Phase II Trial of Adjuvant De-Escalated Radiation + Concurrent and Adjuvant Nivolumab for Intermediate-High Risk P16+ Oropharynx Cancer

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Agents	IND#	Supply
nivolumab	141,230	Investigational

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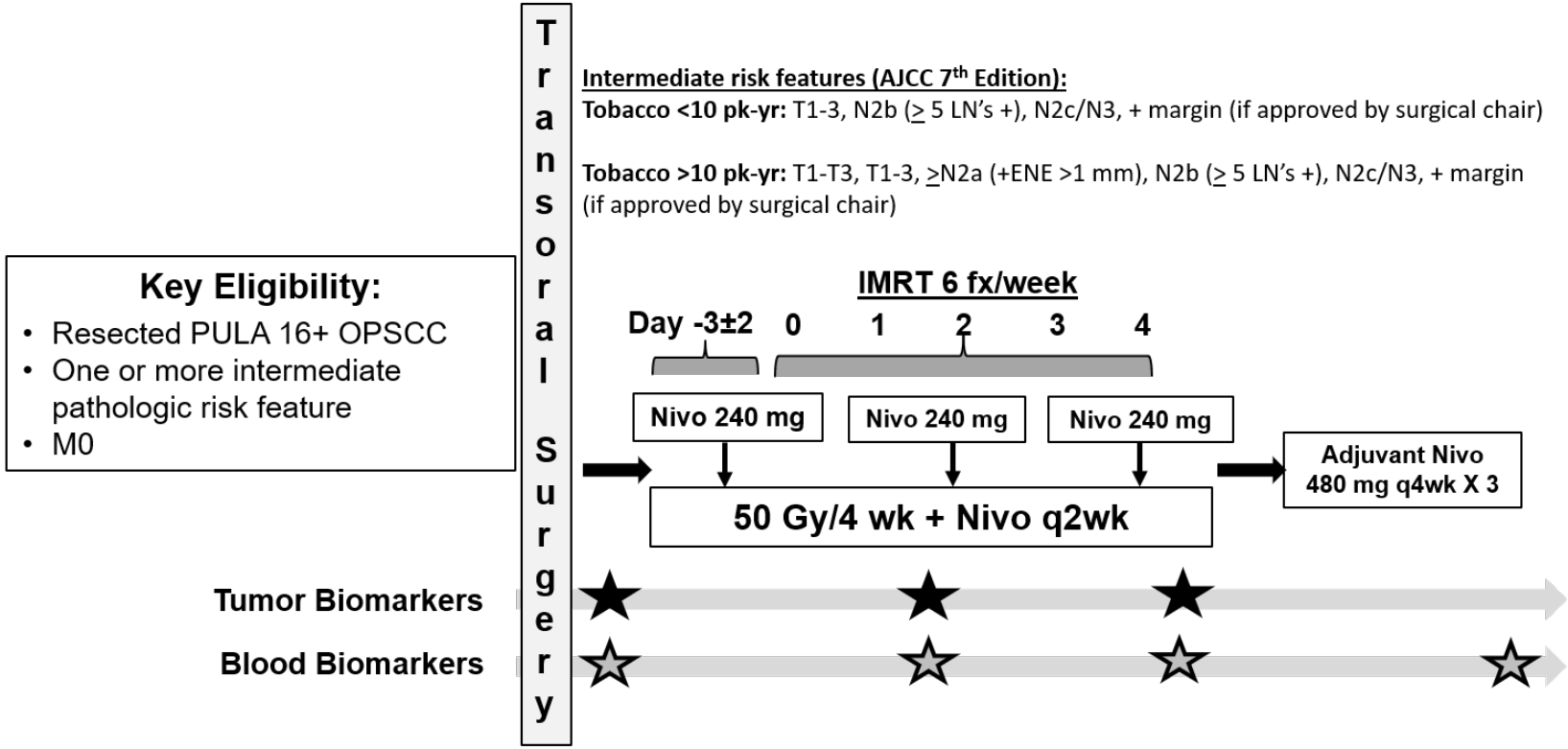
Phase II Trial of Adjuvant De-Escalated Radiation + Concurrent Nivolumab for Intermediate-Risk P16+ Oropharynx Cancer



Co-Primary endpoints: 2-year Disease-free survival, 1-year PEG dependence
Secondary endpoints: QOL, Distant metastatic control, locoregional control, overall survival
Paired tumor/TME/blood biomarkers

Nivolumab will be administered at 240 mg IV q2 weeks during radiotherapy, and at 480 mg IV q4 weeks for 6 doses after RT. Radiotherapy to receive IMRT to 50 Gy/2 Gy per fraction/6 fxs per week, with the first dose of nivolumab delivered at day -3 ± 2 days prior to RT. RT will be delivered daily for 4 days, with 2 fractions on day 5 per week. After 4 weeks, this will total 48Gy, with an additional day to reach 50Gy.

Eligibility Overview:

Inclusion (AJCC 7th Edition):

- P16+ squamous cell carcinoma of the oropharynx
- Tobacco <10 pack years (pk-yr): T0-3 plus any one of the following: >N2b (> 5 LN's +), N2c/N3, +ENE >1 mm, or + margin (if approved by surgical chair) OR
- Tobacco >10 pk-yr: T0-3 plus any one of the following: any N2, N3, +ENE >1 mm, or + margin (if approved by surgical chair)
- M0
- Age >18, gender neutral
- ECOG performance Status 0-1
- Patients must have undergone gross surgical removal with transoral surgery + neck dissection for p16+ OPC
- Patients undergoing tonsillectomy are eligible and do not require additional surgery if all gross disease removed
- Adequate hematologic, renal and hepatic function for cisplatin

Exclusion:

- P16-negative
- T4 primary
- T4, or ≤N1
- Gross residual disease after surgery
- Female patient lactating or pregnant
- Prior radiation or chemotherapy for head and neck cancer
- Prior immunotherapy agents
- Prior head and neck cancer treated < 5 years (surgery only)
- Unstable cardiac disease
- Patients with active/history of autoimmune, rheumatologic disease which may affect vital organ function or on immunosuppressive agents or systemic steroids for any medical condition
- Uncontrolled undercurrent illness, such as CHF, active infection
- Psychiatric illness or other social issues limiting compliance

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LIST OF ABBREVIATIONS AND DEFINITIONS	
Abbreviation	**Definition**
ACE	angiotensin converting enzyme
AE	adverse event
AHNS	American Head and Neck Society
AIDS	acquired immunodeficiency syndrome
ALC	absolute lymphocyte count
ALT	alanine transaminase
AST	aspartate transaminase
CMV	cytomegalovirus
CRT	chemoradiotherapy
CTEP-AERS	Cancer Therapy Evaluation Program Adverse Event Reporting System
CTV	clinical target volume
CVA	cerebrovascular accident
DFS	disease-free survival
DNA	deoxyribonucleic acid
DSMB	data safety monitoring board
DSMC	data safety monitoring committee
EBV	Epstein-Barr virus
ECOG	Eastern Cooperative Oncology Group
eCRF	electronic case report form
ENE	extranodal extension
EORTC	European Organisation for Research and Treatment of Cancer
ERT	external radiation therapy
FR	future risk
GI	gastrointestinal
GTV	gross tumor volume
Gy	gray (unit of ionizing radiation)
HBV	hepatitis B virus
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HNC	head and neck cancer
HNSCC	head and neck squamous cell carcinoma
HPV	human papillomavirus

HR	high risk
IHC	immunohistochemistry
IMRT	intensity modulated radiotherapy
IR	intermediate risk
IRRC	independent radiology review committee
ITIM	immunoreceptor tyrosine inhibitory motif
ITSM	immunoreceptor tyrosine-based switch motif
IVRS	interactive voice response system
LRC	locoregional control
mAb	monoclonal antibodies
MBS	modified barium swallow
MDSC	myeloid-derived suppressor cells
MEL	melanoma
MHC	major histocompatibility complex
MLR	mixed lymphocyte reaction
MOA	midline oral avoidance
mPFS	median progression-free survival
NSCLC	non-small cell lung cancer
OAR	organs at risk
OPC	oropharyngeal cancer
OPSCC	oropharyngeal squamous cell cancer
ORR	overall response rate
OS	overall survival
PBMC	peripheral blood mononuclear cells
PEG	percutaneous gastronomy
PFS	progression-free survival
PFSR	progression-free survival rate
PORT	postoperative radiotherapy
PRO	patient-reported outcomes
PS	performance status
PTV	planning target volume
PULA	previously untreated, locally advanced
QOL	quality of life
RT	radiotherapy

RTOG	Radiation Therapy Oncology Group
SAE	serious adverse event
sAg	surface antigen
SLP	speech language pathologist
SOP	standard operating procedure
TIA	transient ischemic attack
TLM	transoral laser CO_2 microsurgery
TME	tumor microenvironment
TORS	transoral robotic surgery
TOS	transoral surgery
TSH	thyroid stimulating hormone
ULN	upper limit of normal

1. Introduction

1.1 Study Disease

Head and neck cancer remains a significant cause of morbidity worldwide, with approximately 400,000 new cases per year. Squamous cell carcinoma is the most common histological type, accounting for >90% of head and neck tumors. At presentation, more than half of patients present with advanced locoregional disease.[1] Ongoing advances in multidisciplinary management of this complex and multi-varied disease process are resulting in improved function, organ preservation, quality of life and survival. Major developments include primary chemoradiotherapy (CRT) for unresectable disease with the goal of organ preservation, the addition of chemotherapy to adjuvant radiotherapy (RT) and improvement in surgical and radiation techniques.[2] A consistent result of these aggressive multi-modality approaches is improvement in local-regional control but the impact on the development of metastases is variable. Despite these advances, 50% of all patients recur either locally or at distant sites (30%).[2] A minority of patients will undergo successful surgical salvage of recurrent disease. While single institution series evaluating intensified CRT regimens suggest a shift in failure pattern to distant metastases, better control of local disease remains paramount to improve survival of patients with head and neck squamous cell carcinoma (HNSCC).[2]

1.2 HPV Positive Oropharynx Tumors

The incidence of base of tongue and tonsillar carcinomas has been increasing over the past decade, especially in individuals under the age of 45.[3] This change has been attributed to the increasing prevalence of human papillomavirus (HPV) infection in developed countries, the practice of oral sex and increasing number of sexual partners.[3] Interestingly, patients with HPV-positive SCC have shown better overall survival and higher cure rates as compared to those with HPV-negative SCC.[4] HPV is now recognized to play a role in the pathogenesis of HNSCC.[5] Both molecular and epidemiologic studies demonstrate that approximately 60% of oropharynx cancers, specifically of the lingual and palatine tonsils, are HPV associated.[5]

HPV16 driven Oropharyngeal Squamous Cell cancers (OPSCC) is now recognized as a rising global epidemic both in the USA and abroad, with expected peak in incidence by 2030.[1] Patients who develop HPV16+ oropharyngeal cancer (OPC) tend to be younger, never or former smokers, and primarily male. Nearly 70% of reported OPC cases in the USA are HPV16+OPC.[2] Current treatment standards are associated with a higher risk of significant debilitating short and long term side effects. The prognosis of HPV16+ OPSCC particularly with patients with < 10 pk-yr history of smoking is excellent, approaching 90% or better with a high probability of long-term survival, but with the optimal strategy yet to be defined. A retrospective analysis of RTOG 0129 survival outcomes after *standard Cisplatin and 70 Gy ERT exposed three risk groups (FR, IR, HR based on HPV,* smoking status and stage, setting the stage for new clinical risk-adaptive and de-escalation trials, (RTOG 1016, ECOG 3311, NRG HN002). The current 7th edition AJCC staging system is outdated and does not reflect risk stratification based on HPV. New recommendations to re-classify staging for HPV16 + OPC have been proposed by an international collaborative group for the 8th edition of AJCC recognizing favorable outcomes in this group. Patients previously classified as stage II-IV would now be stage II (T1-T2N2 or T3N0-N2).[3] I

High-risk HPV genotypes (i.e. 16, 18, and 31) are known to be tumorigenic in human epithelial tissues. The E6 and E7 viral oncoproteins of high-risk HPV promote tumor progression by inactivating the *TP53* and *Rb* tumor suppressor gene products, respectively.[6] These tumors appear to be clinically and molecularly distinct from HPV-negative tumors. HPV-positive tumors are more likely to arise from the oropharynx, exhibit poor differentiation and basaloid morphologic features, and present at a lower T stage than HPV-negative primaries.[5-9]

Recently, HPV-associated head and neck carcinoma, largely presenting in the oropharynx, has

been identified and appears to be rapidly increasing in incidence.[8,10] In the US, some two-thirds of patients with OPSCC have HPV-associated tumors. Hence, in 2010 approximately 4200 squamous cancers of the oropharynx caused by tobacco and alcohol and 8400 new HPV-associated oropharynx cancer presented for treatment. HPV-associated OPSCC typically present as smaller primary tumors than those caused by substance abuse. Because HPV-associated OPSCC more frequently present in a younger population and seem particularly responsive to treatment with a better overall survival,[11] attention has begun to focus reduction of treatment toxicity. In particular, attention has been focused on the development of late effects of CRT as the number of survivors have increased. While the organ-preservation CRT approach has become a standard of care,[12,13] there remain serious concerns about both short and long-term toxicity. Furthermore, the changing epidemiology of HPV-associated OPSCC has caused many to re-think this approach. Given the potential long-term sequelae of radiation therapy for a younger population,[14] an alternative treatment paradigm is needed. The clearly better prognosis of this group of patients supports re-evaluation of adjuvant treatment intensity and, in particular, the prognostic and predictive role of traditional pathologic biomarkers obtained at surgery.

Results from ECOG 2399 using induction chemotherapy with carboplatin and paclitaxel followed by CRT with Taxol/70Gy showed that HPV-positivity in OPC patients was associated with a significantly improved overall response to 2 cycles of paclitaxel/carboplatin induction chemotherapy (82% vs. 55%, p=0.01), as well as 2-yr PFS (85% vs. 50%, p=0.05) and overall survival (94% vs. 58%p=0.004) following weekly paclitaxel/RT.[15] Although acute toxicity was acceptable with this regimen, a substantial number of OPC patients have long-term consequences following CRT. In E2399, 49% of OPC patients had moderate to severe swallowing impairment 3 months following treatment, and 3% were still PEG dependent after 12 months. These results have generated interest in less toxic regimens for HPV-positive patients who experience substantial treatment side effects with contemporary CRT regimens.

In this study, 64% of OPC patients had HPV-positive tumors, as measured in-situ hybridization for the HPV subtype 16. The presence of HPV deoxyribonucleic acid (DNA) correlated well with p16 expression (kappa = 0.80; 95% CI, 0.73 to 0.87). Patients with HPV-positive tumors had significantly increased overall survival (OS) as well as PFS compared to patients with HPV-negative tumors. Furthermore, after adjusting for demographics, T stage, N stage, smoking, patients with HPV-positive OPC had a 58% reduction in the risk of death and a 51% reduction in risk of progression or death. Patients with HPV-negative tumors had a 25.1% reduction in OS at 3 (57.1% vs 82.4%) when compared to patients with HPV-positive tumors.[16] Local-regional relapse at 3 years was 21% higher in patients with HPV-negative tumors: 35.1% (95% CI: 26.4 - 43.8) versus 13.6% (95% CI: 8.9 - 18.3) for HPV-positive tumors ($p < 0.001$). These poor outcomes for HPV-negative patients occur despite the gradual trend toward increasing intensification of treatment with altered fractionation schema,[17] concurrent chemoradiation, [18,19] multi-drug induction chemotherapy,[20] and targeted molecular therapies.[21] For patients with HPV-negative tumors altering the method of radiation delivery and the dosing and/or types of concurrent chemotherapy is not sufficient to improve oncologic outcomes. Because HPV-associated head and neck cancers more frequently present in a younger population and seem particularly responsive to treatment with a better overall survival,[22] attention has focused on the subpopulation of > 10 pack-year smoking and N2-N3, whose prognosis is worse (60% - 70% 2-year progression-free survival (PFS)) as well as HPV-negative head and neck cancer (HNC) patients, whose clinical outcome has not improved despite intensification of standard chemotherapeutic agents and combinations. Thus, novel therapeutic approaches, such as immune modulation and blockade of suppressive immune cells and signals, are needed in clinical evaluation.

1.3 Role of Surgery in Head and Neck Cancer

Our central hypothesis is that transoral surgery (TOS) is feasible and effective in low- to intermediate-risk, HPV+ OPSCC patients. We hypothesize that this permits pathologic-risk adjusted

reduction in adjuvant therapy and radiotherapy treatment planning benefits and may be associated with favorable functional and quality of life benefits without negatively impacting oncologic results. We will test this hypothesis in a single arm phase II design, to gather prospective data that will be essential to guide the design of a future, randomized phase III trial comparing the surgery/adjuvant therapy with standard non-surgical therapy.

The current standard of care for primary nonsurgical treatment of locally advanced HNSCC is concurrent platinum-based CRT, which has been shown to significantly improve OS, PFS, and/or locoregional control compared with RT alone or the sequential administration of chemotherapy and RT.[2] In a meta-analysis of 63 trials with nearly 11,000 patients with HNSCC, the addition of chemotherapy to RT resulted in an absolute survival improvement of 6% at 5 years.[23] The results of this meta-analysis were confirmed in subsequent updated meta-analyses, the most recent of which included 93 randomized trials and 17,346 patients.[15] Cisplatin CRT regimen is efficacious but also associated with significant toxicities and is suitable for patients with good performance status and without severe comorbidities.[24] In addition to the 3-weekly schedule, a variety of other cisplatin schedules of administration have been employed (e.g. weekly).[25]

The last twenty years have seen many advances in the management of HNSCC. The recognition that, through combined modality therapy, many advanced cancers could be controlled without a highly morbid operation (and without compromising the chance for cure) led to the development of new treatment schedules and the incorporation of new agents in the therapeutic armamentarium. These approaches were largely predicated on the assumption that normal tissue preservation would equate to functional preservation most notably for swallow function. Unfortunately, organ preservation does not always equate to functional preservation. These apparent therapeutic gains have been accompanied by significant early and late toxicity due to CRT.[26] Chronic aspiration and dysphagia have been identified as important, but often underreported late toxicities of organ preservation regimens for HNSCC. Severe (grade 3-4) late laryngopharyngeal toxicity was reported in 43% of HNSCC survivors evaluated in a pooled analysis of 3 RTOG concurrent CRT trials.

It is now clear that late swallowing injury is at least related to the dose of the radiotherapy and the use of concurrent chemotherapy. Both have been established as independent risk factors in several multivariate analyses.[27-29] Dose correlation studies suggest that the threshold upon which late injury to the swallowing muscles such as the constrictor muscles occur in the range of 55-60 Gy when a large volume of the muscles are exposed to these doses of radiation. In addition, recent data show that most patients who develop severe refractory dysphagia years after radiotherapy for HNSCC have been treated with doses of 70 Gy or more.[30] Hence, one strategy to reduce the risk of late swallowing injury would be to de-intensify the dose of radiation, particularly in patient populations with a favorable prognosis. Initial hypotheses that these young patients, with less morbidity, would tolerate treatment better and have less quality of life (QOL) impairment have been refuted; in fact, evidence suggests a greater acute QOL disadvantage in this cohort.[31,32] Thus, attention has focused on the development of late effects from CRT as the number of survivors have increased.

While the organ-preservation CRT approach has become a standard of care.[12,13] there remain serious concerns about toxicity, both short and long-term. Furthermore, the changing epidemiology of head and neck cancer has caused many to re-think this approach. Given the potential long-term sequelae of radiation therapy for a younger population[14], an alternative treatment paradigm must be found, particularly for patients with oropharyngeal SCC. A common transoral route of exposure, incorporating minimally invasive techniques with transoral laser CO_2 microsurgery (TLM) [33] and transoral robotic surgery (TORS)[34,35] has emerged.[36]

Role of transoral surgery (TOS) for OPSCC

As HPV-associated OPSCC more frequently present in a younger population and seem particularly responsive to treatment with a better overall survival,[11] attention has begun to focus on the reduction

of treatment toxicity. TORS dramatically limits the morbidity of surgical exposure and substantially reduces the acute and late effects of resection. It is important to recognize that the morbidity of past surgeries was a function of the injury that occurred with the required transcervical neck exposure. What is not clear is to what extent resection of important swallowing structures impact on this. The experience to date with TLM and TORS would suggest that resection can be safely performed for T1-2 oropharyngeal tumors without contributing to increased late swallowing complications as measured by dependence on percutaneous gastrostomy (PEG) tube. This is a particular attractive approach as HPV-associated OPSCC typically present as smaller primary tumors than those caused by substance abuse.[37,38]

TOS for OPSCC using traditional headlight visualization, C02 laser-based TLM and more recently, robotic-assisted surgery, has been practiced at an increasing number of North American institutions. Case series suggest that excellent long-term function may be anticipated after resection. Indications, contraindications, standards of practice and outcome reporting are being defined. Surgical resection of OPSCC can be a curative single modality for appropriately selected Stage I-III tumors and for many Stage IV tumors when combined with standard adjuvant therapy. The adjuvant therapy that has been applied has been based on clinical studies evaluating adjuvant therapy for squamous cell carcinomas in multiple tumor sites.[39,40] Clearly, patients who receive single modality transoral surgery have the functional advantage of swallowing preservation as a result of the ability to spare adjacent musculature critical to swallowing function. Whether this advantage is maintained with the addition of adjuvant radiation or chemoradiation remains unknown. Thus, the role of modern low-morbidity resection in the multidisciplinary management of Stage III-IV oropharynx cancer remains undefined.

The Head and Neck Committees of the Radiation Therapy Oncology Group and the University of Pittsburgh Cancer Research Group (ECOG-ACRIN) have performed surgical trials in the recent past. Surgical interest in cooperative group activity remains high. For example, ECOG 4393 represented a large study evaluating surgical margins, demonstrating the ability to perform surgical/adjuvant trials. While only a handful of institutions initially pursued transoral resection, it is now undertaken at an increasing number of academic medical centers increasing clinical investigation by qualified academically-oriented head and neck surgeons increasing the successful collection and storage of fresh, untreated tumor for scientific investigation. Numerous retrospective single-institution reports and a few important multicenter trials have generated significant enthusiasm for these transoral approaches in the multidisciplinary approach. In addition, while adjuvant therapy trials for oral cavity carcinoma have been published,[41] little prospectively gathered data on postoperative therapy for $p16^{+}$ OPSCC are available.

HPV-positive SCC, which often presents with a small primary tumor, is particularly amenable to such an approach because the functional deficit resulting from their removal is low. Transoral resection of oropharyngeal cancers using the C02 laser or, more recently, robotic surgery, has been practiced at an increasing number of North American institutions. Furthermore, case series suggest that excellent long-term function may be anticipated after resection of early T1-T2 tumors. The da Vinci surgical robot (Intuitive corp., Sunnyvale, CA) is now FDA-cleared for the resection of T1-T2 cancers of the oropharynx, and the machine is widely available. Robotic and laser transoral resection, while promising and increasingly utilized, should be investigated prospectively to design the most appropriate randomized phase II trial comparing this approach with CRT.

Surgical resection of oropharynx cancer is a curative therapy and can be a single modality for patients with Stage I-III tumors. For many Stage IV patients with intermediate risk features, adjuvant radiation therapy has the advantage in that the RT dose is reduced (50-60 Gy) and may not require the addition of concurrent CT. Hence, surgical therapy has the potential to substantially diminish the application of high-dose radiation treatment as well as CRT for patients who are expected to do well. In those patients with more advanced disease, surgical resection in combination with post-

operative CRT also has the potential to increase locoregional control. Clearly, patients who receive single modality transoral surgery have the functional advantage of swallowing preservation because of the ability to spare adjacent musculature critical to swallowing function. Whether this advantage is maintained with the addition of adjuvant radiation or CRT remains unknown. Thus, the role of modern low-morbidity resection in the multidisciplinary management of Stage III-IV oropharynx cancer remains undefined.

In summary, the suggestion is that cases of HPV-associated OPSCC have a more favorable prognosis in part due the natural biology of the cancer and possibly greater radiosensitivity. In vitro analyses have demonstrated evidence to support that HPV infection can associated with increased intrinsic chemo-radiosensitivity,[42,43] though it is recognized that there is no consensus on this issue. Nevertheless, there is compelling evidence both from the perspective of cancer cytotoxicity and normal tissue functional preservation (see above) to reduce the dose of postoperative radiotherapy in HPV-positive OPSCC to doses on the order of 55 Gy or less.

1.4 Postoperative Radiotherapy (PORT) with or without Cisplatin Chemotherapy

Current postoperative radiotherapy (PORT) doses derive from a series of seminal investigations conducted at MD Anderson Cancer Center.[40,44] The cumulative experiences from these randomized trials demonstrated that for SCC of all anatomic sites in the head and neck (32% of subjects with SCC of the oral cavity), the recommended PORT dose can be pathologically guided with high rates of local-regional disease control. While various risk stratification schema have been evaluated, the presence of a positive margin (not defined) and nodal ENE warrant at least 63 Gy.[45] In the presence of any pathologic risk factors identified in the tumor specimen, an increased risk of local relapse was statistically identified if < 54 Gy was administered compared to 57.6 Gy[40] (63% vs. 92%, p=.02). While the optimal postoperative dose for ENE and positive margins has not been established, several institutional reports have used doses typically in the range of 65-66 Gy or greater.[41,46] There is also indirect supportive evidence that a lower PORT dose may be sufficient when irradiating the pathologically involved neck. Investigators from the Netherlands (University Medical Center Groningen) demonstrated in a large retrospective review of over 800 patients (52% of subjects with SCC of the oral cavity) that postoperative irradiation of the pathologically involved cervical neck to only 56 Gy was associated with 85-93% 5-year regional control rates depending on whether only a single or multiple node were involved (Vergeer et al, *personal communication*).

Neither of these clinical experiences distinguished the local or regional control rates by HPV status and potentially may have represented a predominantly HPV-negative study population based on the predominantly oral cavity SCC patients treated. Nevertheless, it demonstrates that high rates of cancer control may be seen in the pathologically involved site. For these reasons, the optimal postoperative radiation dose has yet to be determined.

The necessity for PORT following surgery to a tumor bed that fails to demonstrate any adverse pathologic features is a controversial practice, rooted historically in the use of transcervical neck exposures and the early and seminal observations of Fletcher[47] that was intended to also address the risk of tumor surgical seeding. The risk of local-regional relapse without adjuvant PORT for transcervical surgery would need to be on the order of 10%. In the setting of a transoral approach where no cervical fascial planes are disrupted, the evidence to date suggests that the risk of local relapse with either TLM or TORS for T1/T2 primary OPSCC is approximately 5%.[48]

While concurrent chemotherapy, typically cisplatin, has been administered for the high-risk patient cohort following surgery, it is clear that the use of chemotherapy can also unnecessarily increase the risk of late swallowing complications.[26-29] Retrospective cohorts of TORS followed by RT have reported on the risk of swallowing complications, but whether reduced dosage (50 Gy vs 60 Gy) should be used in designing the prospective, randomized phase III trial in comparison to CRT is

unknown. This proposal hypothesizes that reduced dose- RT may provide comparable 2-year PFS rates with the potential for reduced, late normal tissue injury for HPV+SCC.

1.5 Role of IMRT and Lower Dose RT in Oropharynx Squamous Cell Carcinoma

A significant long-term toxicity in the irradiated oropharynx cancer patient is xerostomia caused by radiation delivered to the major salivary glands. Technologic advancements that now permit conformal fields using intensity modulated radiotherapy (IMRT) initially applied dose-constraints to reduce the volume of parotid gland parenchyma, and more recently, the contra-lateral submandibular gland exposed to high radiation doses. However, the salivary glands continue to receive lower radiation doses that can still result in long-term xerostomia, albeit of lower severity, despite the use of IMRT. This can still result in significant impairment based on patient reported quality of life measures.

Dysphagia is the primary functional complication encountered after radiotherapy for oropharyngeal cancer. Impaired laryngopharyngeal physiology that results from neuromuscular fibrosis, independent of xerostomia, contributes to radiation-induced dysphagia. Even in the era of IMRT for oropharynx cancer, authors report rates of aspiration ≥1-year of 6% to 31% and g-tube dependence of 6% to 8%.[28,49,50] Recent studies have demonstrated significant associations between swallowing outcomes and dose-volume coverage to key structures after IMRT including the anterior oral cavity, superior pharyngeal musculature, and inferior larynx/CP inlet. Dose-volume correlations have been observed for late objective endpoints of swallowing dysfunction such as nutritional dependence on a gastrostomy tube, measures of swallowing efficiency, aspiration, and swallowing-related QOL.[49,51,52] Pharyngeal dose to superior as well as inferior constrictor musculature is consistently found to relate to a variety of swallowing measures in numerous studies. Threshold pharyngeal doses as low as 50 Gy to the inferior constrictors (V_{50})[51] and as high as 65 Gy to the superior constrictors[49,52] have been significantly associated with aspiration, stricture, and swallowing efficiency. In addition, mean pharyngeal dose is associated with QOL scores.[52] As such, there exists supportive evidence that reductions in the prescribed RT dose to the pharynx and neck offer the potential to reduce the risk of both objective and patient-reported evidence of late RT-induced swallowing dysfunction. Based on these data, a dose threshold of at least 55 Gy to the superior pharyngeal musculature is felt to portend dysphagia. Moreover, IMRT did not historically use dose-limiting constraints with the primary goal of preserving swallowing function. These data also suggest early guidelines for dose-constraints to dysphagia-specific organs-at-risk using IMRT that may further improve long-term functioning after treatment for HNSCC.

Given the favorable prognosis that has been well described for the HPV-associated OPSCC patient, we hypothesize that the prescribed RT dose may be safely reduced following transoral surgical resection and pathologic risk stratification for the risk of relapse. On the other hand, patients with traditional high-risk pathologic features would be treated with current CRT to 66 Gy. Similarly, low-risk patients could be observed. For the intermediate-risk patient, we hypothesize that the prescribed dose may be safely reduced from a standard intermediate-risk prescription of 60 Gy to 50 Gy without compromise in local-regional control rates. Moreover, we expect a reduction in the development of both objective and patient-reported measures of late RT toxicities.

Radiotherapy dose reduction has been studied in the recently completed E1308. This study prospectively examined the oncologic efficacy of reducing the RT dose to 54 Gy following a complete clinical response to induction CT. No pathologic evaluation of the primary site was required. The long-term results of this trial remain pending but early locoregional control (LRC) and disease-free survival (DFS) in complete responders, excluding T4 cancers and > 10 pk-yr tobacco exposure, are encouraging and comparable to standard dose radiation. Thus, the current hypothesis is predicated on transoral resection leaving a comparable, if not favorable, microscopic burden of residual cancer cells. Theoretical mathematical modeling of radiation response and cancer control in human solid tumors has been extensively reported and is based on the modeling

of reported local-regional control rates. Withers et al has evaluated the published literature and concluded that a dose of 50 Gy is associated with a 90% control rate for subclinical microscopic cancer. Evaluation of the clinical data has permitted mathematical modeling of the biologic effect of fractionated RT demonstrating that it may be modeled with linear quadratic equation, with most solid human tumors requiring an average of 3 Gy (D_0) to reduce the surviving cells to 37% which reflects the intrinsic biology of the cell to the radiation and its repair response. Modeling suggests that a cytoreduction of 10^{-10} is required to achieve a 90% probability tumor control rate summarized by the D_{10} parameter that represents the relative dose that would be required to sterilize a tumor with 90% probability of tumor control. The D_{10} can be represented by: $D_{10} = 2.3 \times D_0$, where 2.3 is the natural logarithm of 10. Thus, the dose required would be: $D_{10} = 2.3 \times D0 = 2.3 \times 3 = 6.9$ Gy.

The probability of achieving tumor control is influenced by the number of tumor cells present. While this is largely unknown and likely varies from patient to patient, it has been estimated that 10^9 cells may be present in a typical 4 cm tumor mass. Thus, the estimated modeled dose required would be: 10 x 6.9 Gy = 69 Gy.

For a tumor cytoreduced to microscopic burden, it is estimated that there may be 10^7 or less residual cancer cells. Thus, it has been estimated that the radiation dose required to obtain a 90% likelihood of cure is: D8 = 8 x 6.9 Gy = 55.2 Gy

This dose is consistent with the minimum dose (57.6 Gy) that has been found to be required in patients with pathologic evidence of risk for recurrence (intermediate-risk group).

This proposal will randomize patients to an experimental arm of 50 Gy based on the hypothesis that HPV-associated cells will be more radiosensitive modeled by a decrease in the D_0 of approximately 10% (2.7 Gy instead of 3 Gy).

Non-Surgical Risk Adaptive and De-escalation Trial Strategies for HPV+ OPC:
While awaiting results of the completed RTOG 1016 de-escalation trial for HPV + OPC comparing Cisplatin to Cetuximab with standard radiation (70 Gy), the NRG is currently conducting a Phase II randomized trial of de-escalated radiation (60 Gy) +/- cisplatin chemotherapy for favorable risk OPC-SCC, HPV16+, < 10 pack-yrs smoking. ECOG 1308, a phase II randomized risk-adaptive trial reported LRC > 95% at 2 years, in which patients demonstrating a complete clinical response at the primary site after induction Chemo-Biologic therapy, received substantial de-escalated radiotherapy (54 G) + Cetuximab, with no compromise in LRC or DFS.

Surgical Risk Adaptive Strategies for HPV+OPC:
Recent enthusiasm has emerged for the utilization of trans-oral surgery with neck dissection for HPV 16+ OPC in which Stage I-II, favorable patients are observed rather than receive adjuvant therapy with few primary or reginal neck failures. (T1-2, N0-1).[4] However, risk stratification to define intermediate and high-risk groups in the post- surgical setting for HPV+ OPC is unclear. The ECOG is currently conducting a randomized, risk adjusted treatment Intensity Trial (ECOG 3311) in which HPV16+ OPC, stage III-IV (cT1-2, N1-2b) undergo TORS followed by either observation (FR), IMRT alone to 50 or 60 Gy (IR) or for higher risk patients, IMRT 66 Gy + weekly Cisplatin, with a primary endpoint of PFS at 2 years. However, the doses in this trial for traditional IR and HR are equivalent or even higher than the doses currently employed in the Phase II NRG trial for definitive cases. Smoking status is not part of the randomization or associated with risk groups but is a stratification variable. Prior to HPV discovery, RTOG 9501, and the EORTC, based on two similar trials with extended follow-up > 10 years, re-defined high risk as either having + margins/ and or +ENE with marginal benefit to addition of cisplatin. Patients were not stratified or randomized based on smoking history. HPV as a causative factor in OPC was not known at that time. Subsequently, N2 lymph nodes stage was changed to intermediate risk (with no benefit to Cisplatin), forming the basis for RTOG 0920, stratified by HPV status, a randomized trial for intermediate risk patients to receive 60 Gy + /-

Cetuximab. This trial is accruing slowly and has not been completed and radiation doses for the HPV 16+ patients are similar to the NRG HN 002 trial, with no de-escalation. For high risk HPV- patients, The RTOG 1216, is conducting a randomized three arm adjuvant trial to evaluate Docetaxel+/- Cetuximab, versus weekly Cisplatin, with ERT dose ranging from 60-66 Gy. This trial excludes many OPC patients even with HR features because of HPV 16+ is detected > 70% of cases.

Commonly accepted high risks factors for recurrence in the adjuvant setting, such as positive margins, ENE, alone or combined with intermediate risk factors including multiple nodal involvement, LVI, +PNI, which have formed the basis of trials exploring the efficacy of concurrent chemotherapy, EGFR inhibitors or both, may not apply to HPV16 + OPC. Although recognized as a risk factor in the definitive setting (0129 trial), the impact of smoking history in the HPV+ patients after surgery is not clear and needs to be prospectively evaluated. A recent retrospective study of 201 patients with OPC that underwent surgery with/without adjuvant radiotherapy observed that for HPV 16+ cases, common risk factors described above were not independent predictors of survival, representing a different biological disease. New prognostic markers should therefore be incorporated into future trial design.[5] A more recent surgical series reported by Kharytaniuk et al at AHNS meeting in 2016, found no negative prognostic value impacting RFS with + ENE in HPV+ patients compared to HPV-.

In summary, recognition of HPV16+ OPC as a distinct biological disease from HPV 16- SCC with more favorable outcomes has therefore led to clinical trial designs to de-escalate standard therapy (reduced dose and site of radiotherapy, more limited surgical resection, de-intensified chemotherapy and substitution with targeted therapeutics. Novel therapeutic opportunities now present themselves to better define IR and HR HPV+ in the adjuvant setting that has significant global implications. This has also led to investigations to identify possible biomarkers and genomic expression of antigens to utilize a more precision approach. This trial design evaluates the traditional intermediate and high-risk cohorts from ECOG 3311 which will close in the near future and investigates de-escalation of both radiation dose (50 Gy compared to 60-66 Gy), the need for chemotherapy in the setting of lower doses, and the emerging role and efficacy of concurrent and adjuvant PD-1 checkpoint inhibitor, Nivolumab. This combination of RT plus anti-PD-1 immunotherapy has shown safety, without dose reduction, using pembrolizumab (Powell, *Journal of Clinical Oncology* 35, no. 15_suppl (May 2017) 6011-6011) or nivolumab (Gillison, ASTRO H&N Phoenix 2018, abstract accepted).

Rationale for refining Risk Stratification based on Biomarkers

The application of targeted therapies in the last decade has been limited primarily due to a lack of actionable therapeutic biomarkers. Currently, only Cetuximab has been approved as a targeted agent in HNSCC irrespective of HPV. However, response to Cetuximab does not correlate with EGFR expression/ amplification. ALK and ROS1, have been identified in the past as possible actionable targets, but in HNSCC, these appear to be rare.

Large comprehensive genomic surveys of HNSCC have now demonstrated divergent genomic pathway mutations and drivers of HPV 16+ OPC from HPV 16-. HPV 16+, harbor few genomic alterations of P53 and/or CDKN2A, presumably due to activity of the HPVE6 and E7 viral oncoproteins.[6] They also appear to display less genomic complexity as compared with HPV- disease. HPV+ lack focal RTK amplifications but do display a higher rate of focal *PIK3CA* amplification and mutation. *PIK3CA* alterations have been reported as therapeutic biomarkers in this patient population based on cell line and patient derived xenograft studies.[14] HPV-associated HNSCCs also demonstrate enrichment for copy-number gains in *TRAF3* and *E2F1* and a lack of *CCND1* amplification when compared with HPV-negative disease. HPV 16+ driven cancers display both mutations and fusions in the *FGFR3* gene.

Study rationale for addition of PD-1 targeted immune checkpoint inhibition

Immunotherapy has now emerged as an alternative approach based on recent success in melanoma, lung and renal cell cancer. Checkpoint inhibitors and CTLA-4 inhibitors are being investigated in HNSCC in both the recurrent/metastatic setting with recently reported promising results (CheckMate

Trial NCT01860430, and NCT01935921) and in the definitive setting with CTLA-4 inhibitors (Ipilimumab). Pembrolizumab, a PD-1 blocker, was recently shown in a Phase I trial to have promising response outcomes in HPV+ recurrent HNSCC.

The effects of standard of care therapy on immune response (CD4 (+), CD8(+) T cells, regulatory T cells(Treg) and myeloid-derived suppressor cells(MDSC) in HNSCC suggest an immunosuppressive effect. Standard Chemo-radiotherapy and radiotherapy to both sites of gross and elective risk nodal regions in HNSCC have been found to reduce circulating T cell responses and upregulate MDSCs. PD-1 expression on CD 4(+) T cells are up-regulated by 2.5-fold after CRT. PD-1 blockade resulted in in downregulation of MDSC, as well as TAM, CD47/SIRP pathway, and upregulated effector T cells and dendritic cells.[7] Lower doses of radiotherapy without chemotherapy after surgery for HPV+ OPC may create an optimal microscopic tumor microenvironment that promotes neo-antigen expression and an abscopal effect without promoting a negative immunosuppressive environment. Combining this approach with PD-1 inhibition may lead to non-redundant immune response through several pathways that is additive and sustained.

Programmed Cell Death-1 (PD-1; CD279) is a cell surface signaling molecule that delivers inhibitory signals that regulate the balance between T cell activation and tolerance by interacting with its ligands, PD-L1 (CD274; B7-H1) and PD-L2 (B7-DC/CD273). PD-1 is a 55 kD type I transmembrane protein that is a member of the CD28 family of T-cell regulatory receptors, which also includes CTLA-4, ICOS, and BTLA.[1] PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells.[2] Its ligands, PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems.[3,4] PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM), that when phosphorylated, delivers a negative signal to the lymphocyte by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region.[5,6] Evidence for a negative regulatory role of PD-1 comes from studies of PD-1-deficient mice. PD-1-deficient mice develop various autoimmune phenotypes, including dilated cardiomyopathy and a lupus-like syndrome with arthritis and nephritis.[7-9] The emergence of these autoimmune phenotypes is dependent upon the genetic background of the mouse strain; many of these phenotypes emerge at different times and show variable penetrance. In addition to the phenotypes of null mutations, PD-1 inhibition by antibody-mediated blockade in several murine models has been found to play a role in the development of autoimmune diseases such as encephalomyelitis, graft-versus-host disease, and type I diabetes.[10-12] Taken together, these results suggest that PD-1 blockade has the potential to activate anti-self T-cell responses, but these responses are variable and dependent upon various host genetic factors. Thus, PD-1 deficiency or inhibition is not accompanied by a universal loss of tolerance to self-antigens.

Preclinical animal models of tumors have shown that blockade of PD-1 by monoclonal antibodies (mAbs) can enhance the anti-tumor immune response and result in tumor rejection. This suggests that host mechanisms limit the antitumor response. [13-15,23-25]

In humans, PD-L1 is constitutively expressed on macrophage-lineage cells, activated T cells, lung, vascular endothelial cells, and placental syncytiotrophoblasts.[53] Aberrant expression of PD-L1 by tumor cells has been reported in a number of human malignancies. [26-29,54-56] PD-L1 expressed by tumor cells has been shown to enhance apoptosis of activated tumor-specific T cells in vitro.[30] Moreover, the expression of PD-L1 may protect the tumor cells from the induction of apoptosis by effector T cells.[31] Retrospective analyses of several human tumor types suggest that tumor over-expression (as measured by immunohistochemistry) of PD-L1 may permit immune evasion by tumors. In renal cell carcinoma, high surface expression levels of PD-L1 on tumor cells are related to tumor aggressiveness. Patients with high tumor d/or lymphocyte PD-L1 levels are 4.5 times more likely to die from their cancer than patients exhibiting low levels of PD-L1 expression.[32]

PD-L1 and PD 1 expression may be virally mediated in HNSCC and represent a potential biomarker to blockage with checkpoint inhibitors.[57] PD-L1 expression however is variable and not clearly understood. HPV- SCC have also been shown in RNA sequencing TCGA data to express PD-L1. It remains unclear, nor accepted as to the optimal method of PD-L1 measurement for patient stratification for future trials or whether PD-L1 expression predicts for response to checkpoint inhibitors. This has led to a search for other tumor biomarkers in addition to immune cell profiling to refine patient selection. Somatic gene alterations in HNSCC responsible for immune evasion, inflammation, and antigen presentation may play a role in response to checkpoint inhibition. PI3K expression in particular may be one such marker.[58] Other investigations reported in metastatic solid tumors include possible association between checkpoint response and genomic instability due to mismatch repair deficiency leading to immune stimulation against epitopes,[59] mutational burden and improved outcomes in melanoma and NSCLC with checkpoint inhibitors[60] and the possible correlation of between neoantigen burden and response to immunotherapy. Neoantigen specific T-cell therapy that exposes epitopes derived from genetic aberrations, has demonstrated promising results when combined with checkpoint inhibition.[61,62] Emerging evidence in pre-clinical and clinical studies strongly suggest that Radiotherapy, creates an abscopal effect by releasing tumor specific neoantigens, eliciting and immune response that combined with checkpoint inhibitors, results in a more robust and sustained T-cell immune response.[63-65] Nivolumab is a fully human, IgG4 (kappa) isotype, mAb that binds to PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-γ release in the MLR.[33] The effect of nivolumab on antigen-specific recall response was investigated using a cytomegalovirus (CMV)-restimulation assay with human peripheral blood mononuclear cells (PBMCs), and was evaluated by ELISA. These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-g secretion from CMV-specific memory T cells in a dose-dependent manner.

Clinical Efficacy of Nivolumab for R/M HNSCC

The clinical efficacy of nivolumab in SCCHN has been established study CA209141 a randomized, open-label, Phase 3 trial that compared nivolumab, a fully human anti-programmed death 1 (PD-1) monoclonal antibody, to investigator's choice (IC) of systemic therapy in patients with recurrent or metastatic SCCHN who progressed from a platinum containing therapy. At a preplanned interim analysis, the median OS was 7.5 months (95% CI 5.5 to 9.1) with nivolumab versus 5.1 months (95% CI, 4.0 to 6.0) with IC. There was a 30% reduction in the risk of death for patients on the nivolumab arm (hazard ratio 0.70; 97.73% CI 0.51 to 0.96; P=0.0101) over standard of care. In addition, the overall safety profile of nivolumab was favorable compared to standard of care. Clinical benefit seen in this chemotherapy pre-treated SCCHN suggests the potential clinical activity of nivolumab in earlier treatment settings. Two large, global randomized studies are investigating the combination of nivolumab with ipilimumab in the first-line recurrent/metastatic setting (CA209-714 and CA209-651).

Rationale for Combining Nivolumab with Radiotherapy

In addition to direct cytotoxic effects, radiotherapy may induce an immune effect important to tumor cell death.53 Preclinical data support synergy between checkpoint inhibitors and radiotherapy. Mouse models of poorly immunogenic tumors have demonstrated that concomitant administration of anti-CTLA-4 antibodies and radiotherapy results in antitumor T cell responses both in the radiation field as well as outside of it (an abscopal effect). PD-1 blockade after completion of radiotherapy also has been shown to induce rejection of persistent tumors in mouse models. Combination PD-1 blockade and anti-CD137 stimulation increased response to radiotherapy in a mouse model of triple negative breast cancer,56and PD-L1 blockade concomitant with radiotherapy improved survival in comparison to either therapy alone in mouse models of glioma.57 In human patients, case-reports support the existence of a clinically significant abscopal effect for patients with melanoma who have received ipilimumab prior to radiotherapy. These data support a hypothesis that radiotherapy-induced cell death may result in alterations in the tumor immune environment (via upregulation of MHC class I, ICAM-1, CD80) as well

as presentation of novel tumor and generation of anti-tumor immune responses.60 In addition to novel antigen presentation, recent in vivo data indicate that radiotherapy can induce increased PD-L1 expression in tumors and thereby inhibit activation of cytotoxic CD8+ T cell responses, thus reducing the efficacy of radiotherapy. Concurrent administration of anti-PD1 antibodies improved response to radiotherapy and survival in mouse models whereas sequential therapy did not. These data support a hypothesis that checkpoint inhibitors administered prior to or concomitant with radiotherapy can induce clinically significant anti-tumor immune responses induced by "vaccination" to tumor-specific antigens exposed during radiation-induced cell death. Such a phenomenon may be particularly relevant to viral-induced tumors, such as HPV-positive SCCHN and to highly genetically unstable tumors such as HPV-negative SCCHN.

Existing Data on Nivolumab in Combination with Radiotherapy
Preliminary safety data are available from CA209-143, a study of nivolumab combined with radiotherapy and temozolomide in participants with newly-diagnosed Glioblastoma Multiforme (GBM). In September 2016, the interim analysis from Cohorts 1c and 1d in the study were reported64 which investigated the safety of nivolumab plus radiotherapy with or without temozolomide in methylated/unmethylated newly diagnosed GBM. Fifty-three participants received nivolumab with radiation alone (n=53) or with radiation plus temozolomide (n=57). Most participants were still on treatment at data cutoff. Six participants in Cohort 1c discontinued treatment due to increased transaminases (n=3) and asthenia, fatigue, and hypotension (n=1 each). In Cohort 1d, 4 participants discontinued treatment due to increased ALT, increased lipase, herpes simplex virus (HSV) encephalitis, and acute kidney injury (n=1 each). Five participants died in each cohort. Causes of death included disease progression (n=4) and unknown (n=1) in Cohort 1c and disease progression (n=3), palliative care only due to HSV encephalitis and clinical decline (n=1), and unknown (n=1) in Cohort 1d. The most common treatment-related serious adverse events (TRSAEs) and treatment-related adverse events (TRAEs) are reported below. These data suggest that nivolumab is well tolerated when given in combination with radiotherapy. No AEs attributable to combination of nivolumab with RT were identified.

Summary of Nivolumab Clinical Activity in the Metastatic Setting
The PK, clinical activity, and safety of nivolumab have been assessed in approximately 32 clinical studies sponsored by BMS or Ono Pharmaceutical Co., Ltd. (ONO): 11 Phase 1 studies, 13 Phase 2 studies, and 8 Phase 3 studies. Approximately 7,600 subjects have received nivolumab in single- or multiple-dose Phase 1/2/3 studies or studies with nivolumab in combination with other therapeutics (ipilimumab, cytotoxic chemotherapy, anti-angiogenics, and targeted therapies).

In **CA209003**, the clinical activity of nivolumab was demonstrated in a variety of tumor types, including melanoma, RCC, and NSCLC. Clinical activity was noted across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg). In CA209003, a total of 306 subjects with melanoma, RCC, and NSCLC have been evaluated for clinical activity. A response of either CR or PR, as determined by investigator assessed tumor evaluations based on RECIST 1.1 criteria has been reported at all dose levels.

In NSCLC, the most active doses were 3 and 10 mg/kg. The overall response rate (ORR) of 17% was reported with a 48-week PFS rate (PFSR) of 22% (95% CI: 15-30%), and a 24-month overall survival rate of 24% (95% CI: 16-32%). Only a single response (1/33) was reported at 1 mg/kg. Durable responses were observed in both squamous and non-squamous subtypes.

Historically, ORR of 5% to 10% and median PFS (mPFS) of 2 to 3 months has been reported with docetaxel treatment in previously-treated NSCLC subjects. A complete response (CR) or partial response (PR) was reported in 31% (95% CI: 22% - 41%) of the 107 response-evaluable subjects with melanoma treated with nivolumab monotherapy Q2W at doses ranging from 0.1 to 10

mg/kg in CA209-003. The responses were durable with a PFSR at 24 weeks of 38% (95% CI: 28 - 47%) and OS at 24 months of 48% (95% CI: 38-57%). Of the 34 response evaluable RCC subjects in CA209-003, responses were reported in both the 1 mg/kg (5 of 18 subjects, 27 %) and 10 mg/kg (5 of 16 subjects, 31%) treatment groups. PFSR at 24 weeks was 33% (95% CI: 14 - 55%) in the 1 mg/kg and 37% (95% CI: 14 - 61%) in the 10 mg/kg nivolumab treatment groups. OS at 24 months was 51% (95% CI: 30 - 64%) and 44% (95% CI: 20 - 66) in the 1 mg/kg and 10 mg/kg groups, respectively.

In **CA209037,** the ongoing Phase 3 study for subjects with previously-treated advanced melanoma of nivolumab (3 mg/kg administered by intravenous [IV] infusion every 2 weeks [Q2W]) vs investigator's choice therapy, as of 30-Apr-2014, 120 nivolumab-treated and 47 subjects in the investigator's choice arm are available for determination of the ORR using RECIST 1.1 criteria. As determined by imaging plus clinical review by an Independent Radiology Review Committee (IRRC), the ORR for nivolumab vs the reference arm is 31.7% vs 10.6%, respectively. Four subjects in the nivolumab arm had a CR, whereas no subjects in the reference arm had a CR. Median progression-free survival was 4.7 months (95% CI: 2.3-6.5) vs 4.2 months (95% CI: 2.1 - 6.3) with a 6-month PFS rate of 48% (95% CI: 38 - 56) vs 34% (95% CI: 18 - 51) in the nivolumab (n = 122) vs reference arm (n = 60), respectively. In addition, recent clinical trial data in MEL **(CA209066)** and NSCLC **(CA209017)** has demonstrated OS benefit. In **CA209066**, a phase 3 study of 418 previously untreated metastatic melanoma patients without a BRAF mutation, 1-year overall survival was 72.9% (95% CI: 65.5 to 78.9) in the nivolumab group as compared to 42.1% (95% CI: 33.0 to 50.9) in the dacarbazine group (P<0.001). The median PFS was 5.1 months in the nivolumab group versus 2.2 months in the dacarbazine group (hazard ratio for death or progression of disease, 0.43; 95% CI, 0.34 to 0.56; P<0.001). The objective response rate was 40.0% (95% CI, 33.3 to 47.0) in the nivolumab group versus 13.9% (95% CI, 9.5 to 19.4) in the dacarbazine group (odds ratio, 4.06; P<0.001). The survival benefit with nivolumab versus dacarbazine was observed across prespecified subgroups, including subgroups defined by status regarding the programmed death ligand 1 (PD-L1). Additional supportive data for the clinical activity of nivolumab in advanced melanoma has been shown in a cohort of 107 advanced melanoma subjects in an outpatient setting who enrolled between 2008 and 2012. In 107 patients with advanced MEL treated with nivolumab**,** objective responses were observed in 31% of patients. Median OS (62% with two to five prior systemic therapies) was 16.8 months, and 1- and 2-year survival rates were 62% and 43%, respectively. Median PFS (mPFS) was 3.7 months (95% CI, 1.9 to 9.1 months), with 1- and 2-year PFS rates of 36% (95% CI, 27% to 46%) and 27% (95% CI, 17% to 36%), respectively. In **CA209017**, a phase 3 trial in 272 patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy, subjects were randomized to nivolumab 3 mg/kg IV q2 week (n=135) or docetaxel (n=137) at 75 mg/m^2 every 3 weeks. Median OS was 9.2 months in the nivolumab group (95% CI: 7.3-13.3) vs 6.0 months in the docetaxel group (95% CI: 5.1-7.3) (HR of 0.59, P=0.00025).

Summary of Nivolumab Safety in the Metastatic Setting

In clinical trials, nivolumab has demonstrated an acceptable benefit-risk across multiple tumor types, including advanced melanoma, RCC, NSCLC, and some lymphomas. The two clinical trials that have contributed the most to the clinical experiences of nivolumab monotherapy are studies CA209003 and CA20937. Overall, the safety profile is quite similar between these two studies and is discussed further in the sections below. **CA209003** is a completed Phase 1 open label, multiple dose escalation study in 306 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3, or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. A total of 306 subjects were treated with nivolumab in the dose range of 0.1 - 10 mg/kg. No maximal tolerated dose was identified in CA209003. The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occurred in 75.2% of subjects. Of the 306 treated subjects, 303

(99.0%) subjects have at least 1 reported AE regardless of causality. The most frequently reported AEs were fatigue (54.9%), decreased appetite (35.0%), diarrhea (34.3%), nausea (30.1%), and cough (29.4%). Treatment-related AEs were reported in 230 (75.2%) of the 306 subjects. The most frequently reported treatment-related AEs were fatigue (28.1%), rash (14.7%), diarrhea (13.4%), and pruritus (10.5%). Most treatment-related AEs were low grade. Treatment-related high grade (Grade 3-4) AEs were reported in 52 (17.0%) of subjects. The most common treatment-related high-grade AEs were fatigue (2.3%) and diarrhea (1%). Drug-related SAEs occurred in 11.5% of subjects. Grade 3-4 drug-related SAEs reported in at least 2 subjects included: diarrhea (3 subjects, 1.0%), pneumonitis (3 subjects, 1.0%), pneumonia (2 subjects, 0.7%) and lipase increased (2 subjects, 0.7%). Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) include: GI AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, and endocrinopathies. In addition, select AEs include a category for infusion reactions are outlined below in the Table Treatment-related Select Adverse Events by Treatment - All CTC Grades Reported in at Least 10 Treated Subjects in CA209003). Each category is composed of a discrete set of preferred terms, including those of greatest clinical relevance. These select AEs are considered events of interest based on the mechanism of action and were previously referred to as immune-related AEs or immune-mediated AEs. Most high-grade events resolved following the treatment guidelines for the treatment of pulmonary events, GI events, hepatic events, renal events, and endocrine events, respectively. Overall, the safety profile at 3 mg/kg (n = 54) was similar to safety profile across the dose ranges from 0.1 mg/kg to 10 mg/kg (n = 306).

Treatment-related Select Adverse Events by Treatment - All CTC Grades Reported in at Least 10 Treated Subjects in CA209003				
Preferred Term	**3mg/kg n=54**		**Total (0.1 to 10 mg/kg) N=306**	
	Any Grade	Grade 3-4	Any Grade	Grade 3-4
Any Select AE	23 (43)	2 (4)	140 (46)	19 (6)
Any Endocrinopathies	4 (7)	0	29 (10)	3 (1)
Endocrinopathies Thyroid	4 (7)	0	26 (9)	2 (1)
Blood TSH increased	2 (4)	0	11 (4)	1 (0.3)
Hypothyroidism	1 (2)	0	11 (4)	1 (0.3)
Any Skin AEs	12 (22)	0	75 (25)	1 (0.3)
Rash	5 (9)	0	45 (15)	0
Pruritus	3 (6)	0	32 (11)	1 (0.3)
Any GI AE	7 (13)	0	43 (14)	3 (1)
Diarrhea	6 (11)	0	41 (13)	3 (1)
Any hepatic AE	3 (6)	2 (4)	18 (6)	4 (1)
ALT increased	1 (2)	0	11 (4)	1 (0.3)
Any Pulmonary AE	2 (4)	0	17 (6)	6 (2)
Pneumonitis	1 (2)	0	12 (4)	4 (1)
Other Select AE	3 (6)	0	15 (5)	2 (1)
Infusion-related reaction	3 (6)	0	12 (4)	0

Abbreviations: ALT: alanine aminotransferase, TSH: thyroid stimulating hormone. Source: MDX1106-03. Clinical data cut-off date: 18-Mar-2013. Total includes subjects who also received 0.1 mg/kg (n = 17), 0.3 mg/kg (n = 18), 1 mg/kg (n = 86), and 10 mg/kg (n = 131) in addition to those illustrated at 3 mg/kg (n = 54).

Treatment-related AEs leading to discontinuation were reported in 32 (10.5%) of the 306 nivolumab treated subjects on CA209003. The most frequent of these were pneumonitis (8 subjects; 2.6%) and colitis (3 subjects; 1.0%). There were 3 (1%) drug related deaths; each occurred after development of pneumonitis. **CA209037** is an ongoing Phase 3, open-label study of nivolumab (3 mg/kg administered by intravenous [IV] infusion every 2 weeks [Q2W]) vs investigator's choice therapy in subjects with previously-treated advanced melanoma. As of 30-Apr-2014, 268 subjects have been treated with 3 mg/kg IV nivolumab in CA209037 with safety results as outlined below (source document interim CSR, DCN930081508) that are consistent with the Phase 1 experience of CA209003.

In CA209037, nivolumab related AEs of any grade occurred in 67.5% of subjects. Of the 268 subjects treated with nivolumab, 255 (95.1%) subjects had at least 1 reported AE regardless of causality. The most frequently reported treatment-related AEs were fatigue (25.0%), pruritus (16.0%), diarrhea (11.2%), and nausea (9.3%). Most treatment-related AEs were low grade. Treatment -related high grade (Grade 3-4) AEs were reported in 24 (9.0%) of subjects. The most common treatment-related high-grade AEs were fatigue (0.7 %), anemia (0.7%), diarrhea (0.4%), and vomiting (0.4%). Drug-related SAEs occurred in 4.5% of subjects. Grade 3-4 drug-related SAEs

reported in at least 2 subjects included diarrhea (2 subjects, 0.7%). In addition, drug-related SAE of hyperglycemia occurred in 0.7%.

Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immunosuppressants and/or endocrine replacement therapy) were:

- Skin (29.1%) including pruritus (16.0%) and rash (9.3%)
- GI (11.6%) including diarrhea (11.2%) and colitis (1.1%)
- Endocrine (7.8%) including hypothyroidism (7.8%) and hyperthyroidism (1.9%)
- Hepatic (4.5%) including AST increased (4.1%) and ALT increased (2.6%)
- Pulmonary (2.2%) including pneumonitis (1.9%)
- Hypersensitivity/infusion reaction (1.9%)
- Renal (1.5%) including increased creatinine (0.7%), increased urea (0.4%), and
- tubulointerstitial nephritis (0.4%)

In general, these select AEs were considered by the investigator to be related to study drug, except for AEs in the hepatic and renal select AE categories. There were few high-grade select adverse events (n = 20), and most high-grade events (13 of 20) were subsequently resolved, including those for which immunosuppressive therapy was not initiated. Treatment-related AEs leading to discontinuation were reported in 6 (2.2%) of the 268 nivolumab treated subjects in CA209037 including single events of colitis, pancreatitis, increased ALT, increased lipase, autoimmune neuropathy, and demyelination. In CA209037, one subject experienced drug-related grade 5 hypoxia, possibly pneumonitis, in the setting of lymphangitic spread and possible pneumonia.

Taken together, these data from studies from CA209003 and CA209037 highlight the acceptable safety profile with similar trends in AEs in the 574 subjects treated with nivolumab in these 2 studies. Additional details on the safety profile of nivolumab, including results from other clinical studies, are also available in the BMS-936558 (nivolumab) IB.

Rationale For Immunotherapy In Viral-Associated Tumors

As described above, the adaptive T cell response largely depends upon presentation of antigens by major histocompatibility complex (MHC) in the context of an immune-stimulatory environment. Viral proteins, mutated proteins (neoantigens), and spatio-temporally dysregulated self- proteins represent targets of the T cell response that have potential to result in tumor-cell clearance. As evidence, T cell responses to viral antigens in patients with Epstein-Barr virus (EBV)+ or polyoma virus+ tumors can be identified and T cells against tumor neoantigens and self-antigens have been widely reported in the literature. Further, overall survival of both gastric and Merkel cell carcinoma patients is prognostically associated with the presence of tumor infiltrating T cells, suggesting immunosurveillance of tumor growth is taking place.

In Summary:

Can radiotherapy doses be reduced over current standards in the adjuvant setting for HPV+ IR and HR patients, when combined with systemic therapy, and can immunotherapy replace cisplatin chemotherapy further reducing both acute and late toxicity and improving swallowing QOL? How does tobacco exposure affect risk stratification in the post-surgical setting of HPV+ OPC?

1.6 Correlative Studies Background

TP53 Mutation and Prognosis

TP53 mutation is frequent in HPV-negative HNSCC while it is rare in HPV-positive HNSCC. However, it is suggested that HPV-positive patients with mutated *TP53* have a poorer prognosis when compared to HPV-positive patients with wild type *TP53*[66]. In addition, the location of mutations within *TP53* can manifest as an abnormally truncated protein (nonsense mutation), disruption of DNA binding capacities (missense mutation), or without functional consequence (silent mutation)[67] found that 53.3% of HNSCC patients had *TP53* mutations; functionally non-disruptive 33%, disruptive 20%, and wild type 47% (41). The patients with any *p53* mutations associated with the worse overall survival compared to wild-type *TP53* (HR to death, 1.4; 95% confidence interval 1.1-1.8, p=0.009) while the association was stronger with functionally disruptive *TP53* mutation (HR 1.7; 1.3-2.4, p<0.001). Therefore, we hypothesize that the patients with HPV-positive and functionally disruptive *TP53* mutations will have shorter time to disease progression and overall survival compared to patients with wild type *TP53*. In addition to *TP53*, a panel of 200 common cancer-related genes will be sequenced in one assay which may yield novel prognostic and/or predictive biomarkers.

Correlation of radiologic markers with pathologic nodal status

Preoperative CT/MRI scans will be analyzed for nodal stage and prediction of ENE, and correlated with final pathologic nodal stage, presence and extent of ENE absent, microscopic or gross).
HPV DNA measurement and alteration in serum and saliva

HPV DNA and seropositivity to HPV antigens will also be measured quatitatively and qualitatively, before and after surgical and adjuvant treatment to measure stability and predictive ability over time in a prospective treated population. Baseline and posttreatment cytokines are potentially predictive of outcome. Furthermore, the association between serologic markers (detected in blood at baseline and two other timepoints, including cytokines, chemokines, growth factors, and angiogenic factors in blood and treatment efficacy will also be examined. DNA from buffy coat or PBMCs will be analyzed for quantitative and qualitative alterations in HPV DNA. These analyses will be performed under the direction of Robert L. Ferris, MD, PhD.

Oral or serum HPV DNA level may correlate with PFS

Given the ability to detect HPV DNA in salivary and serum specimens, we will perform an exploratory correlation between pre-treatment and post-treatment (1- and 2- year) HPV DNA, using QRT-PCR for HPV E6/E7. The data will be used to determine the feasibility and potential value of incorporating this potential biomarker into the future randomized phase III trial.

Tumor antigen specific cellular immunity

We and others have characterized the antigen specific cellular immune response to OPSCC, including HPV-, EGFR- and other antigens. PBL from pretreatment and post treatment patients will be correlated with disease recurrence, PFS, and OS.

Quantification of HPV DNA and serology in serum and saliva

Presence of HPV DNA and seropositivity has been reported in healthy individuals and HPV/p16+ OPSCC patients, in approximately 60-70% of patients' serum and saliva. We collect blood and saliva from all patients for prediction of clinical response based on quantitative or qualitative alterations in these biomarkers in each specimen type after therapy and correlated with clinical outcome/response and Arm of adjuvant therapy.

1.7 Clinical Functional Outcomes

Clinical outcomes are those readily tracked by the clinical assessment team and trialist, most of which reflect assessments utilized in routine clinical practice.

1.8 Functional Swallowing Outcomes

Swallowing is a complex biomechanical process involving 5 cranial nerves and over 25 muscles in the upper aerodigestive tract. Swallowing impairments can occur as the result of surgery alone, radiotherapy or CRT. Although there are many ways to report swallowing outcomes, the modified barium swallow (MBS) study remains the only measure that defines physiology and is predictive of adverse health effects (i.e., pneumonia). Although patient-reported outcomes provide an important, complementary perspective of swallowing abilities, they do not accurately reflect swallowing competency. Much of our knowledge of aspiration and physiologic impairment comes from data of laryngeal preservation trials that aggregate functional outcomes from multiple sites of HNSCC and show aspiration rates up to 40% in unselected cohorts, and in up to 80% of symptomatic patients when laryngopharyngeal function is impaired. These data based on findings from MBS studies confirm that when physiology is impaired, patients have high rates of aspiration, much of which is undetected by patient report because of a lack of sensory awareness. Hence, silent aspiration has been reported more than 50% of patients who aspirate.[2,3,6] Data specific to patients with oropharyngeal primary tumors continue to demonstrate a high burden of dysphagia. In a population-based analysis of over 8,000 HNSCC, patients with cancers of the oropharynx had the second-highest prevalence of dysphagia.[5] In addition, 31% of patients demonstrated elevated occurrences of aspiration relative to baseline >1 year after treatment, and 22% developed pneumonia in a trial of chemoIMRT that was designed to protect dysphagia-organs-at-risk using dose-constraints for oropharyngeal cancer.[6] Furthermore, aspiration based on MBS findings was significantly predictive of pneumonia in this trial of chemoIMRT for oropharyngeal cancer ($p=0.017$, Se 80%, Sp 60%), and silent aspiration was evident on MBS studies in 63% of patients who developed pneumonia. In addition, pharyngeal residue on MBS studies was significantly associated with the development of pneumonia after [7] chemoIMRT ($p<0.01$).[6,7] These results offer compelling support for the examination of swallowing physiology (i.e., “airway protection” and “pharyngeal transit”) as these health-related endpoints cannot be obtained by PROs. Thus, we propose to evaluate swallowing using MBS studies as the primary objective functional measure of this trial.

1.9 Patient-Reported Outcomes (PRO)

Patient-reported outcomes (PRO) will include head-and-neck specific symptoms (MDASI-HN), cancer and head and neck-specific quality of life (FACT-H&N), swallowing perception and performance (MDADI), voice outcomes (VHI-10), and overall health status (EQ-5D). Additionally, ability to return to employment will be assessed using a return to work instrument in use by RTOG. Head and neck-specific symptoms include issues of dry mouth, mucositis and mucosal sensitivity, shoulder and neck discomfort, and skin changes as well as swallowing and voice-related problems. It is well documented that head and neck cancer patients experience a profound, acute decrement in the level of general physical functioning and general cancer-specific QOL because of both surgery and adjuvant RT/CRT. Data regarding the late effects of treatment on disease-specific function is more limited; however, available studies indicate that a significant percentage of patients fail to return to baseline functioning. Patient-perception of swallowing performance has been shown to be associated with long-term swallowing related quality of life, and to remain depressed from baseline levels after treatment for oropharyngeal cancers.[8] Voice-related changes that include alterations in resonance, pitch variation, loudness, and quality (i.e., hoarseness, raspiness, etc) more commonly result from treatments that affect the oropharynx, compared with articulatory changes that result from management of oral cavity cancers.

2. Objectives

2.1 Primary Objective

The dual primary objectives of the study are (1) to test the hypothesis that the proposed adjuvant de-escalation strategy (TORS + 50Gy RT + Nivolumab cancer) is equivalent (non-inferior) to current standard of care cisplatin chemotherapy + standard 60-66 Gy radiation, and (2) to demonstrate a reduction in the rate of PEG tube dependence at one year.

Primary Hypotheses: We hypothesize that HPV + OPC is a distinct immunologic disease with a more favorable prognosis compared to HPV- OPC and represents a novel opportunity for de-escalation strategies in the adjuvant setting in Intermediate-Risk p16+ OPC groups after trans-oral resection (TORS). Risk-Adaptive de-escalation through a combination of TORS surgical resection followed by de-escalated RT (50 Gy accelerated fractionation) and concurrent Nivolumab immunotherapy in HPV+ OPC patients will result in similar PFS compared to historical results of standard CRT studies (60-66 Gy +/- Cisplatin) in the adjuvant setting, typically recommended for Intermediate and High Risk patients (HPV-, >4 metastatic nodes, + extensive ENE, + margins), as well as improvement in secondary endpoints of reduced toxicity, and patient QOL measures.

We further hypothesize that RT combined with concurrent and adjuvant Nivolumab will offer similar PFS outcomes to historical trials using cisplatin-based CRT through reduced tumor microenvironment immune suppression, enhanced systemic immune activation and response, and reduced toxicity by eliminating standard chemotherapy and allowing de-escalated RT.

2.2 Secondary Objectives

- To estimate the following oncological outcomes:
    - LRC at 1 and 2 years
    - Acute toxicity at 1 and 6 months
    - Late toxicity profiles at 1 and 2 years
    - To determine patterns of failure (LRC vs Distant recurrence at 1, 2 years)
    - Evaluate pre-surgical and post swallowing function outcomes.
    - To determine QOL (PRO)
    - Evaluate the impact of current smoking, former smoking history < and > 10 pack years.
- To assess and compare early and late toxicities associated with TOS and the different doses of adjuvant PORT.
- To evaluate QOL, swallowing perception and performance, voice outcomes, and head and neck symptoms.

2.3 Laboratory Research Objectives

Paraffin-embedded tumor block or 20 5-um sections will be sent to Dr. Ferris's lab for translational biomarker studies:

- To correlate tumor TP53 mutation and other associated mutation profiles with pathologic findings, with PFS and other outcome parameters in patients with resectable HPV-associated OPSCC after the above treatments.
- To investigate the usefulness of biomarkers in predicting PFS and biomarkers, including tumor genomics, plasma cytokine/chemokines, cellular immunity to HPV, and oral HPV DNA

3. Eligibility Criteria

Each of the criteria that follows must be met for a patient to be considered eligible for this study. For each patient, an eligibility checklist must be completed and maintained in the patient's chart.

NOTE: In calculating days of tests and measurements, the day a test or measurement is done is considered Day 0. Therefore, if a test is done on a Monday, the Monday four weeks later would be considered Day 28.

3.1 Inclusion Criteria

- Age >/= 18 years.
- ECOG performance status of 0 or 1.
- Patients must have newly diagnosed, histologically or cytologically confirmed squamous cell carcinoma or undifferentiated carcinoma of the oropharynx. Patients must have been determined to have resectable oropharyngeal disease. Patients with primary tumor or nodal metastasis fixed to the carotid artery, skull base or cervical spine are not eligible.
- Patients must have intermediate risk factors, as described below as determined by imaging studies (performed < 45 days prior to registration) and complete neck exam, from the skull base to the clavicles. The following imaging is required: CT scan of neck only with IV contrast or MRI. PET scan of HN and chest with *IV contrasted* CT correlation is encouraged prior to enrollment.
    - **Intermediate risk features:**
        - **Tobacco <10 pk-yr: T0-3 plus any one of the following: ≥N2b (≥ 5 LN's +), N2c/N3, +ENE >1 mm, or + margin (if approved by surgical chair) OR**
        - **Tobacco >10 pk-yr: T0-3 plus any one of the following: any N2, N3, +ENE >1 mm, or + margin (if approved by surgical chair)**
- Patients must have no evidence of distant metastases (M0)
- Patients must have biopsy-proven p16+ oropharynx cancer; the histologic evidence of invasive squamous cell carcinoma may have been obtained from the primary tumor or metastatic lymph node. It is required that patients have a positive p16 IHC (as surrogate for HPV) status from either the primary tumor or metastatic lymph node.
- Carcinoma of the oropharynx associated with HPV as determined by p16 protein expression using immunohistochemistry (IHC) performed by a CLIA approved laboratory.
- No prior radiation above the clavicles.
- Patients with a history of a curatively treated malignancy must be disease-free for at least two years except for carcinoma in situ of cervix, differentiated thyroid cancer, melanoma in-situ (if fully resected), and/or non-melanomatous skin cancer, or clinically negligible in judgement of investigator.
- Patients with the following within the last 6 months prior to registration must be evaluated by a cardiologist and/or neurologist prior to entry into the study.
    - Congestive heart failure > NYHA Class II
    - CVA / TIA
    - Unstable angina
    - Myocardial infarction (with or without ST elevation)
- Patients must have acceptable renal and hepatic function within 4 weeks prior to registration as defined below:
    - Absolute neutrophil count ≥1,500/mm^3
    - Platelets ≥ 100,000/mm^3
    - Total bilirubin ≤ the upper limit of normal (ULN)
    - Calculated creatinine clearance must be > 60 ml/min using the Cockcroft-Gault formula: (140-age)*wt (kg)/([Cr]*72). For women the calculation should be multiplied by 0.85
- Women must not be pregnant or breast-feeding. All females of childbearing potential must have a blood test or urine study within 2 weeks prior to registration to rule out pregnancy. A female of childbearing potential is any woman, regardless of sexual orientation or whether

they have undergone tubal ligation, who meets the following criteria: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).
    - **NOTE**: Women of childbearing potential and sexually active males are strongly advised to use an accepted and effective method of contraception.
- Patient without intercurrent illness likely to interfere with protocol therapy.
- Patients must not have uncontrolled diabetes, uncontrolled infection despite antibiotics or uncontrolled hypertension within 30 days prior to registration.

3.2 Exclusion Criteria

- Any serious or uncontrolled medical disorder that, in the opinion of the investigator, may increase the risk associated with study participation or study drug administration, impair the ability of the subject to receive protocol therapy, or interfere with the interpretation of study results.
- Subjects with active, known or suspected autoimmune disease. Subjects with vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger are permitted to enroll.
- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.
- Treatment with any chemotherapy, radiation therapy, biologics for cancer, or investigational therapy within 30 days of first administration of study treatment (subjects with prior radiation, cytotoxic or investigational products < 4 weeks prior to treatment might be eligible after discussion between investigator and sponsor, if toxicities from the prior treatment have been resolved to Grade 1 (NCI CTCAE version 4).
- Known positive test for hepatitis B virus surface antigen (HBV sAg) or hepatitis C virus ribonucleic acid (HCV antibody) indicating acute or chronic infection. Subjects who test positive for HCV antibody but negative for HCV ribonucleic acid are permitted to enroll.
- Known history of testing positive for human immunodeficiency virus (HIV) and CD4 count < 200 or known acquired immunodeficiency syndrome (AIDS).
- Any Grade 4 laboratory abnormalities.
- History of allergy to study drug components.
- History of severe hypersensitivity reaction to any human monoclonal antibody.
- Prisoners or subjects who are involuntarily incarcerated.
- Subjects compulsorily detained for treatment of either a psychiatric or physical (e.g., infectious disease) illness.

4. Registration Procedures

Patient must be registered within a maximum of 8 weeks following surgery.

4.1 Required Information

Patient must be stratified/classified into one of the following risk categories:

- **Tobacco <10 pk-yr: T0-3 plus any one of the following: >N2b (> 5 LN's +), N2c/N3, +ENE >1 mm, or + margin (if approved by surgical chair) OR**
- **Tobacco >10 pk-yr: T0-3 plus any one of the following: any N2, N3, +ENE >1 mm, or + margin (if approved by surgical chair)**

Patients not categorized into the appropriate risk category will be considered ineligible for the study.

4.2 Eligibility Verification

- Patients must meet all the eligibility requirements listed in Section 3.1.
- Patients must provide a signed and dated, written informed consent form.
- Treatment should start within ten working days after registration.
- Submission of pathology materials for diagnostic review and classification is mandatory

4.3 Participation in Modified Barium Swallow (MBS) Studies

The MBS studies are optional; however, they will be required at baseline and after treatment for patients from external sites that have declared participation in the MBS studies, and strongly encouraged from external sites that use the MBS study as standard-of-care for patients with swallowing dysfunction.

5. Treatment Plan

5.1 Post-operative Management

Postoperative Radiation Therapy
Modality: Accelerator x-ray beams with nominal energy of at least 4 MV shall be used. Linear accelerators must be capable of delivering treatment using multi-leaf collimation.

Intensity Modulated Radiation Therapy (IMRT) is mandatory for this study. (VMAT (Volumetric Modulated Arc Therapy is allowed if the site has been previously approved by the NRG-QARC) Guidelines developed by the NCI for the use of IMRT in clinical trials should be followed. (See IROC website, http://www.irocri.qarc.org).

Calibration: All therapy units used for this protocol shall have their calibrations verified by the IROC Houston QA Center (RPC).

CT Simulation: CT simulation will be required in all patients. A thermoplast mask shall be used for patient immobilization (shoulders along with head strongly encouraged, although an alternative method of ensuring reproducible shoulder position is acceptable) for both CT-simulation and for each daily treatment. A bite block is encouraged to immobilize the tongue base, as well as to separate the uninvolved palate when possible. IV contrast is not required in patients if appropriate pre-operative CT scans and/or MRI or PET are available for nodal site delineation. Slice thickness of ≤ 3mm is required. The patient should be simulated and immobilized with the neck in a neutral position as best tolerated by the patient that will be reproducible daily. Surface delineation of surgical scars with radio-opaque markers will also be required at the time of CT simulation.

Image Fusion: Additional images of the patient in the treatment position such as with MRI and 18-fluorodeoxyglucose PET will be permitted to facilitate the treatment planning process. However, the primary image set for the treatment planning will be the CT image set.

Organs at Risk (OAR) Delineation

In general, the OARs that require delineation are dictated by the superior and inferior extent of the planning target volumes. For example, if the superior extent of the target volume extends to the level of the C1 vertebral body, the brainstem at this level will need to be delineated.

OARs that are suggested for delineation include the following if they lie within the superior and inferior extent of the planning target volumes**:**

- spinal cord
- brainstem
- right and left middle and inner ears
- right and left globe of the eye
- right and left lacrimal gland
- right and left optic nerves
- optic chiasm
- right and left lens
- superior constrictor muscle
- middle constrictor muscle
- inferior constrictor muscle
- cricopharyngeus muscle
- esophagus
- endolarynx:
    - This volume will consist of the tissues medial and contained within the laryngeal cartilage and will include the endolaryngeal structures from the level of the tip of the suprahyoid epiglottis to the inferior extent of the cricoid cartilage that does not overlap with any adjacent Planning Target Volume (PTV). This OAR will be gapped from the adjacent PTV by 5-15 mm. Where the adjacent PTV is to be prescribed 50 Gy, the endolarynx will be gaped from the PTV by 5 mm
- right and left parotid glands
- right and left submandibular glands
- skin
- midline oral avoidance (MOA)
    - This midline avoidance structure will include the portion of the oral cavity and oropharynx that is not included in the planning target volume. The avoidance structure will be delineated such that there is a gap between the avoidance structure and the adjacent PTV that may range from 5-15 mm. Where the adjacent PTV is to be prescribed 50 Gy, the MOA will be gaped from the PTV by 5 mm.
- mandible

Additional OARs that may be contoured but not required include

- right and left temporal-mandibular joint
- right and left thyroid gland
- right and left brachial plexus
- laryngeal cartilage
- hyoid bone
- thyroid gland

Planning OARs

For critical neurologic OARs such as the brainstem, spinal cord, chiasm and optic nerves, a systematic margin of 2 mm may be added to generate additional planning OAR volumes (PRVs).

To avoid the potential under-dosing of the CTV-N50 volumes where they overlap with the deep parotid lobes, a planning parotid volume may be delineated that represents the non-overlap portion of the parotid glands. This planning OAR will be referred to as “parotid-PTV.”

Target Volumes Delineation and Definitions: The definition of volumes will be in accordance with ICRU Reports #50 and #62. Target volume nomenclature shall include the following:

- Gross Tumor Volume (GTV) is defined as all known areas of pre-operative gross disease determined from CT, MRI, clinical information, and endoscopic findings. Grossly involved lymph nodes are defined as any lymph node ≥1cm or nodes with a necrotic center or that have abnormal FDG uptake on PET. It is strongly encouraged that the radiation oncologist outlines the radiographic extent of the primary tumor and neck nodes along with neuro-radiologist. Whenever possible, it is recommended that diagnostic images be fused to the planning CT scan image dataset to more accurately determine the GTV. The gross tumor at the primary site will designated as GTV-P, and clinically involved gross lymph nodes are designated GTV-N.

- Clinical Target Volume (CTV) is defined as all areas that may have subclinical carcinoma based on assessment of the preoperative imaging, intraoperative findings by the surgeon and the final pathologic evaluation. Where there are potential discordant findings especially between the final pathology and the intraoperative findings typically with regards to the extent of the primary tumor, communication between the radiation oncologist and the surgeon is required for a consensus to be reached regarding the original extent of the primary carcinoma.

- Planning Target Volume (PTV) will provide a margin around the CTVs to compensate for variabilities in daily treatment set up, patient positioning, and internal organ motion. A minimum of 3 mm and a maximum of 5 mm around the CTVs is required in all directions to define each respective PTV (i.e. PTV-P50, PTV-N50)The extent of the PTV margin is influenced by the set-up reproducibility at each institution. Daily IGRT is encouraged (ROI C1-2) to reduce setup variability.

Guidelines for Target Volume Delineation

- CTV-P50: CTV-P50 will represent the primary invasive tumor base. As the surgery will be transoral, the need to comprehensively treat the surrounding normal tissues that would otherwise be at risk for tumor seeding is not a major consideration. The primary factor influencing the delineation of the CTV-P50 volume should be influenced by the intra-operative assessment of the invasive base of the tumor. These findings should be compared to the preoperative imaging to reconcile any discrepancy. CTV-P50 should not include the preoperative intra-luminal extent of the primary tumor that did not invade the oropharyngeal mucosa. This volume shall include a 3-5 mm margin of uncertainty around the estimated extent of the invasive tumor base that is deemed at risk.

- CTV-N50: CTV-N50 will represent the dissected cervical nodal volume found to have nodal metastases. This nodal volume will include the peripheral extent of the sternocleidomastoid muscle laterally and medially, will include a portion of the levator scapulae and the scalene muscles.

- CTV-N45: CTV-N45 will represent the either dissected cervical nodal volumes found not to have nodal metastases or the undissected contralateral cervical neck when it is treated. This nodal volume will include the peripheral extent of the sternocleidomastoid muscle laterally and medially, will include a portion of the levator scapulae and the scalene muscles. Anteriorly, the posterior aspect of the submandibular gland and the medial pterygoid muscle will be the anterior boundary of level II nodal region.

For the ipsilateral dissected neck, CTV-N50 should be extended to nodal volumes adjacent to pathologically involved nodal volumes. For example, if the neck dissection reveals nodal metastases in level II, the adjacent level I and level V should be included in CTV-N50. This nodal volume will include the peripheral extent of the sternocleidomastoid muscle laterally and medially, will include a portion of the levator scapulae and the scalene muscles.

Indications for inclusion of the lateral retropharyngeal lymph nodes include the presence of ipsilateral level II nodal metastases or primary tumor extension to involve the posterior pharyngeal mucosa or suspected to be at risk due to involvement of the posterior tonsil pillar mucosa. The ipsilateral lateral retropharyngeal lymph nodes lie medial to the internal carotid artery and are predominantly located at the level of C1 vertebral body and occasionally at the C2 vertebral body level. The medial retropharyngeal lymph nodes are not to be delineated.

The contralateral retropharyngeal lymph nodes will be delineated as part of CTV-N45 when there are clinical/pathologic findings of ipsilateral retropharyngeal lymph node metastases.

For the contralateral undissected neck, CTV-N45, the nodal volume should include the contralateral level II, III and IV nodal regions beginning at the level of the posterior digastric muscle. This nodal volume will include the peripheral extent of the sternocleidomastoid muscle laterally and medially, will include a portion of the levator scapulae and the scalene muscles.

Ipsilateral neck will be permitted, i.e. omitting the contralateral CTV-N45when the mucosal invasive base of the tumor is > 1 cm from the midline mucosa as judged at the time of the surgery. For base of tongue cancers, the primary tumor adverse pathologic features including the positive surgical margins should not be present on the medial tumor specimen. For base of tongue cancers, the primary tumor should also not demonstrate a deep invading tumor front at the time of the surgery. The distance from the midline mucosa will require documentation including the mucosal surface that is involved when the contralateral CTV-N50 is omitted. Omitting the contralateral neck CTV-N50 is not permitted for N2c tumors and where clinical/pathologic findings of ipsilateral retropharyngeal lymph node metastases.

IMRT Prescription and Treatment Planning: The prescription dose will be administered to the PTV50 at 2.0 Gy per fx delivered 6 fractions/week. PTV 45 Gy will be delivered concurrently using SIB. Treatment breaks, if necessary, should not exceed 5 treatment days and the reason(s) for the break must be clearly recorded in the treatment record. Any treatment break(s) exceeding two (2) treatment days for reasons other than toxicity/illness will be considered a protocol deviation. The reason for the missed treatment or treatments must be clearly indicated in the copy of the patient's treatment record.

- P50 and PTV-N50: will be prescribed 50 Gy in 25 daily fractions, 6 fractions per week.
- PTV-N45: will be prescribed 45 Gy in 25 daily fractions, 6 fractions per week with SIB

Tissue Heterogeneity: The dose calculation shall consider the effect of tissue heterogeneities. The method used for tissue heterogeneity calculations shall be reported. The dose prescription is to be based on a dose distribution corrected for heterogeneities.

No specific beam arrangements will be specified. Commonly, a co-planar beam arrangement is used.

Treatment Planning Objectives: The treatment plan(s) used for each patient will be based on an analysis of the volumetric dose, including dose-volume histogram (DVH) analyses of the PTVs and critical normal structures. Inverse optimization algorithms will be used to achieve at least 95% of the volume of the specified PTVs is covered by the prescribed isodose surface while meeting the dose limitations to the delineated OARs.

Priority	Structure Name	Treatment Planning Objective				
		Coverage	Volume	OAR Maximum Dose Constraint (Gy)	OAR Partial Volume Dose Constraint	
					Volume	Dose (Gy)
1	PTVs	D95 = prescription dose				
1	spinal cord		1 cc	45 Gy		
1	brainstem		1 cc	54 Gy		
1	R and L optic nerve		0.1 cc	45 Gy		
1	optic chiasm		0.1 cc	45 Gy		
2	R and L optic nerve PRV		0.1 cc	50 Gy		
2	R or L parotids				50%	< 20 Gy
2	R and L parotids combined				mean	< 26 Gy
2	midline oral avoidance		5 cc	45 Gy	50%	< 35 Gy
2	endolarynx		1 cc	50 Gy	50%	< 30 Gy
2	cricopharyngeus		1 cc	50 Gy	50%	< 30 Gy
2	esophagus		1 cc	45 Gy		
2	R and L middle and inner ear		0.1 cc	45 Gy		
2	R and L optic globe		1 cc	50 Gy		
2	R and L lacrimal gland		1 cc	40 Gy		
2	R and L lens		1 cc	30 Gy		
2	mandible		1 cc	60 Gy		
2	skin		5 cc	60 Gy		
3	submandibular gland contralateral to the side of the neck dissection*				50%	< 35 Gy

*when the contralateral level I nodal group is not part of CTV-N50

For treatment planning purposes, the dosimetric constraints that will be used for each phase of the IMRT treatment planning will be modified by a proportion that reflects the maximum dose for that phase to the total prescription dose.

Definitions of Dosimetric Variation - Minor Variation/Major Variation: To avoid a minor variation: no more than 3% volume of the PTV will receive greater than 108% of the prescribed dose, and no tissue (target or non-target) shall receive more than 110% of the prescribed dose. In addition, no more than 5% volume of any PTV shall receive less than 95% of the prescribed PTV dose, and no more than 1% of the PTV volume receives less than 93% of the prescribed dose. Reported doses for PTVs shall include the prescription dose, maximum point dose for each PTV, % PTV receiving 110%, 108% and 95% and 93% dose. Also, the mean dose must be reported.

Repeat Simulation and Planning: There are circumstances where it may be appropriate to repeat a patient's simulation. Examples may be when there is excessive weight loss and either the thermoplast mask is no longer tight or the patient's external contour no longer matches the original contour due to weight loss. The original PTVs should continue to be treated to the original volume.

Definitions of Deviations in Protocol Performance

Dose:

- Minor deviation: The delivered dose to the prescription volume differs from protocol specification by more than 5% but less than 10%.
- Major deviation: The delivered dose to the prescription volume differs from protocol specification by more than 10%.

Dose Uniformity:

- Minor deviation: More than 3% of the PTV receives more than 108% of the prescription dose or more than 1% of the PTV receives less than 93% of the prescription dose.
- Major deviation: More than 5% of the PTV receives more than 115% of the prescription dose.

Volume:

- Minor deviation: Margins for PTV less than specified, or field(s) excessively large.
- Major deviation: GTV (or corrected GTV if not appropriately drawn) not included within the 95% dose volume.

Treatment Breaks:
More than two missed treatment days for any reason other than a toxicity is considered a deviation.

- Minor deviation: 3-5 days.
- Major deviation: > 5 days

Evaluation After Completion of Concurrent Therapy
Patients will be re-evaluated after the completion of treatment to assess clinical and radiographic response by complete head and neck exam and imaging studies.

Patients with persistent disease will be evaluated and where indicated undergo appropriate surgical resection.

5.2 Administration of Nivolumab

Nivolumab will be administered at a fixed dose of 240 mg over 30 minutes IV every 2 weeks during radiotherapy, and at 480 mg over 60 minutes IV every 4 weeks for 6 doses after radiotherapy. The first dose will be given prior to the first fraction of radiation (Day 1) on Day -5 (+/- 2 days) and continued every 2 weeks (+/- 2 days). Nivolumab will thus be given in weeks 2 and 4 of radiotherapy.

Adjuvant nivolumab will then be given for a total of 6 additional doses after the completion of radiotherapy every 4 weeks (+/- 7 days), starting in the second or third week after the completion of radiotherapy.

There are no recommended premedications for nivolumab.

Doses of nivolumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment.

Dose delay criteria apply for all drug-related AEs. Treatment delay up to 6 weeks for nivolumab from the last dose are allowable (any dose delays greater than these will require approval from the medical co-chair).

Radiation therapy should not be delayed.

Dosing modifications:
There will be no dose modifications allowed for the management of toxicities of individual subjects.

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

Nivolumab should be delayed for the following:

- Any Grade ≥ 2 non-skin, drug-related adverse event, except for fatigue and laboratory abnormalities
- Any Grade ≥ 3 skin drug-related AE
- Any Grade ≥ 3 drug-related laboratory abnormality with the following exceptions for lymphopenia, aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin or asymptomatic amylase or lipase:
    - Grade 3 lymphopenia does not require a dose delay
    - If a subject has a baseline AST, ALT, or total bilirubin that is within normal limits, delay dosing for drug-related Grade 2 toxicity
    - If a subject has baseline AST, ALT, or total bilirubin within the Grade 1 toxicity range, delay dosing for drug-related Grade ≥ 3 toxicity
    - Any Grade ≥ 3 drug-related amylase or lipase abnormality that is not associated with symptoms or clinical manifestations of pancreatitis does not require dose delay. The Medical Co-chair should be consulted for such Grade ≥ 3 amylase or lipase abnormalities.
- Any AE, laboratory abnormality or inter-current illness which, in the judgment of the investigator, warrants delaying the dose of study medication.

Nivolumab Dose Discontinuation Due to Drug-Related AE(s)
Treatment with nivolumab should be permanently discontinued for any of the following:

- Any Grade 2 drug-related uveitis or 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 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction, regardless of duration;
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities:
- Any Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.

- Any Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.
- Any 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
        - AST or ALT > 5 -10x ULN for > 2 weeks
        - AST or ALT > 10x ULN
        - Total bilirubin > 5 x ULN
        - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset. The Medical Co-chair should be consulted for Grade 4 amylase or lipase abnormalities
    - 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
- AST or ALT more than 5 times the upper limit of normal (ULN) or total bilirubin more than 3 times the ULN, for any duration of time
- Grade 3 adrenal insufficiency regardless of whether adequately controlled with physiologic hormone replacement
- Grade 3 myocarditis
- Requirement for 10 mg per day or greater of prednisone or equivalent for management of immune-related adverse reactions for more than 12 weeks
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

Criteria to Resume Nivolumab Dosing

Subjects may resume treatment with nivolumab when the drug-related AE(s) resolve(s) to Grade ≤ 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.
- Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- 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 Medical Co-chair.
- Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Dose delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted above.

Nivolumab Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours as an SAE if criteria are met. Infusion reactions should be graded according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Event (CTCAE, Version 4.0) guidelines.

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

Treatment Recommendations for Nivolumab Infusion Reactions
For Grade 1 symptoms: (mild reaction; infusion interruption not indicated; intervention not indicated)
• Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.
For Grade 2 symptoms: (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours)
• Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). • For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325-1000 mg should be administered >30 minutes before nivolumab infusion. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.
For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [e.g., renal impairment, pulmonary infiltrates]. Grade 4: Life threatening; pressor or ventilatory support indicated).
• Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

In case of late-occurring hypersensitivity symptoms (e.g., appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (e.g., oral antihistamine or corticosteroids).

Duration of Nivolumab
Nivolumab will be given for a total of 9 doses, as detailed above, or until progressive disease, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. For all subjects, global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time is allowed, if necessary.

5.3 Adverse Event Reporting Requirements and Procedure

Purpose
Adverse event (AE) data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of the patients enrolled, as well as those who will enroll in future studies using similar agents.

- **Routine reporting:** Adverse events are reported in a routine manner at scheduled times during the trial using UPMC coordinating center (for external sites).
- **Expedited reporting:** In addition to routine reporting, certain adverse events must be reported in an expedited manner for timelier monitoring of patient safety and care. The following sections provide information and instructions regarding expedited adverse event reporting.

Definitions
- **Adverse Event (AE):** Any untoward medical occurrence associated with the use of a drug in humans, whether considered drug related. Therefore, an AE can be ANY unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether considered related to the medicinal product.

- **Life-threatening adverse event or life-threatening suspected adverse reaction:** An adverse event or suspected adverse reaction 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 or suspected adverse reaction that, had it occurred in a more severe form, might have caused death.

- **Serious adverse event or serious suspected adverse reaction:** An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical events 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 or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

- **Suspected adverse reaction:** Any adverse event for which there is a reasonable possibility that the drug caused the adverse event. For the purposes of IND safety reporting, "reasonable possibility" means there is evidence to suggest a causal relationship between the drug and the adverse event. Suspected adverse reaction implies less certainty about causality than adverse reaction, which means any adverse event caused by a drug.

Adverse reaction means any adverse event caused by a drug. Adverse reactions are a subset of all suspected adverse reactions where there is reason to conclude that the drug caused the event.

- **Unexpected adverse event or unexpected suspected adverse reaction:** An adverse event or suspected adverse reaction is considered "unexpected" if it is not listed in the investigator brochure or is not listed at the specificity or severity that has been observed; or, if an investigator brochure is not required or available, is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure referred only to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure listed only cerebral vascular accidents. "Unexpected," as used in this definition, also refers to adverse events or suspected adverse reactions that are mentioned in the investigator brochure as occurring with a class of drugs or as anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

- **Attribution:** An assessment of the relationship between the adverse event and the protocol treatment, using the following categories.

ATTRIBUTION	**DESCRIPTION**
Unrelated	The AE is ***clearly NOT related*** to treatment
Unlikely	The AE is ***doubtfully related*** to treatment
Possible	The AE ***may be related*** to treatment
Probable	The AE is ***likely related*** to treatment
Definite	The AE is ***clearly related*** to treatment

- **CTCAE:** The NCI Common Terminology Criteria for Adverse Events provides a descriptive terminology that is to be utilized for AE reporting. A grade (severity) is provided for each AE term.

- **Expectedness:** Any adverse event, the type or severity of which is consistent with the current investigator's brochure, product label, and/or the protocol document.

Reporting Procedure

Internal Reporting Requirements: All events meeting the definition of a serious adverse event should be reported according to the internal departmental SAE checklist and SAE form. Copies should be sent to:

1. Investigator
2. crssafetysubmissions@upmc.edu
3. Local Institutional Review Board when reporting requirements are met.

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 the internal departmental 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.

In addition to completing appropriate patient demographic and suspect medication information, the report should include as applicable the following information that is available at the time of report within the Sections of the departmental SAE form:

- CTCAE term(s) and grade(s)
- current status of study drug
- all interventions to address the AE (testing and result, treatment and response)
- hospitalization and/or discharge dates
- event relationship to study drug

Follow-up Reports: Additional information may be added to a previously submitted report by adding to the original departmental SAE form and submitting it as follow-up or creating supplemental summary information and submitting it as follow-up with the original departmental SAE form.

Reporting adverse events to the responsible IRB: In accordance with applicable policies of the University of Pittsburgh Institutional Review Board (IRB), the Investigator will report, to the IRB, any observed or volunteered adverse event that is determined to be 1) *associated with the investigational drug or study treatment(s)*; 2) *serious*; and 3) *unexpected*. Adverse event reports will be submitted to the IRB in accordance with the respective IRB procedures.

Applicable adverse events will be reported to the IRB as soon as possible and, in no event, later than 10 calendar days following the sponsor-investigator's receipt of the respective information. Adverse events which are 1) associated with the investigational drug or study treatment(s); 2) fatal or life-threatening; and 3) unexpected will be reported to the IRB within 24 hours of the Sponsor-Investigator's receipt of the respective information.

Follow-up information to a reported adverse event will be submitted to the IRB as soon as the relevant information is available. If the results of the Investigator's follow-up investigation show that an adverse event that was initially determined to not require reporting to the IRB does, in fact, meet the requirements for reporting; the Investigator will report the adverse event to the IRB as soon as possible, but in no event later than 10 calendar days, after the determination was made.

5.4 Dose Modifications

All toxicity grades below are described using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0.

All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP website (http://ctep.cancer.gov).

The use of colony stimulating factors (G-CSF, GM-CSF), and amifostine are explicitly discouraged. Erythropoietin stimulating agents, such as erythropoietin, and darbepoetin, are prohibited.

5.5 Supportive care and Other Assessments

Patient Reported Outcomes (PROs)
Quality of Life (QOL) assessments will be performed at baseline, end of treatment, and at 3, 6, 12, and 24 months after completion of treatment. If an additional tumor assessment is done prior to 3 years from study entry, one final QOL assessment is requested. QOL will continue to be collected for all patients post recurrence.

Paper questionnaires will be completed by the patient, and then data from the questionnaire should be provided within 7 days of completion. The original copy needs to be kept in the study subject's research binder.

Rehabilitation
It is strongly encouraged that all patients be referred for an assessment by a certified physical therapist after the completion of concurrent therapy. Components of the evaluation should include: neck shoulder and jaw range of motion, general conditioning level, the degree of treatment related fatigue, and postural issues. Patients with significant levels of deconditioning, postural abnormalities, or decrease in range of motion may require physical therapy. Occupational therapy may be needed in patients with extreme degrees of dysfunction. Patients with lymphedema should be referred for lymphedema therapy which should include: education, manual lymph drainage and the use of compression garments.

Speech and Language Pathology
Swallowing assessment and therapy is considered a critical component of care for all head and neck cancer patients. An MBS study will be required at baseline and after treatment as standard-of-care for patients with swallowing dysfunction. Assessments should be done by a trained Speech-Language Pathologists (SLP). The SLP should be consulted during treatment planning and should provide routine follow-up throughout the trajectory of the patient's treatment and recovery. The treating physician should communicate with the SLP to coordinate care in those patients found to have significant swallowing abnormalities. Critical component of the swallowing evaluation should include: 1) identification of any swallowing abnormalities, 2) recommendations for further testing, 3) formation of a treatment plan, 4) dietary recommendations, and 5) clear identifications of patients at risk for aspiration. Patients should be referred immediately for evaluation if any of the following "trigger symptoms" are identified: coughing or clearing the throat before, during or after eating, inability to control food, liquids or saliva in the oral cavity, complaint of difficulty swallowing or food "sticking" in the throat, nasal regurgitation of food, or pocketing of food in the cheek.

All supportive measures consistent with optimal patient care will be given throughout the study.

5.6 Duration of Therapy

- Patients will receive protocol therapy unless:
- Treatment is interrupted for 4 consecutive weeks; patient's protocol treatment will be discontinued
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued
- Patient develops unacceptable toxicity; then the patient will discontinue protocol therapy
- Patients may withdraw consent and withdraw from the study at any time for any reason

5.7 Duration of Follow-up

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression, even if non-protocol therapy is initiated, and for survival for 5 years from the date of registration.

6. Measurement of Effect

6.1 Time to Progression

This interval will be measured from the date of entry on the study to the appearance of new metastatic lesions or objective tumor progression.

6.2 Methods of Measurement

Imaging based evaluation is preferred to evaluation by clinical examination. The same imaging modality must be used throughout the disease evaluation.

CT and MRI: CT and magnetic resonance imaging (MRI) are the best currently available and most reproducible methods for measuring target lesions.

Chest X-Ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by an aerated lung. However, CT is preferable.
Tumor Markers: Tumor markers alone cannot be used to assess response.

Clinical Examination: Clinically detected lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For skin lesions, documentation by color photography, including a ruler to estimate size of the lesion, is recommended. Photographs should be retained at the institution.

Cytology and Histology: Cytologic confirmation of the neoplastic nature of any effusion that appears or worsens during treatment is required when the measurable tumor has met response or stable disease criteria.

Ultrasound: Ultrasound may be used only as an alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules.

7. Schedule of Assessments

NOTE: There is a window of ±1 week available for scheduling treatment and/or procedures at the discretion of the Investigator/Sub-investigator. This applies also if a course is missed or a subject's treatment and/or testing day(s) need to be rescheduled due to the subject’s inability to comply with the study calendar (i.e., hospitalizations, business, vacation plans, travel from long distances for study treatment, in advance of the scheduled date to allow ready access to the result(s), reduce financial burden on the subject [i.e. non-UPMC insurance coverage] or reduce travel inconvenience, illness, transportation issues, holidays, family emergencies, etc.).

	Screening[1]	Day -5 ± -2	Adjuvant Nivolumab	EOT[10]	LTFU
Medical history, physical exam, vital signs	X	X	X	X	
Height	X				
Weight	X	X	X	X	
ECOG performance status	X	X	X	X	
CBC w/diff, platelets	X[1]	X	X	X	
Amylase, lipase	X		X		
TSH	X[7]		X		
Serum chemistry	X[1]	X	X	X	
Serum pregnancy test	X[1]				
QOL questionnaires	X			X	X[9]
Adverse event evaluation	X	X	X	X	
Disease evaluation by clinical methods[2]	X		X[2]	X[2]	X[2]
CT scan/MRI[2]	X		X[2]	X[2]	X[2]
SLP consult with MBS[3]	X			X	X[3]
Tumor tissue	X				
Blood and saliva biomarkers[8]		X	X	X	X
IMRT					
Nivolumab[5,6]		X	X		

[1]Pre-study laboratory assessments should be done ≤ 4 weeks before registration.

[2]Disease evaluation by clinical methods and a CT and/or MRI to assess all measurable or non-measurable sites of disease will be obtained at screening (≤ 4 weeks before registration), symptomatically during IMRT, every 3 months during adjuvant nivolumab treatment starting from end of radiation therapy, every 6 months for 3 years, and annually for 2 more years to confirm standard of care assessments.

[3]SLP = speech language pathologist; MBS = modified barium swallow; Required for participation at screening and 6 and 24 months after treatment, and if MBS is performed as standard of care.

[4]All labs may be completed within 7 days of surgery.

[5]Nivolumab 240mg IV every two weeks

[6]Nivolumab 480mg every 4 weeks for 6 doses.

[7]TSH to be drawn for baseline status. Is not an eligibility criterion

[8]Blood biomarkers will be drawn at screening, week 0: Day -3 (± 2 Days), every 4 Weeks (post Week 4) x 24 Weeks (± 7 Days), EOT. For LTFU: Every 3 Months x 24 Months then every 6 Months x 3-5 Years from completion of radiation therapy

a. Serum Cytokines/Chemokines
b. HPV DNA (blood & saliva)
c. Tumor antigen specific cellular immunity
d. Lymphocyte Markers

[9]QOL's will be collected for LTFU at 3, 6, 12, 24 months from completion of radiation therapy

[10] EOT should coincide with 6 month CT scan post radiation therapy.

8. Nivolumab Formulation and Procurement

Product Description / Class and Dosage Form	Potency	IP/Non-IMP	Blinding	Packaging	Storage Conditions (per label)
BMS-936558-01 (Nivolumab) Solution for Injection*	100 mg (10 mg/mL)	IP	Open Label	10 mL per vial (5 or 10 vials/carton)	Store at 2° - 8 °C. Protect from light and freezing.

*May be labeled as either "BMS-936558-01" or "Nivolumab"

Investigational Product

An investigational product, also known as investigational medicinal product in some regions, is defined as a pharmaceutical form of an active substance or placebo being tested or used as a reference in a clinical study, including products already with a marketing authorization but used or assembled (formulated or packaged) in a way different from the authorized form, or used for an unauthorized indication, or when used to gain further information about the authorized form. The investigational product should be stored in a secure area according to local regulations. It is the responsibility of the investigator to ensure that investigational product is only dispensed to study subjects. The investigational product must be dispensed only from official study sites by authorized personnel according to local regulations. In this protocol, the investigational product is nivolumab.

Storage and Dispensing

The product storage manager should ensure that the study drug is stored in accordance with the environmental conditions (temperature, light, and humidity) as determined by BMS. If concerns regarding the quality or appearance of the study drug arise, the study drug should not be dispensed and contact BMS immediately.

Investigational product documentation (whether supplied by BMS or not) must be maintained that includes all processes required to ensure drug is accurately administered. This includes documentation of drug storage, administration and, as applicable, storage temperatures, reconstitution, and use of required processes (eg, required diluents, administration sets).

Infusion-related supplies (eg, IV bags, in-line filters, 0.9% sodium chloride injection, 5% dextrose injection) will not be supplied by the sponsor and should be purchased locally if permitted by local regulations.

Please refer to the current version of the Investigator Brochure and/or pharmacy reference sheets for complete storage, handling, dispensing, and infusion information for nivolumab.

Nivolumab is to be administered as an IV infusion. At the end of the infusion, flush the line with a sufficient quantity of dextrose or normal saline.

Selection and Timing of Dose for Each Subject

Dosing modifications:

There will be no dose modifications allowed for the management of toxicities of individual subjects.

Dosing window:
Subjects may be dosed no less than 12 days between doses. A dose given more than 3 days after the intended dose date will be considered a delay. A maximum delay of 6 weeks between doses is allowed.

Treatment Compliance
Treatment compliance will be monitored by drug accountability as well as the subject's medical record and eCRF.

Destruction of Study Drug
For this study, study drugs (those supplied by BMS or sourced by the investigator) such as partially used study drug containers, vials and syringes must be destroyed on site.

Any unused study drugs can only be destroyed after being inspected and reconciled by the responsible Study Monitor unless study drug containers must be immediately destroyed as required for safety, or to meet local regulations (eg, cytotoxic agents or biologics).

On-site destruction is allowed provided the following minimal standards are met:

- On-site disposal practices must not expose humans to risks from the drug.
- On-site disposal practices and procedures are in agreement with applicable laws and regulations, including any special requirements for controlled or hazardous substances.
- Written procedures for on-site disposal are available and followed. The procedures must be filed with the site's standard operating procedures (SOPs) and a copy provided to BMS upon request.
- Records are maintained that allow for traceability of each container, including the date disposed of, quantity disposed, and identification of the person disposing the containers. The method of disposal, i.e., incinerator, licensed sanitary landfill, or licensed waste disposal vendor must be documented.
- Accountability and disposal records are complete, up-to-date, and available for the Monitor to review throughout the clinical trial period.

If conditions for destruction cannot be met the responsible Study Monitor will make arrangements for return of study drug.

It is the investigator's responsibility to arrange for disposal of all empty containers, provided that procedures for proper disposal have been established according to applicable federal, state, local, and institutional guidelines and procedures, and provided that appropriate records of disposal are kept.

9. Statistical Considerations

The purpose of this phase II trial of $p16^{+}$ OPSCC patients that will undergo transoral surgery followed by de-intensified adjuvant radiotherapy plus nivolumab is to demonstrate equivalent oncologic outcome with fewer adverse effects and improved quality of life when compared to the standard of care

9.1 Objectives

The dual primary objectives of this phase II study are (1) test the hypothesis that the proposed adjuvant de-escalation strategy (TORS + 50Gy RT + Nivolumab cancer) has equivalent (non-inferior) 2-year PFS. PFS is survival without local, regional or distant disease progression; patients who do not progress or die while disease – free will be censored and (2) to demonstrate a reduction in the rate of PEG tube dependence at one year.

Secondary objectives include estimating recurrence patterns, assessing quality of life (QOL) and swallowing function before and after treatment and evaluating toxicity.

With improved outcomes for p16+ oropharyngeal cancers treatment de-escalation is a critical and topical subject for a controlled clinical. This trial tests the hypothesis that de-escalating treatment of intermediate risk p16+ oropharyngeal cancer patients benefits them by providing equivalent oncologic outcome with superior quality of life.

The first hypothesis to be tested is that oncologic outcome following de-escalation is clinically equivalent to conventional standard systemic therapy with transoral robotic surgery (TORS) plus adjuvant cisplatin and 60-66 Gy radiation. The definition of non-inferiority is clearly within a desired clinical window of equivalence, defined as 2-year PFS, not less than 10% lower than expected under standard-of-care. Therefore, the design is to establish the non-inferiority of the experimental therapy (TORS + Nivolumab + 50 Gy radiation). The second hypothesis to be tested is de-escalation is warranted, by virtue of a clinically meaningful improvement in quality of life as measured by reduced G tube patency.

The decision to select a single arm trial is based on the following: A two arm randomized non-inferiority trial would be prohibitively expensive, infeasible (approximately 600 patients would be needed) and delay results for five years. This single-arm trial is feasible and is powered to produce a definitive result in 3 years from 1st accrual. The comparison is a to large-well characterized contemporaneous subset of the ECOG 3311 trial with similar pathologic features as we propose in our new trial, that received cisplatin and standard dose radiotherapy in Arm D of ECOG 3311. Patients recruited to ECOG 3311 are expected to be similar to our patients at the University of Pittsburgh, a large tertiary-care academic medical center, in part since we were the #1 largest accrue in the US to ECOG 3311 (Dr. Ferris is PI of that trial as well).

9.2 Sample Size and Accrual Rate

Approximately 135 eligible subjects will be enrolled in this multicenter clinical trial that will be conducted at approximately 25 UPMC sites and up to 5 external sites in North America.

The first primary objective is to demonstrate that TORS with de-escalation RT (50Gy) and Nivolumab is equivalent (not inferior) to the standard of care of chemotherapy + standard 60-66 Gy radiation. The first primary endpoint is probability of progression free survival where an event is any type of disease progression or recurrence (local, regional or distant). In this definition deaths from other cancers, other non-cancer causes or treatment related deaths are censored. The historical control for the study is based part upon the results of Huang [9] in which the probability of 3 year OS was approximately 65% for high risk (Group III,T4 or N3, age < 70) HPV+ patients treated with chemoradiation and that 3 year OS is an approximation of two year PFS. Since there is not an ideal, published cohort to use, the trial is designed to investigate whether TORS with 50 Gy RT + Nivolumab is not inferior to standard of care chemotherapy + standard 60-66 Gy radiation.

We plan to devote 2 years of accrual and one year of additional follow-up. We assume that the experimental arm is not inferior to the standard if the 2-year PFS is not less than 55%, 10% less than the assumed standard. Thus 55% 2-year TTP for de-escalation RT + Nivolumab is considered not inferior to the 65% 2-year PFS for Cisplatin + 60-66 Gy RT.

Using a one-tailed exponential test (using he maximum likelihood estimator for the hazard rate of the exponential distribution) at $\alpha = .10$, 135 patients will provide 90% power to reject the null hypothesis that the experimental arm is inferior (less than 55% 2-year PFS) when the underlying 2-year PFS is 65%.

The second primary objective is to demonstrate reduction in feeding tube dependence. We will compare 1-year PEG tube dependence for patients who have not progressed to the SOC. Based on

unpublished results from RTOG 0234 for 84 patients treated with RT + cisplatin + cetuximab, 67 (80%) did not have disease progression at one year. Of these, 11 (16%) were dependent upon a feeding tube one year after the start of treatment. Assuming a 15% PEG tube SOC rate, we wish to demonstrate a 50% improvement or to 7.5% due to the proposed de-escalation regimen. We assume the same 1 year non-progression rate of 80% which suggests 80% of 135 or 108 patients will be candidates for a feeding tube at one year. A one tailed exact binomial test with 108 patients at alpha = .06 will have 80% power to detect a reduction in 1 year PEG tube rate from 15% to 7.5%. Using the Bonferroni inequality, the type I error for testing both primary hypotheses is 16% with 135 patients.

Thus, we require accrual of 45 patients/yr for 3 years (135 total) with one year of additional follow-up.

9.3 Secondary Objectives

Secondary endpoints include toxicity, recurrence patterns, overall survival, swallowing function, and patient-reported outcomes.
Toxicity. For each arm, all treated patients will be evaluated by CTCAE version 4.0. Descriptive statistics will be provided by grade and type of toxicity.). The proportion of radiation-attributable grade III/IV toxicities will be estimated with 95% confidence intervals. These confidence intervals will be informally compared to published rates for standard of care radiation. In addition, frequencies of toxicity by grade in each arm will be compared with the Jonckheere-Terstra test

Recurrence Patterns Kaplan-Meier estimates with confidence intervals will be prepared for local, regional and distant recurrence. In addition, cumulative incidence functions will be estimated for local, regional and distant recurrence as well as death in the absence of disease progression. Gray's test will be applied to test differences in cumulative incidence patterns between treatment arms.

Overall Survival. Overall survival will be determined as the time from registration onto the study until death from any cause. Patients who were alive at the time of analysis will be censored at the date last known alive. Kaplan-Meier estimates will be calculated, along with their corresponding 95% confidence intervals. The median, 1-year, and 2-year survival rates will be estimated. Only eligible and treated patients will be analyzed for overall survival (by arm).

Swallowing Function and Voice. Descriptive statistics will be provided with confidence intervals for swallowing function, evaluated using the MBS ratings, PSS-HN normalcy of diet scale, and the validated survey MDADI instrument. Longitudinal analysis will be performed on each of these measures. All eligible and treated patients (on both steps) will be analyzed for PSS-HN diet scale, MDADI, and VHI-10. The MBS analysis will be performed on eligible and treated patients only if accrued at vetted participating centers.

Quality of Life. The primary variable of interest in the QOL analysis is the individual change in the FACT-H&N total score from baseline (prior to TOS) to 6 months post-RT. The within-patient change in FACT_H&N score will be calculated and tested with the signed rank test or Friedman's' test for more than 2 sequential observations per patient.

9.4 Data Safety Monitoring Plan

Investigator/Sub-investigators, regulatory, CRS management, clinical research coordinators, clinical research associates, data managers, and clinic staff meet regularly in disease center Data Safety Monitoring Boards (DSMB) to review and discuss study data to include, but not limited to, the following:

- serious adverse events
- subject safety issues
- recruitment issues

- accrual
- protocol deviations
- unanticipated problems
- breaches of confidentiality

All toxicities encountered during the study will be evaluated on an ongoing basis according to the NCI Common Toxicity Criteria Version 4.0. All study treatment associated adverse events that are serious, at least possibly related and unexpected will be reported to the IRB. Any modifications necessary to ensure subject safety and decisions to continue or close the trial to accrual are also discussed during these meetings. If any literature becomes available which changes the risk/benefit ratio or suggests that conducting the trial is no longer ethical, the IRB will be notified in the form of an Unanticipated Problem submission and the study may be terminated.

All study data reviewed and discussed during these meetings will be kept confidential. Any breach in subject confidentiality will be reported to the IRB in the form of an Unanticipated Problem submission. The summaries of these meetings are forwarded to the UPMC Hillman Cancer Center Data Safety Monitoring Committee (DSMC) which also meets monthly following a designated format.

For all research protocols, there will be a commitment to comply with the IRB's policies for reporting unanticipated problems involving risk to subjects or others (including adverse events). DSMC progress reports, to include a summary of all serious adverse events and modifications, and approval will be submitted to the IRB at the time of renewal.

Protocols with subjects in long-term (survival) follow-up or protocols in data analysis only, will be reviewed bi-annually.

Both the UPMC Hillman Cancer Center DSMC as well as the individual disease center DSMB have the authority to suspend accrual or further investigate treatment on any trial based on information discussed at these meetings.

All records related to this research study will be stored in a locked environment. Only the researchers affiliated with the research study and their staff will have access to the research records.

Safety Monitoring

Adverse events are graded per CTCAE version 4. The primary endpoint for evaluating safety is dose-limiting toxicity (DLT). The period of observation for a DLT is from day -3 (first dose of nivolumab) through to 4 weeks after the completion of radiotherapy. A DLT is defined as:

1. Any ≥ grade 3 adverse event that is related to nivolumab that does not resolve to grade 1 or less within 28 days;

2. A delay in radiotherapy of > 2 weeks due to toxicity related to nivolumab;

3. Inability to complete radiotherapy due to toxicity related to nivolumab;

Patient safety will be monitored continuously using Bayesian methods. The presence or absence of a treatment-related DLT as defined above will be tabulated and used to compute the posterior probability of an excessive DLT rate. A 25% DLT is expected and acceptable; a 40% DLT rate is considered excessive. If the posterior probability is .80 or greater, that 40% or more of treated subjects experience a treatment related DLT, the study will be suspended pending review by the DSMC. This posterior probability will be calculated from the study's accumulating data and a weakly informative prior

distribution. If π denotes a random variable representing the proportion of subjects who will experience a treatment related DLT, we assume π has a prior beta distribution with parameters a = .75 and b = 2.25, which is consistent with an expected DLT rate of 25%.
Selected values of the posterior distribution PP (π ≥ .40 | DLTs and prior) are shown in the table below. Also shown are the binomial probabilities of suspending the study for the observed count of DLT's.
Number of subjects observed to have treatment-related DLTs needed to suspend the study

Subjects	Treatment-Related DLTs	PP (π > 25%)*	Pr (X ≥ r|p = 0.25)
5	4	.937	.087
10	6	.805	.166
20	11	.857	.128
30	15	.812	.175
40	20	.861	.130
50	24	.836	.156
60	28	.815	.178
70	33	.858	.136
80	37	.842	.152
90	41	.828	.166
100	45	.816	.179
110	49	.805	.190
120	54	.843	.153
130	58	.834	.162

*π is the DLT rate. The minimum acceptable upper bound of a treatment-related DLT is 25%. PP (π > 25%) is the posterior probability that the RLT rate exceeds this 25% upper bound. This posterior probability of an DLT is calculated from the prior distribution, the number of subjects treated and the observed number of treatment-related RLTs. The table above presents the minimum number of subjects experiencing treatment-related DLTs (i.e., those DLTs judged to be possibly, probably, or related to Nivolumab) that would dictate suspension of the trial in accordance with the stopping rule.

9.5 Gender and Ethnicity

The total accrual goal will be 135 patients without regard to all ethnic groups

9.6 Observer-Assessed Outcomes

Performance Status (PS): Performance status will be assessed using the ECOG performance status scale and must be 0-1 at baseline for study eligibility. Changes in ECOG PS will be tracked at all PRO endpoints.

Weight Loss: The degree of weight loss may contribute to fatigue, weakness and deconditioning. Weight loss during therapy will be documented as well as post-treatment weight changes.

Tracheostomy and Enteral Feeding Tube Status: The presence of either assistive device will be tracked prospectively at all PRO time points.

Charlson Comorbidity Index: Comorbidity will be documented by chart abstraction at baseline.

Head and Neck Cancer Specific Performance Status: The Performance Status Scale (PSS-HN)[68] is a clinician-rated instrument consisting of 3 questions: normalcy of diet, public eating, and understandability of speech. The PSS-HN has been psychometrically validated and recommended by the National Comprehensive Cancer Network for measurement of swallowing and speech

performance in patients with head and neck cancer. It is not a PRO; it can be completed quickly by the trialist without adding to patient burden.

Swallowing Endpoint: Swallowing outcomes will be measured as a secondary endpoint of this trial using modified barium swallow (MBS) studies according the assessment schedule. A standardized contrast medium (Varibar® thin liquid and pudding contrast, Bracco Diagnostics, Inc. Princeton, NJ) and digitally record MBS studies (30 frames/second) must be used. Three swallowing outcomes will be rated by the SLP conducting the MBS study and reported by research staff: 1) laryngeal penetration (yes, no); 2) aspiration (no, sensate, silent), and 3) pharyngeal residue (no, < 50%, > 50%). These have been selected as universal items generally reported by swallowing clinicians that have been shown to significantly predict pneumonia in patients with oropharyngeal cancers. Prevalence of these dysphagia endpoints will be estimated at each time point.

9.7 Patient Reported Outcomes (PRO)

Quality of Life: Quality of life will be assessed using the Functional Assessment of Cancer Therapy – Head and Neck Cancer (FACT-H&N). The FACT-H&N (version 4)[17] consists of a cancer-specific questionnaire, FACT-G, in addition to 12 H&N cancer-specific items (the HN subscale). FACT-G is a 27-item measure that assesses general cancer quality of life [Cella, 1993; Cella, 1997]. The FACT-G contains 4 subscales: physical, social/family, emotional, and functional well-being. Individuals are asked to indicate how true 27 statements are for them, using the past 7 days as the timeframe. Responses range from not at all (0), to very much (4) on a 5-point scale. Psychometric properties of the FACT-G have been examined in a variety of oncology populations with alpha coefficients ranging from .65 to .89 [Cella, 1997]. After reverse coding selected items in the physical and emotional subscales, items are summed to provide total subscale scores, which will be used in our analyses. Using this scoring, higher values reflect better quality of life. [45]. The full FACT-H&N provides a summary score for overall head and neck cancer related QOL and has been used frequently in clinical trials.

Head and Neck Symptom Burden: The MD Anderson Symptom Inventory-Head & Neck (MDASI-HN[12]) measures treatment related symptom burden in head and neck cancer patients. The MDASI measures both severity and burden of symptoms and their effect on patients' daily activities, using a numeric rating scale of 0-10. This instrument includes 13 core symptoms and 9 head and neck specific items. The instrument was validated in a cohort of more than 200 patients. The coefficient alpha was highly reliable. The MDASI takes less than 5 minutes for patients to complete. [12,13,69,70]

Swallowing and Voice: Data regarding swallowing perception and performance and voice outcomes will be obtained from the MD Anderson Dysphagia Inventory (MDADI) [71] and Voice Handicap Index-10 (VHI-10).

The MDADI measures swallowing-related quality of life (QOL) in patients with swallowing dysfunction in a 20 – item written questionnaire. It evaluates the patient's physical (P), emotional (E) and functional (F) perceptions of swallowing dysfunction. This instrument has been psychometrically validated in head and neck cancer patients.

The VHI-10 [23]is a patient self-assessment instrument that quantifies patients' perception of their voice handicap. It evaluates patient's physical (P), emotional (E), and functional (F) perceptions of voice and has shown to be highly reliable for internal consistency and test-retest stability. The VHI-10 utilizes a 10-item questionnaire in which the patient circles the response that most accurately reflects his or her own experience on a linear scale (from "never" to "always").

Return to Work: Return to work will be tracked prospectively following treatment. While this data is patient reported, it does not generate a score requiring psychometric validation. It has been judged to have face validity and is brief and practical for use in a clinical trial.

9.8 Exploratory Objectives

Prognostic Biomarkers. Biomarkers of outcome include laboratory values determined at baseline from patient tissue and serum samples, clinical stage, and smoking history, expressed as pack years. Prognostic biomarkers will be assessed for prognostic impact with proportional hazards regression. Predictive biomarkers will be assessed by a proportional hazards regression model that adds 2nd order interaction with treatment arm. All hypotheses for prognosis and prediction will be simultaneously adjusted for false discovery by the method of Benjamini and Hochberg. Positive claims will be limited to those with a 10% expected false discovery rate.

10. References

1. Hayat MJ, Howlader N, Reichman ME, Edwards BK. Cancer statistics, trends, and multiple primary cancer analyses from the Surveillance, Epidemiology, and End Results (SEER) Program. The oncologist 2007;12:20-37.

2. Forastiere A, Koch W, Trotti A, Sidransky D. Head and neck cancer. The New England journal of medicine 2001;345:1890-900.

3. Shiboski CH, Schmidt BL, Jordan RC. Tongue and tonsil carcinoma: increasing trends in the U.S. population ages 20-44 years. Cancer 2005;103:1843-9.

4. Gillison ML, Koch WM, Capone RB, et al. Evidence for a causal association between human papillomavirus and a subset of head and neck cancers. Journal of the National Cancer Institute 2000;92:709-20.

5. Kreimer AR, Clifford GM, Boyle P, Franceschi S. Human papillomavirus types in head and neck squamous cell carcinomas worldwide: a systematic review. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2005;14:467-75.

6. Gillison ML. Human papillomavirus-associated head and neck cancer is a distinct epidemiologic, clinical, and molecular entity. Seminars in oncology 2004;31:744-54.

7. D'Souza G, Kreimer AR, Viscidi R, et al. Case-control study of human papillomavirus and oropharyngeal cancer. The New England journal of medicine 2007;356:1944-56.

8. Chaturvedi AK, Engels EA, Anderson WF, Gillison ML. Incidence trends for human papillomavirus-related and -unrelated oral squamous cell carcinomas in the United States. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008;26:612-9.

9. Herrero R, Castellsague X, Pawlita M, et al. Human papillomavirus and oral cancer: the International Agency for Research on Cancer multicenter study. Journal of the National Cancer Institute 2003;95:1772-83.

10. Fakhry C, Westra W, Li A, et al. Prognostic significance of human papillomavirus (HPV) tumor status for patients with head and neck squamous cell carcinoma (HNSCC) in a prospective, multi-center phase II clinical trial. 2007 ASCO Annual Meeting Proceedings; 2007; Chicago, IL: Part 1. p. 6000.

11. Adelstein DJ. Induction chemotherapy in head and neck cancer. Hematology/oncology clinics of North America 1999;13:689-98, v-vi.

12. E. R, C. VH, J. GL, et al. A randomized phase III multicenter trial of neoadjuvant docetaxel plus cisplatin and 5-fluorouracil versus neoadjuvant PF in patients with locally advanced, unresectable squamous cell carcinoma of the head and neck. Final analysis of EORTC 24971. Proc Am Soc Clin Oncol; 2006; Atlanta, GA. p. 5516.

13. Posner MR, Hershock DM, Blajman CR, et al. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. The New England journal of medicine 2007;357:1705-15.

14. M.S. K, A.S. G, C. H, et al. Induction chemotherapy (CT) with weekly paclitaxel, carboplatin, and cetuximab for squamous cell carcinoma of the head and neck (HN). 2006 ASCO Annual Meeting Proceedings Part 12006:5520.

15. A.E. A, M.K. G, D.E. H, et al. Phase II trial of neoadjuvant docetaxel (T), cisplatin (P), and cetuximab (E) followed by concurrent radiation (X), P, and E in locally advanced head and neck cancer (HNC). 2008 ASCO Annual Meeting; 2008; Chicago, IL. p. 6002.

16. Feng FY, Kim HM, Lyden TH, et al. Intensity-modulated radiotherapy of head and neck cancer aiming to reduce dysphagia: early dose-effect relationships for the swallowing structures. International journal of radiation oncology, biology, physics 2007;68:1289-98.

17. List MA, D'Antonio LL, Cella DF, et al. The Performance Status Scale for Head and Neck Cancer Patients and the Functional Assessment of Cancer Therapy-Head and Neck Scale. A study of utility and validity. Cancer 1996;77:2294-301.

18. J R, R F, L P, et al. Impact of p16 status on the QOL effects of CRT for locally advanced oropharynx cancer: Results of RTOG 02.02. . 2012 ASCO Annual Meeting Proceedings; 2012; Chicago, IL. p. 5571.

19. Carrara-de Angelis E, Feher O, Barros AP, Nishimoto IN, Kowalski LP. Voice and swallowing in patients enrolled in a larynx preservation trial. Archives of otolaryngology--head & neck surgery 2003;129:733-8.

20. Weinstein GS, O'Malley BW, Jr., Cohen MA, Quon H. Transoral robotic surgery for advanced oropharyngeal carcinoma. Archives of otolaryngology--head & neck surgery 2010;136:1079-85.

21. Sharma A, Mendez E, Yueh B, et al. Human papillomavirus-positive oral cavity and oropharyngeal cancer patients do not have better quality-of-life trajectories. Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery 2012;146:739-45.

22. Moore EJ, Olsen KD, Kasperbauer JL. Transoral robotic surgery for oropharyngeal squamous cell carcinoma: a prospective study of feasibility and functional outcomes. The Laryngoscope 2009;119:2156-64.

23. H.J. W, M. G, B. B, et al. Phase II evaluation of cetuximab (C225) combined with induction paclitaxel and carboplatin followed by C225, paclitaxel, carboplatin, and radiation for stage III/IV operable squamous cancer of the head and neck (ECOG, E2303). 2007 ASCO Annual Meeting Proceedings, Part 1; 2007; Chicago, IL. p. 6015.

24. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. The New England journal of medicine 2006;354:567-78.

25. Burtness B, Goldwasser MA, Flood W, Mattar B, Forastiere AA, Eastern Cooperative Oncology G. Phase III randomized trial of cisplatin plus placebo compared with cisplatin plus cetuximab in metastatic/recurrent head and neck cancer: an Eastern Cooperative Oncology Group study. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2005;23:8646-54.

26. Hall EJ. Radiobiology for the Radiologist. Philadelphia, PA: Lippincott; 1993.

27. Mu D, Hsu DS, Sancar A. Reaction mechanism of human DNA repair excision nuclease. The Journal of biological chemistry 1996;271:8285-94.

28. Zamble DB, Mu D, Reardon JT, Sancar A, Lippard SJ. Repair of cisplatin--DNA adducts by the mammalian excision nuclease. Biochemistry 1996;35:10004-13.

29. Handra-Luca A, Hernandez J, Mountzios G, et al. Excision repair cross complementation group 1 immunohistochemical expression predicts objective response and cancer-specific survival in patients treated by Cisplatin-based induction chemotherapy for locally advanced head and neck squamous cell carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research 2007;13:3855-9.

30. Jun HJ, Ahn MJ, Kim HS, et al. ERCC1 expression as a predictive marker of squamous cell carcinoma of the head and neck treated with cisplatin-based concurrent chemoradiation. British journal of cancer 2008;99:167-72.

31. Carles J, Monzo M, Amat M, et al. Single-nucleotide polymorphisms in base excision repair, nucleotide excision repair, and double strand break genes as markers for response to radiotherapy in patients with Stage I to II head-and-neck cancer. International journal of radiation oncology, biology, physics 2006;66:1022-30.

32. Rubin Grandis J, Melhem MF, Gooding WE, et al. Levels of TGF-alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival. Journal of the National Cancer Institute 1998;90:824-32.

33. Ang KK, Berkey BA, Tu X, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. Cancer research 2002;62:7350-6.

34. Cohen EE, Kane MA, List MA, et al. Phase II trial of gefitinib 250 mg daily in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck. Clinical cancer research : an official journal of the American Association for Cancer Research 2005;11:8418-24.

35. Engelman JA, Zejnullahu K, Mitsudomi T, et al. MET amplification leads to gefitinib resistance in lung cancer by activating ERBB3 signaling. Science 2007;316:1039-43.

36. Psyrri A, Yu Z, Weinberger PM, et al. Quantitative determination of nuclear and cytoplasmic epidermal growth factor receptor expression in oropharyngeal squamous cell cancer by using automated quantitative analysis. Clinical cancer research : an official journal of the American Association for Cancer Research 2005;11:5856-62.

37. Hirsch FR, Varella-Garcia M, Bunn PA, Jr., et al. Epidermal growth factor receptor in non-small-cell lung carcinomas: correlation between gene copy number and protein expression and impact on prognosis. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2003;21:3798-807.

38. Cappuzzo F, Hirsch FR, Rossi E, et al. Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. Journal of the National Cancer Institute 2005;97:643-55.

39. Chung CH, Ely K, McGavran L, et al. Increased epidermal growth factor receptor gene copy number is associated with poor prognosis in head and neck squamous cell carcinomas. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;24:4170-6.

40. Frederick BA, Helfrich BA, Coldren CD, et al. Epithelial to mesenchymal transition predicts gefitinib resistance in cell lines of head and neck squamous cell carcinoma and non-small cell lung carcinoma. Molecular cancer therapeutics 2007;6:1683-91.

41. Temam S, Kawaguchi H, El-Naggar AK, et al. Epidermal growth factor receptor copy number alterations correlate with poor clinical outcome in patients with head and neck squamous cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2007;25:2164-70.

42. Musolino A, Naldi N, Bortesi B, et al. Immunoglobulin G fragment C receptor polymorphisms and clinical efficacy of trastuzumab-based therapy in patients with HER-2/neu-positive metastatic

breast cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2008;26:1789-96.

43. Taylor RJ, Chan SL, Wood A, et al. FcgammaRIIIa polymorphisms and cetuximab induced cytotoxicity in squamous cell carcinoma of the head and neck. Cancer immunology, immunotherapy : CII 2009;58:997-1006.

44. Mustian KM, Griggs JJ, Morrow GR, et al. Exercise and side effects among 749 patients during and after treatment for cancer: a University of Rochester Cancer Center Community Clinical Oncology Program Study. Supportive care in cancer : official journal of the Multinational Association of Supportive Care in Cancer 2006;14:732-41.

45. Cella DF, Tulsky DS, Gray G, et al. The Functional Assessment of Cancer Therapy scale: development and validation of the general measure. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 1993;11:570-9.

46. Slebos RJ, Yi Y, Ely K, et al. Gene expression differences associated with human papillomavirus status in head and neck squamous cell carcinoma. Clinical cancer research : an official journal of the American Association for Cancer Research 2006;12:701-9.

47. Warmerdam PA, van den Herik-Oudijk IE, Parren PW, Westerdaal NA, van de Winkel JG, Capel PJ. Interaction of a human Fc gamma RIIb1 (CD32) isoform with murine and human IgG subclasses. International immunology 1993;5:239-47.

48. Zhang W, Gordon M, Schultheis AM, et al. FCGR2A and FCGR3A polymorphisms associated with clinical outcome of epidermal growth factor receptor expressing metastatic colorectal cancer patients treated with single-agent cetuximab. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2007;25:3712-8.

49. Cella D. The Functional Assessment of Cancer Therapy-Anemia (FACT-An) Scale: a new tool for the assessment of outcomes in cancer anemia and fatigue. Seminars in hematology 1997;34:13-9.

50. Lango MN, Andrews GA, Ahmad S, et al. Postradiotherapy neck dissection for head and neck squamous cell carcinoma: pattern of pathologic residual carcinoma and prognosis. Head & neck 2009;31:328-37.

51. Eisbruch A, Lyden T, Bradford CR, et al. Objective assessment of swallowing dysfunction and aspiration after radiation concurrent with chemotherapy for head-and-neck cancer. International journal of radiation oncology, biology, physics 2002;53:23-8.

52. Rosenthal DI, Lewin JS, Eisbruch A. Prevention and treatment of dysphagia and aspiration after chemoradiation for head and neck cancer. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2006;24:2636-43.

53. Gregoire V, De Neve W, Eisbruch A, Lee N, Van den Weyngaert D, Van Gestel D. Intensity-modulated radiation therapy for head and neck carcinoma. The oncologist 2007;12:555-64.

54. Duggan, M B, BA M, et al. Intensity-Modulated Radiation Therapy (IMRT) with Concurrent Taxane-Based Chemotherapy for Locally-Advanced Head and Neck Cancer (LAHNC): Feasibility, Technique, and Toxicities. 2008 ASCO Annual Meeting Proceedings; 2008; Chicago, IL. p. 509s.

55. Lee NY, O'Meara W, Chan K, et al. Concurrent chemotherapy and intensity-modulated radiotherapy for locoregionally advanced laryngeal and hypopharyngeal cancers. International journal of radiation oncology, biology, physics 2007;69:459-68.

56. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. Lancet 2000;355:949-55.

57. Chen BJ, Chapuy B, Ouyang J, et al. PD-L1 expression is characteristic of a subset of aggressive B-cell lymphomas and virus-associated malignancies. Clinical cancer research : an official journal of the American Association for Cancer Research 2013;19:3462-73.

58. Parsa AT, Waldron JS, Panner A, et al. Loss of tumor suppressor PTEN function increases B7-H1 expression and immunoresistance in glioma. Nature medicine 2007;13:84-8.

59. Segal NH, Parsons DW, Peggs KS, et al. Epitope landscape in breast and colorectal cancer. Cancer research 2008;68:889-92.

60. Snyder A, Makarov V, Merghoub T, et al. Genetic basis for clinical response to CTLA-4 blockade in melanoma. The New England journal of medicine 2014;371:2189-99.

61. Tran E, Turcotte S, Gros A, et al. Cancer immunotherapy based on mutation-specific CD4+ T cells in a patient with epithelial cancer. Science 2014;344:641-5.

62. Carreno BM, Magrini V, Becker-Hapak M, et al. Cancer immunotherapy. A dendritic cell vaccine increases the breadth and diversity of melanoma neoantigen-specific T cells. Science 2015;348:803-8.

63. Golden EB, Demaria S, Schiff PB, Chachoua A, Formenti SC. An abscopal response to radiation and ipilimumab in a patient with metastatic non-small cell lung cancer. Cancer immunology research 2013;1:365-72.

64. Golden EB, Formenti SC. Radiation therapy and immunotherapy: growing pains. International journal of radiation oncology, biology, physics 2015;91:252-4.

65. Twyman-Saint Victor C, Rech AJ, Maity A, et al. Radiation and dual checkpoint blockade activate non-redundant immune mechanisms in cancer. Nature 2015;520:373-7.

66. Licitra L, Suardi S, Bossi P, et al. Prediction of TP53 status for primary cisplatin, fluorouracil, and leucovorin chemotherapy in ethmoid sinus intestinal-type adenocarcinoma. Journal of clinical oncology : official journal of the American Society of Clinical Oncology 2004;22:4901-6.

67. Poeta ML, Manola J, Goldwasser MA, et al. TP53 mutations and survival in squamous-cell carcinoma of the head and neck. The New England journal of medicine 2007;357:2552-61.

68. List MA, Ritter-Sterr C, Lansky SB. A performance status scale for head and neck cancer patients. Cancer 1990;66:564-9.

69. Cleeland CS, Mendoza TR, Wang XS, et al. Assessing symptom distress in cancer patients: the M.D. Anderson Symptom Inventory. Cancer 2000;89:1634-46.

70. Rosenthal DI, Mendoza TR, Chambers MS, et al. Measuring head and neck cancer symptom burden: the development and validation of the M. D. Anderson symptom inventory, head and neck module. Head & neck 2007;29:923-31.

71. Chen AY, Frankowski R, Bishop-Leone J, et al. The development and validation of a dysphagia-specific quality-of-life questionnaire for patients with head and neck cancer: the M. D. Anderson dysphagia inventory. Archives of otolaryngology--head & neck surgery 2001;127:870-6.

72. Andrade Filho PA, Ito D, Deleo AB, Ferris RL. CD8+ T cell recognition of polymorphic wild-type sequence p53(65-73) peptides in squamous cell carcinoma of the head and neck. Cancer Immunol Immunother;59:1561-8.

73. Andrade Filho PA, Lopez-Albaitero A, Gooding W, Ferris RL. Novel immunogenic HLA-A*0201-restricted epidermal growth factor receptor-specific T-cell epitope in head and neck cancer patients. J Immunother;33:83-91.

74. Sirianni N, Ha PK, Oelke M, et al. Effect of human papillomavirus-16 infection on CD8+ T-cell recognition of a wild-type sequence p53264-272 peptide in patients with squamous cell carcinoma of

the head and neck. Clinical cancer research : an official journal of the American Association for Cancer Research 2004;10:6929-37.

75. Albers A, Abe K, Hunt J, et al. Antitumor activity of human papillomavirus type 16 E7-specific T cells against virally infected squamous cell carcinoma of the head and neck. Cancer research 2005;65:11146-55.

76. Kadish AS, Timmins P, Wang Y, et al. Regression of cervical intraepithelial neoplasia and loss of human papillomavirus (HPV) infection is associated with cell-mediated immune responses to an HPV type 16 E7 peptide. Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology 2002;11:483-8.

77. Hoffmann TK, Arsov C, Schirlau K, et al. T cells specific for HPV16 E7 epitopes in patients with squamous cell carcinoma of the oropharynx. International journal of cancer 2006;118:1984-91.

78. Postow MA, Callahan MK, Wolchok JD. The antitumor immunity of ipilimumab: (T-cell) memories to last a lifetime? Clinical cancer research : an official journal of the American Association for Cancer Research 2012;18:1821-3.

79. Gillison ML, D'Souza G, Westra W, et al. Distinct risk factor profiles for human papillomavirus type 16-positive and human papillomavirus type 16-negative head and neck cancers. Journal of the National Cancer Institute 2008;100:407-20.

80. Jie HB, Gildener-Leapman N, Li J, et al. Intratumoral regulatory T cells upregulate immunosuppressive molecules in head and neck cancer patients. British journal of cancer 2013;109:2629-35.

81. Lyford-Pike S, Peng S, Young GD, et al. Evidence for a role of the PD-1:PD-L1 pathway in immune resistance of HPV-associated head and neck squamous cell carcinoma. Cancer research 2013;73:1733-41.

Appendix I Patient Reported Outcomes (PROs)

EQ5D 5L Health Questionnaire
Functional Assessment of Cancer Therapy – Head and Neck Cancer (FACT-HN)
MD Anderson Symptom Inventory-Head & Neck (MDASI-HN)
MD Anderson Dysphagia Inventory (MDADI)
VHI-10


VHI-10.pdf


FACT-HN.pdf


MDADI.pdf


MDASI-HN.pdf


EQ5D 5L Health Questionnaire.pdf

Appendix II: Modified Barium Swallow Study Form

MBS **Modified Barium Swallow Study Form**

Phase II Trial of Adjuvant De-Escalated Radiation + Concurrent and Adjuvant Nivolumab for Intermediate-High Risk P16+ Oropharynx Cancer

INSTRUCTIONS: To be filled out by the speech pathologist after the modified barium swallow study**. Dates are recorded as** mm-dd-yyyy **unless otherwise specified.**

MBS PROTOCOL:
All MBS studies must follow a standard protocol as outlined below.
Additional bolus presentations or swallowing strategies may be tested after completing bolus trials in the study protocol, at the discretion of the clinician conducting the MBS study.
Studies will be done in lateral and AP views with focus fixed on the soft palate superiorly, cricopharyngeus inferiorly, lips anteriorly, and cervical spine posteriorly.
Video-recordings will require time code imprints accurate to 0.01 seconds (30 frames/second). Video-recordings between 15-30 frames/second will be accepted as long as the recording rate is clearly documented in advance. Video-recordings below 15 frames/second will not be accepted.
Studies must be recorded in AVI or MPEG format. All centers must use the Kay Digital Swallowing Workstation for the studies; or alternatively, can convert files to AVI of MPEG format.
Centers must use Varibar products. Consistencies and quantities are listed below. Liquids must be administered first to avoid confounding the results from remaining residue in the pharynx after solid consistencies.
A dime must be taped to the subject's chin during the swallowing study. The circular shape of the dime minimizes the impact of head rotation and the known diameter of the dime allows for calibration of pixels per cm and thus calculation of distances and areas on the lateral view of the x-ray.
Lateral view:

- 5mL thin (2 trials, tsp). Instruction to the patient: *please hold this in your mouth until asked to swallow.*
- 20mL thin (1 trial). Instruction to the patient: *please try to take the whole amount and hold it in your mouth until I ask you to swallow*. Self-administration is optimal, but clinician administration is acceptable.
- 5mL pudding (1 trial tsp). Instruction: *swallow when you are ready.*
- 1/2 cookie or cracker, barium coated - coated with 3 ml (1/2 tsp) of Varibar pudding (1 trial). Instruction to the patient: *chew this up and swallow when you feel comfortable and ready to swallow.*

A-P view:
10mL thin (1 trial). Instruction: slightly raise your chin (neutral position, not tucked or extended), hold this in your mouth until asked to
RATING RULES:
Rate MBS outcomes below on the basis of bolus trials in the University of Pittsburgh protocol. Do not rate based on additional bolus trials that are administered outside of the protocol or based on bolus trials in which a swallow strategy/posture was tested. Please select a SUMMARY RATING based on the highest level of impairment you observe on any bolus trial in the protocol.

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1 DATE OF MBS _____-_____-_____	**2 □TIME OF MBS** 1. Baseline 2. After surgery (before adjuvant therapy) 3. Six months after treatment 4. Twenty-four months after treatment

Outcome Variables	**Definition**	**Scoring Rules** (Rate the worst of impairment across all bolus trials in the MBS protocol)	**Rating**
3 LARYNGEAL PENETRATION	PENETRATION: Bolus enters the larynx but does not pass below the TVFs	Select "1" if LARYNGEAL PENETRATION occurred on any bolus in the protocol.	□ No penetration (0) □ Penetration (1)
4 ASPIRATION	ASPIRATION: Bolus enters the larynx and passes below the TVFs. SENSATE: attempts to eject aspirate from airway (e.g., cough, throat clear) SILENT: no effort to eject aspirate from airway (no cough, throat clear)	Select the highest level of aspiration that occurred during the protocol. Select "1" if SENSATE ASPIRATION ocurred on any bolus in the protocol, but silent aspiration NEVER occurred. Select "2" if SILENT ASPIRATION occurred on any bolus in the protocol.	□ No aspiration (0) □ Yes, sensate (1) □ Yes, silent (2)
5 PHARYNGEAL RESIDUE	RESIDUE: bolus remaining on or within the pharynx at the conclusion of the initial swallow. The conclusion of the initial swallow is when the hyoid bone returns to rest. If the patient spontaneously swallows several times to clear the bolus, residue is rated after the 1st swallow attempt.	Rate the highest level of residue that occurred during the protocol. Select "0" is no residue or only pharyngeal coating occurred during the protocol. Select "1" if pharyngeal residue of <50% of the original bolus remained in the pharynx on any bolus in the protocol. Select "2" if pharyngeal residue of half or more of the original bolus	□ No residue (0) □ <50% pharyngeal residue (1) □ ≥ 50% pharyngeal residue (2)

		remained in the pharynx on any bolus in the protocol.	

PERSON COMPLETING FORM:

NOTE: This form is for reference only. The MBS information for each registered patient will be entered directly into the UPMC database.