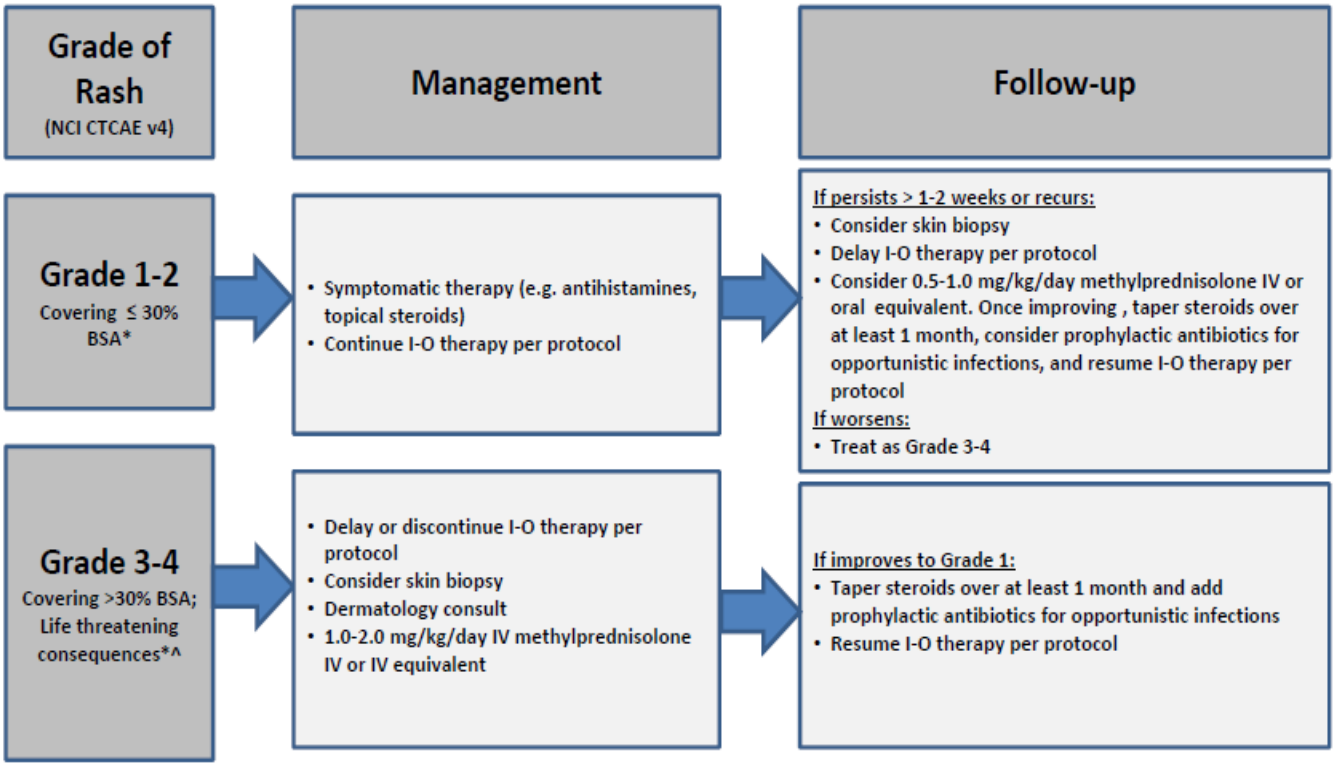
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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.

Grade of Neurological Toxicity (NCI CTCAE v4)	Management	Follow-up
Grade 1 Asymptomatic or mild symptoms; Intervention not indicated	• Continue I-O therapy per protocol	Continue to monitor the patient. If worsens: • Treat as Grade 2 or 3-4
Grade 2 Moderate symptoms; Limiting instrumental ADL	• Delay I-O therapy per protocol • Treat symptoms per local guidelines • Consider 0.5 to 1.0 mg/kg/day methylprednisolone IV or PO equivalent	If improves to baseline: •Resume I-O therapy per protocol when improved to baseline If worsens: • Treat as Grade 3-4
Grade 3-4 Severe symptoms; Limiting self-care ADL; Life-threatening	• Discontinue I-O therapy per protocol • Obtain neurology consult • Treat symptoms per local guidelines • 1.0-2.0 mg/kg/day IV methylprednisolone IV or IV equivalent • Add prophylactic antibiotics for opportunistic infections	If improves to Grade 2: • Taper steroids over at least 1 month If worsens or atypical presentation: • Consider IVIG or other immunosuppressive therapies per local guidelines

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

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16.0 Appendix B

Study Management During Public Health or Civil Emergency or Restrictions

Changes to protocol-required items were made to minimize or eliminate immediate hazards or to protect the life and well-being of research participants (e.g., to limit exposure to infectious pathogens).

These changes may be implemented and/or adapted without causing a deviation or considered minor deviations during a national emergency. HOWEVER, the usual protocol parameters must be reinstated when the emergency is over or whenever local authorities and policies permit.

1) When possible, visits may be conducted remotely using phone or video.
2) Physical exam and vital sign measurements may be missed if visits are conducted remotely.
3) Study-specific imaging can be as previously required, combining to make as few visits and encounters for the patient as possible. PET scans can be completed. It is possible that tests such as the videofluoroscopy may be deferred; see point #9 below.
4) Questionnaires can be mailed, faxed, or sent through the patient portal to the patient. These documents may be returned via mail, faxing, or bringing to the clinic on a subsequent appointment.
5) Saliva will not be collected per protocol clarification letter Adv00042400 (finalized in amendment to version 3.0).
6) Blood correlative collections will continue at baseline and during each weekly treatment visit. Samples in follow-up visits will be on a case-by-case basis and may be collected if there is another clinical lab appointment already required for that visit.
7) Clinical labs can be collected at local labs for follow-up visits.
8) Consent/re-consent can be performed over the phone/remotely or via SignNow, an FDA 21 Part 11 & HIPPA compliant tool offered through University of Michigan Health Information Technology Services (HITS).
9) When staff is not available to complete the videofluoroscopy tests, due to staffing changes and interruptions, these may be skipped and listed as deviations, or deferred.
10) It is permissible that baseline labs, dental evaluation, standard of care primary tumor specimen collection, and standard clinical imaging, to be done at local facilities, if needed.