RTOG FOUNDATION

RTOG 3504

(ClinicalTrials.gov NCT #: 02764593)

SAFETY EVALUATIONS OF NIVOLUMAB (ANTI-PD-1) ADDED TO CHEMORADIOTHERAPY (CRT) PLATFORMS IN PATIENTS WITH INTERMEDIATE AND HIGH-RISK LOCAL-REGIONALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

Amendment 4: December 26, 2017

RTOG Foundation Collaboration with Bristol-Myers Squibb

RTOG 3504

A Limited Participation Study

SAFETY EVALUATIONS OF NIVOLUMAB (ANTI-PD-1) ADDED TO CHEMORADIOTHERAPY (CRT) PLATFORMS IN PATIENTS WITH INTERMEDIATE AND HIGH-RISK LOCAL-REGIONALLY ADVANCED HEAD AND NECK SQUAMOUS CELL CARCINOMA

Sponsor: RTOG Foundation

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Protocol Acceptance
On behalf of the RTOG Foundation, Inc.

Walter J. Curran, Jr., MD
RTOG Foundation Chairman

Date: December 26, 2017

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***(ClinicalTrials.gov NCT #* NCT02764593*)* (5/5/2016)**

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Protocol Agents

Agent	Supply	IND #	IND Sponsor
Cisplatin	Commercial	Exempt	N/A
Cetuximab	Commercial	Exempt	N/A
Nivolumab	Bristol-Myers Squibb, clinical supply	IND# 129841	RTOG Foundation, Inc.

Participating Sites: A list of sites participating in the trial can be accessed on the RTOG website.

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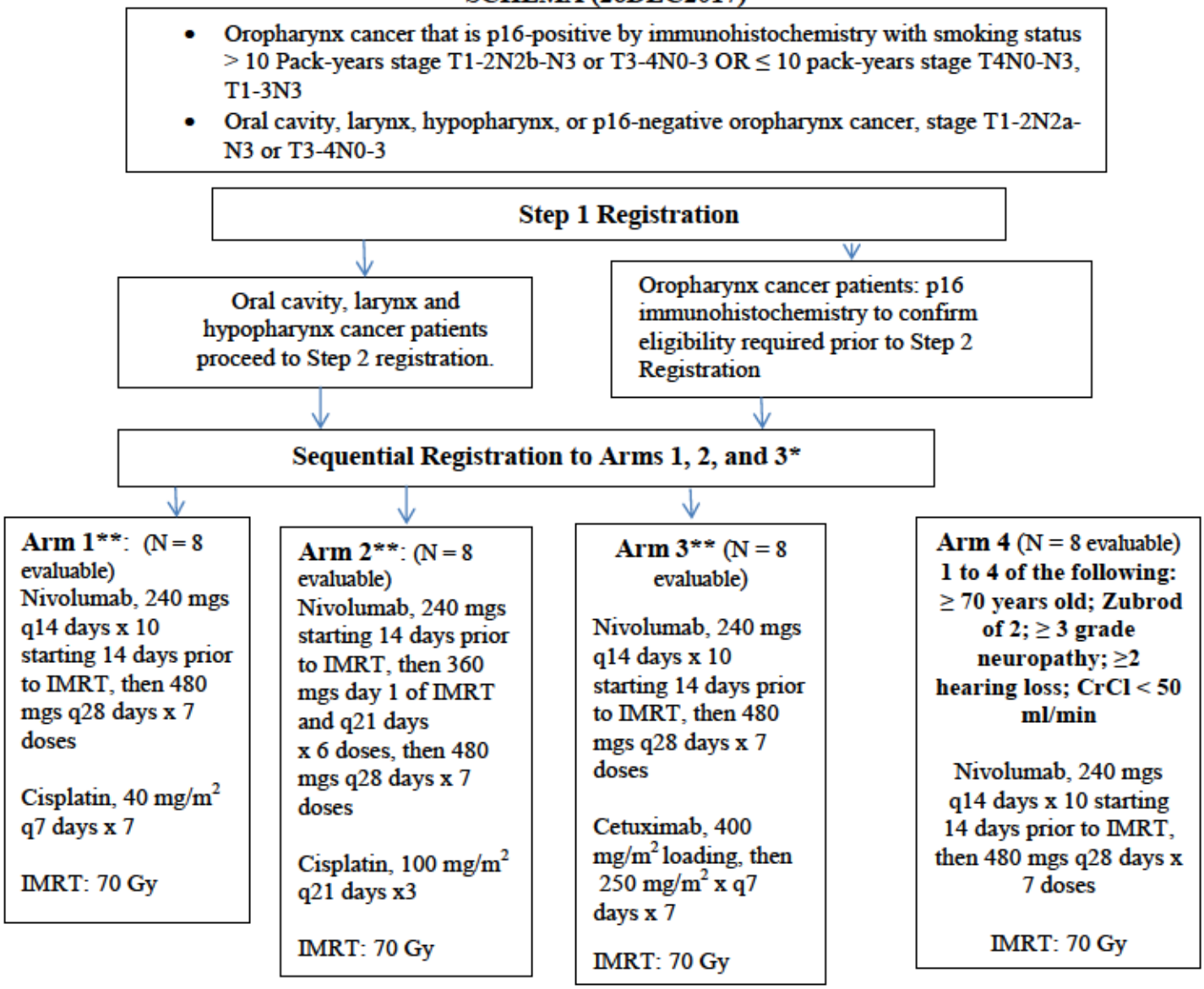
Safety Evaluations of Nivolumab (Anti-PD-1) Added to Chemoradiotherapy (CRT) Platforms in Patients with Intermediate and High-Risk Local-Regionally Advanced Head and Neck Squamous Cell Carcinoma

SCHEMA (26DEC2017)



*** All patients will be registered to Arm 1 until the sample size is reached, then to Arm 2, then to Arm 3.**
****Note: The feasibility of 7 months of adjuvant nivolumab will be determined in the first 8 evaluable patients.**

1. OBJECTIVES

1.1 Primary Objectives (26Dec2017)

- To evaluate the safety of the addition of nivolumab (anti PD-1 immunotherapy) to chemoradiotherapy with weekly cisplatin (40 mg/m^2/week x 7) for patients with intermediate or high-risk head and neck squamous cell carcinoma (HNSCC) (Arm 1);
- To evaluate the safety of the addition of nivolumab (anti PD-1 immunotherapy) to chemoradiotherapy with high-dose cisplatin (100 mg/m^2 q 21 days x 3) for patients with intermediate or high-risk head and neck squamous cell carcinoma (HNSCC) (Arm 2);
- To evaluate the safety of the addition of nivolumab (anti PD-1 immunotherapy) to chemoradiotherapy with weekly cetuximab (400 mg/m^2 load, 250 mg/m^2/week x 7) for patients with intermediate- or high-riskhead and neck squamous cell carcinoma (HNSCC) (Arm 3);
- To evaluate the safety of the addition of nivolumab (anti PD-1 immunotherapy) to radiotherapy for patients with intermediate or high-risk head and neck squamous cell carcinoma (HNSCC) with one to four of the following: age $\geq$ 70 years; Zubrod Performance Status 2; baseline grade $\geq$ 3 neuropathy; grade $\geq$2 hearing loss; CrCl < 50 ml/min (Arm 4).

1.2 Secondary Objective

To evaluate the safety, feasibility and patient compliance with adjuvant administration of single agent nivolumab to a maximum of 1 year of therapy (nivolumab, 480 mgs q28 days x 7)

2. BACKGROUND

2.1 Study Overview

The study is a safety evaluation of the addition of nivolumab to several chemoradiotherapy platforms with weekly cisplatin, high-dose cisplatin, cetuximab or radiotherapy alone. The 4 arms will include 32 evaluable patients. Patients with intermediate- or high-risk HNSCC will be sequentially assigned to receive (Arm 1) nivolumab (240 mgs q14 days x 10) starting on day -14 prior to IMRT with weekly cisplatin (40 mg/m^2 X 7)-based chemoradiotherapy then (Arm 2) nivolumab (240 mgs on day -14 prior to IMRT followed by nivolumab 360 mgs q 21 days x 7) with high-dose cisplatin (100 mg/m^2 IV day 1, 22, and 43)-based chemoradiotherapy then (Arm 3) nivolumab (240 mgs q14 days x 10) with cetuximab-based chemoradiotherapy. Arm 4 is open for platinum-inelgible patients (see below). In the event that > 2 of 8 evaluable patients experience a dose-limiting toxicity (DLT), the arm will be considered not worthy of further study due to safety concerns. If $\leq$ 2 of 8 patients experience a DLT in Arm 1, the regimen will be considered worthy of additional study. The study will also evaluate the safety and feasibility of adjuvant administration of nivolumab 480 mgs q28 days x 7, starting 3 months after end of RT. Feasibility will be evaluated in the first eight patients on any arm and if more than 4 receive less than 7 doses adjuvant therapy will be considered infeasible.

In melanoma and lung cancer adjuvant trials, single agent nivolumab is administered for up to a year after primary therapy. This time frame is based upon observations in recurrent metastatic disease demonstrating prolonged time to steady state antibody levels,

as well as delayed responses to therapy beyond 4 months of therapy. In theory, continued immunotherapy during this time frame may facilitate immune clearance of micro-metastatic disease and prevent or prolong disease progression. The optimal duration of adjuvant immunotherapy is unknown both in animal models and in human subjects. Also unknown are the potential long-term toxicities of this therapy in head and neck cancer patients. Historically, head and neck cancer patients are poorly inclined toward adjuvant therapies, and rates of refusal or discontinuation of adjuvant therapies included in clinical trials are high. Therefore, we will evaluate the safety and feasibility of adjuvant immunotherapy in the patient population. In this protocol, the term "adjuvant therapy" will be defined as administration of nivolumab starting 3 months after completion of chemoradiotherapy for 7 months.

2.2 Head and Neck Cancer

HNSCC is a major cause of morbidity and mortality worldwide, with over 610,000 new cases diagnosed each year (Ferlay 2011). The American Cancer Society estimates that 53,640 new cases and 11,520 deaths from HNSCC occurred in the U. S. in 2013 (Siegel 2013). While the majority of HNSCC worldwide are attributable to tobacco and alcohol use, oral HPV infection is newly appreciated as the principal cause of a distinct form of HNSCC (Gillison 2008). These cancers arise predominantly from the tonsil and base of tongue within the oropharynx. While incidence rates for HNSCC overall declined from 1992-2005 in the U.S., the incidence rates for oropharyngeal cancer are rising (Jemal 2013). An analysis of NCI SEER oral cancer specimens revealed that the incidence rates for HPV-negative oropharyngeal cancer decreased by 50% from 1984-2004, whereas rates for HPV-positive oropharyngeal squamous cell carcinoma (OPC) increased by 225% during the same time period (Chaturvedi 2011). It is hypothesized that these trends are due to known reductions in tobacco smoking in the U.S. over the last several decades concomitant with increasing rates of oral HPV infection. HPV-positive OPSCC is projected to be the predominant type of HNSCC in the U.S. by 2030 (Chaturvedi 2011, Pignon 2009).

2.3 HPV and Head and Neck Cancer Survival

Tumor HPV status has been shown to be a strong, independent prognostic biomarker for patients with HNSCC treated with cisplatin- or cetuximab-based RT (Rosenthal 2014). Patients with HPV-positive OPSCC have a 58% (HR 0.42, 95%CI 0.27-0.66) reduction in risk of death when compared to patients with HPV-negative OPSCC (Ang 2010), after adjustment for other prognostic factors. HPV-positive cancers have been shown to have higher response rates to chemotherapy and CRT (Fakhry 2007), resulting in higher local-regional disease control. Furthermore, the combination of HPV status, pack-years of tobacco smoking, and tumor stage has been shown to classify patients as having a low, intermediate, or high risk of death. Three-year rates of OS were 93% (95%CI, 88.3-97.7) in the low-risk group, 70.8% (95%CI 60.7-80.8) in the intermediate-risk group, and 46.2% (95%CI 34.7-57.5) in the high-risk group (Ang 2010, Gillison 2012). Novel therapies are thus needed in both intermediate and high-risk patients to improve both local-regional control and reduce risk of distant metastases.

Additional analyses conducted by O'Sullivan, et al. (2013) have indicated that patients with p16-positive OPSCC with T4 or N2C-N3 disease have a high-risk of disease progression, even if tobacco exposure is < 10 pack-years. Therefore, these patients are

also considered eligible for this clinical trial. The sample size calculations presented in this protocol consider the outcome of all of these eligible patients based on observations from RTOG 0522.It is important to note that many of the clinical trials investigating the impact of tumor HPV status on survival have utilized a validated surrogate; tumor p16-expression status as measured by immunohistochemistry. P16-expression has been shown to have ~92% sensitivity and ~90% specificity in comparison to the gold standard of expression of high-risk HPV oncogenes E6 and E7 (Jordan 2012).

2.4 Primary CRT for Head and Neck Cancer

The majority (~60%) of HNSCC patients is diagnosed with local-regionally advanced disease, and the 5-year survival for this subset is heavily dependent on HPV status. The current nonsurgical standard of care for the majority of patients with local-regionally advanced (Stage III-IV) oropharynx, larynx, hypopharynx, and unresectable oral cavity cancers is organ preservation CRT. Cisplatin-based CRT has been shown to improve local-regional control, PFS, and OS when compared to radiotherapy alone. Altered fractionation of radiation does not seem to eliminate the benefit of the addition of concurrent chemotherapy (Budach 2006, Blanchard 2011, Bourhis 2012). A recent meta-analysis estimated the absolute benefit of concomitant chemoradiotherapy over radiotherapy to be 6.5% at 5-years for all head and neck cancer patients (Pignon 2009). A recently completed, large randomized phase III trial (RTOG 1016) is testing whether CRT with cisplatin vs. cetuximab results in equivalent survival or whether one or the other regimen is superior in p16-positive oropharynx cancer patients. Surveys of community oncology practices indicate approximately equivalent use of cisplatin- and cetuximab-based CRT for the primary treatment of HNSCC.

While high-dose cisplatin (75-100 mg/m^2) every 21 days is the most common schedule used (Brizel 1998, Beckmann 2005, Forastiere 1993, Jeremic 2000, Quon 2011, Bachaud 1996), bolus cisplatin (75-100 mg/m^2 every 21 days) is associated with frequent toxicities such as nausea and vomiting, renal impairment, cytopenias, and ototoxicity. As a result of these toxicities, ~ 30% of individuals in randomized clinical trials in RTOG do not receive all 3 cycles of chemotherapy (Forastiere 2003, Ang 2010). To overcome these challenges, several clinical trials have investigated weekly cisplatin schedules. Weekly schedules have ranged in dose between cisplatin 20-50 mg/m^2/week. A randomized study of 20 mg/m^2/week failed to show improvement vs. radiation alone (Quon 2011). However, other schedules of higher dose weekly cisplatin (33-40 mg/m^2 with radiation) have proven to be effective, feasible, and tolerable in HNSCC (Medina 2006, Maguire 2011, Chan 2005). For nasopharyngeal cancer, randomized clinical trials have demonstrated a survival advantage for cisplatin 30 mg/m^2/week in comparison to radiotherapy alone for stage II disease (Chen 2011) and for cisplatin 40 mg/m^2/week for stage II-IV disease (Chan 2004). For HNSCC, a French randomized trial also demonstrated a survival benefit from cisplatin 50 mg/week (~30 mgs/m^2) in comparison to RT alone (Bachaud 1996) and doses as low as cisplatin 6 mg/m^2/day of RT have also shown a survival benefit, with high treatment delivery and reduced toxicity (Jeremic 2004).

Whatever the regimen, a formal analysis of cisplatin dosing indicated that a cumulative dose of cisplatin 200 mg/m^2 concurrent with radiation is most often associated with

meaningful improvement in tumor control and/ or survival (Ang 2004). Weekly regimens are more broadly tolerable and therefore, more amenable as a platform on which to add additional chemotherapeutic or biological anti-cancer agents. This change to a weekly cisplatin dosing has been the approach of the RTOG for several of its recent studies, including in the adjuvant setting for high-risk patients (RTOG 0234 and 1216) and low-risk HPV-positive cancer (NRG-HN002). Fortunately, the use of immunosuppressive steroids for control of nausea is not usually necessary with weekly dosing. This trial will include an evaluation of the safety and feasibility of the addition of nivolumab to both cisplatin regimens (cisplatin 40 mg/m^2/week x 7 with nivolumab [240 mgs] every 14 days and cisplatin 100 mg/m^2 day 1, 22 and 43 of radiotherapy with nivolumab [5 mg/kg] every 21 days),

Interestingly, data exist that cisplatin CRT in an HPV-positive murine HNSCC model requires the adaptive immune system to mediate the optimal therapeutic effect (Spanos 2009), supporting the combination with anti-PD-1 mAb blockade to enhance this effect, as proposed here.

The addition of cetuximab, a monoclonal antibody targeted to the EGFR receptor, has been shown in a single randomized controlled trial to increase local-regional, progression-free survival (PFS) and 5-year overall survival (OS) (by 9%) in comparison to radiation therapy alone (Bonner 2006, Bonner 2010). Subgroup analysis revealed that the benefit of cetuximab was greater for a patient with a clinical profile consistent with HPV-positive OPSCC (male, age < 65 years, low T stage, advanced N stage, good performance status) (Bonner 2010). These data prompted the RTOG to evaluate whether substitution of cisplatin with cetuximab results in comparable 5-year OS for patients with local-regionally advanced HPV-positive oropharyngeal cancer (RTOG 1016). Recently, the benefit of cetuximab for HPV-positive OPSCC was retrospectively evaluated using tumor specimens from the original Bonner trial, demonstrating significant clinical benefit in p16-positive OPSCC patients from the addition of cetuximab to radiotherapy (Rosenthal 2014). In Kaplan-Meier analysis, cetuximab significantly improved overall survival (OS, 3-year 88 vs. 72%, HR 0.38, 95%CI 0.15-0.94) in comparison to radiotherapy alone among patients with p16-positive OPSCC. RTOG 1016 has met its accrual goals, but definitive results from this study are not likely to be available until 2018. In anticipation of the results of RTOG 1016, we have included a cetuximab-based chemoradiotherapy arm this trial.

Because of the toxicities associated with cisplatin-based radiotherapy, a significant number of patients cannot receive cisplatin. This includes patients with a Zubrod Performance Status of 2, for whom radiotherapy alone is the standard of care (NCCN guidelines). Patients also may not be considered candidates for cisplatin based upon preexisting renal insufficiency (CrCl <50), hearing loss, or peripheral neuropathy. Additionally, meta-analysis of cisplatin trials as well as a subset analyses of the Bonner cetuximab study have not demonstrated improvement over radiotherapy alone among individuals 70 years of age and older. Therefore, radiotherapy alone (or cetuximab RT) is the current standard of care for a subset of patients (age > 70 years, Zubrod PS 2, intolerant to cisplatin). This trial will also therefore include a nivolumab RT arm to

evaluate the safety and feasibility of this regimen in this patient population.

2.5 Head and Neck Cancer and Immunity

Immune dysfunction may play a role in the pathogenesis and progression of HNSCC. Down-regulation of T cell function has been reported in HNSCC, and is mediated by multiple mechanisms including: reduced expression of co-stimulating molecules of the B7-CD28 family (Albers 2005); increased expression of PD-L1 in tumor cells and tumor associated fibroblasts; and loss of HLA-class I and selective down-regulation of HLA-A, B, C locus expression resulting in defective antigen presentation (Lopez-Albaitero 2006, Leibowitz 2013). Additionally, HPV-positive HNSCC patients have expanded populations of virus-specific T cells with an ineffective antitumor phenotype (Albers 2005).

Monoclonal Antibody-Based Immunotherapy of HNSCC

Today the most widely used form of cancer immunotherapy is mAb therapy (Ferris 2010). This includes tumor antigen (TA)-targeted mAbs, cytokine-targeted mAbs, tumor necrosis factor receptor (TNFR)-family costimulatory targeted mAbs and immune checkpoint-targeted mAbs. The most extensively studied (and FDA approved for HNSCC) of these is cetuximab, a mouse–human chimeric IgG1 anti-epidermal growth factor receptor mAb (Yewale 2013). EGFR is an attractive target in HNSCC because it is overexpressed in 80–90% of HNSCC and leads to tumor cell proliferation, invasion, angiogenesis, tumor survival, and consequently, poor survival and prognosis (Rubin Grandis 1998).

Anti-EGFR mAb mediate antigen-specific immune responses to targeted tumors through two major mechanisms: direct killing via lytic immune cell (NK cell or monocytes) and complement fixation, or opsonization of tumor for phagocytosis and subsequent antigen processing. The latter would induce TA-specific cytotoxic T lymphocytes (CTL) to recognize and lyse tumor cells. One of the most direct methods by which antibodies can cause tumor lysis is via antibody-dependent cellular cytotoxicity (ADCC) mediated by NK cells and probably monocytes and neutrophils. The extent of ADCC is heavily influenced by genetic polymorphisms in FcγRIIIa, also known as CD16 (Lopez-Albaitero 2009), however confirmatory clinical data in HNSCC patients are lacking. In addition to direct activation of NK cell lysis of tumor cells, TA-specific mAbs can elicit CD8+ T cell responses to tumor-derived antigens through interaction with FcγRs on antigen-presenting cells (APC). This antigen-specific T cell activation was noted in 78% of patients treated with trastuzumab for breast cancer and this activation seemed to correlate positively with clinical response (Taylor 2007, Hershman 2007). Specific T cell activation has been demonstrated in HNSCC patients treated with cetuximab (Lee 2011, Srivastava 2013), alone or in combination with cisplatin chemotherapy.

Immune Checkpoints and Inhibitors

T cell activation occurs through a combination of T cell receptor engagement and co-stimulatory molecules. The duration and extent of immune responses, for example to infections, is regulated by "immune checkpoints" or inhibitory pathways which prevent excessive inflammatory responses as well as development of autoimmunity. Immune

checkpoints have also been shown to play an important role in the tumor microenvironment and can be manipulated as a mechanism of tumor immune evasion (Ramsay 2013). The immune checkpoint pathways are mediated by ligand and receptor interactions, and examples include cytotoxic T-lymphocyte antigen-4 (CTLA-4) and its ligands CD80 and CD84 and programmed death-1 (PD-1) and its ligands PD-L1 and PD-L2. Blocking anti-CTLA-4 Ab therapy results in rejection of murine cancers (Leach 1996). A mAb against CTLA-4, ipilumumab, was the first drug in this class to demonstrate clinical benefit and was approved by the FDA for patients with metastatic melanoma (Hodi 2010). Tremelimumab is also available for CLTA-4 targeting. More recently, anti-PD-1 or PD-L1 Abs have demonstrated clinical efficacy, alone (Topalian 2012, Hodi 2012, Hamid 2013) or in combination with ipilimumab (Callahan 2012).

PD-L1 Pathway Targeting in HNSCC

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that also includes CD28, CTLA 4, ICOS, and BTLA. PD-1 contains an intracellular membrane proximal immunoreceptor tyrosine inhibitory motif (ITIM) and a membrane distal immunoreceptor tyrosine-based switch motif (ITSM). Two ligands specific for PD-1 have been identified: PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T-cell activation upon binding to PD-1 in both murine and human systems. PD-1 delivers a negative signal, suppressing type 1 based antitumor immunity (Li 2014) by the recruitment of SHP-2 to the phosphorylated tyrosine residue in the ITSM in its cytoplasmic region, skewing the immune response away from a beneficial "type 1" response. PD-1 is primarily expressed on activated T cells, B cells, and myeloid cells. 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. Tumor immune evasion can occur by high tumor expression of PD-L1 and/or tumor immune infiltration by PD-1+ T lymphocytes. Preliminary analyses indicate that PD-L1 is expressed in 50-60% of HNSCC, and that tumor infiltration by PD-1+ Treg may be more common for HPV-positive than HPV-negative HNSCC. Strome and colleagues reported membrane and or intracytoplasmic PD-L1 expression in 66% (16 of 24) of HNSCC. Badoual and colleagues reported tumor infiltration by PD-1+ CD8+ and PD-1+CD4+ lymphocytes was more common among HPV-positive than HPV-negative HNSCC (Concha-Benavente 2016). In 33 (55%) of 64 HNSCC, high levels of PD-L1 expression were observed, but there was no association between PD-L1 expression and tumor HPV status (Badoual 2013). Jie and colleagues observed higher expression of immune-checkpoint receptors (CTLA-4 and PD-1) in intratumoral Treg cells than on matched peripheral blood samples from 27 patients with HNSCC (2013). These data strongly support a role for PD-1 inhibition in the therapy of HNSCC. Recent data show that circulating T cells and NK cells express detectable co-inhibitory checkpoint receptors, and correlate with disease stage and status (Badoual 2013, Jie 2013, Lyford-Pike 2013, Jie 2015).

Integration of Anti-PD-1 Based Immunotherapy into Previously Untreated, Locally Advanced HNSCC

For HPV-positive, previously untreated, locally advanced (PULA) HNSCC, the clinical

need is more targeted, less toxic therapy, and to determine the sequencing and optimal chemo-radiation regimens that do not inhibit immunotherapeutic efficacy. Specifically trials need to harness this novel systemic therapy to make an impact on the burden of uncommon, though lethal distant metastatic disease for "high-risk" advanced disease (T4, N2c/N3, >10 pack-year smokers) HPV-positive patients. Trials include eliminating systemic cytotoxic chemotherapy by combining IMRT with cetuximab and anti-CTLA-4 mAb (ipilimumab, NCT01935921), in which the overlap of mAb exposure begins at week 5 of cetuximab/RT. Additionally, "intermediate risk" HPV-positive and "high-risk" HPV-negative patients could be treated with concurrent, weekly cisplatin CRT.

For HPV-negative PULA HNSCC patients, disease free survival (DFS) has not improved beyond the historical 50% rate for decades – despite concomitant treatment intensification. Thus, the clinical impact of immunotherapy would be to improve DFS, given that intensification using conventional modalities has been unacceptably toxic. Intensifying therapy to enhance survival using anti-PD-1 mAb plus CRT must be tested for HPV-negative disease. Thus, for HPV-positive and HPV-negative locally advanced HNSCC, checkpoint inhibitors (anti-PD-1 or anti-CTLA-4) are being developed for adjuvant, post-operative PULA HPV-negative disease combined with cisplatin/IMRT, or for upfront treatment of "high risk" advanced disease stage HPV-positive or HPV-negative PULA HNSCC, in combination with concomitant cisplatin- or cetuximab-IMRT (Jie 2015), while reversing immunosuppressive signals on circulating and tumor infiltrating T cells. Recently a phase I trial reported safety of the combination of anti-PD-1 pembrolizumab with cisplatin chemoradiation, using a regimen similar to that planned in this trial (Powell, ASCO, 2016).

<u>Checkpoint Receptor Targeted mAbs in Combination with Cetuximab</u>
Cetuximab therapy alters expression of checkpoint receptors on circulating and intra-tumoral TIL. Specifically, the frequency of Treg suppressor cells that express CTLA-4 and PD-1 are enriched in the tumor microenvironment (Jie 2013, Jie 2015). Furthermore, cetuximab therapy increased the frequency of CD4+CD25hiCD39+FOXP3+ Treg ($p=0.01$), indicating that this treatment expands Treg in patients with HNSCC. CTLA-4+/CD39+ cells were significantly increased among the majority of CD4+FOXP3+ Treg from patients prior to and after cetuximab treatment, indicating that CTLA-4 targeting may provide enhanced benefit in cetuximab treated patients (Jie 2015). Recent data in NSCLC indicates that the EGFR pathway may contribute to regulation of PD-L1 expression (Akbay 2013), a finding corroborated in HNSCC (Concha-Benavente and Ferris, unpublished data).

These emerging data support the incorporation of checkpoint inhibitory mAb into conventional HNSCC therapy, either to deplete Treg or to disrupt the PD-1: PD-L1 suppressive signal transmitted to CD8+ effector T lymphocytes. These suppressed NK cells and T cells express the negative regulatory PD-1 receptor, at higher levels and generating greater inhibitory signals in tumor infiltrating lymphocytes, providing strong rationale for combining cetuximab with anti-PD-1 mAb therapy in a curative setting in which traditional cytotoxic chemotherapy may impart deleterious effect(s) on the generation and proliferation of beneficial antitumor lymphocyte responses.

Checkpoint Inhibitors and Radiotherapy

In addition to direct cytotoxic effects, radiotherapy may induce an immune effect important to tumor cell death (Demaria 2005). 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) (Demaria 2005, Dewan 2009). PD-1 blockade after completion of radiotherapy also has been shown to induce rejection of persistent tumors in mouse models (Deng 2014). Combination PD-1 blockade and anti-CD137 stimulation increased response to radiotherapy in a mouse model of triple negative breast cancer (Verbrugge 2012) and PD-L1 blockade concomitant with radiotherapy improved survival in comparison to either therapy alone in mouse models of glioma (Zeng 2013). In human subjects, case-reports support the existence of a clinically significant abscopal effect for patients with melanoma who have received ipilimumab prior to radiotherapy (Postow 2012, Stamell 2013). 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 (Teng 2015).

In addition to novel antigen presentation, recent in vivo data indicate that radiotherapy can induce increased PDL1 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 (Dovedi 2015, Dovedi 2014).

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 (Formenti 2012). Such a phenomenon may be particularly relevant to viral-induced tumors, such as HPV-positive HNSCC and to highly genetically unstable tumors such as HPV-negative HNSCC.

Nivolumab Dose and Schedule

Nivolumab monotherapy has been extensively studied in NSCLC patient populations with body weight normalized dosing (mg/kg). Nivolumab pharmacokinetics (PK) and exposures of patients have been characterized by population pharmacokinetic (PPK) analysis of data collected from these studies, together with PK data from several phase I, II, and III clinical studies of nivolumab monotherapy in solid tumors. Nivolumab PK was determined to be linear, with dose proportional exposures over a dose range of 0.1 to 10 mg/kg. Nivolumab clearance and volume of distribution was found to increase with increasing body weight, but the increase was less than proportional, indicating that a mg/kg dose represents an over-adjustment for the effect of body weight on nivolumab PK. Conversely, given the relationship between nivolumab PK and body weight, a flat dose is expected to lead to lower exposures in heavier patients, relative to the exposures in lighter patients.

The table below presents summary statistics of the estimated nivolumab steady-state trough, peak, and time-averaged concentration (Cminss, Cmaxss, and Cavgss, respectively) in NSCLC patients receiving 3 mg/kg, together with corresponding statistics of exposures predicted for a flat nivolumab dose of 240 mg. It should be noted that a dose of nivolumab 240 mg is identical to a dose of 3 mg/kg for patients weighing 80 kg, which is the approximate median body weight of NSCLC patients in the 3 phase II and III clinical studies of nivolumab monotherapy in NSCLC patients. As evident from the data presented in the table, the geometric mean values of Cminss, Cmaxss, and Cavgss with flat dosing are slightly (< 15%) higher than that produced by a 3 mg/kg dose, and the coefficient of variation (cv%) in these measures of exposure are only slightly (< 10%) greater than that of 3 mg/kg dosing.

Summary Statistics of Nivolumab Steady-state Exposure

Nivolumab Dose	Cminss Geo. Mean [ug/mL] (cv %)	Cmaxss Geo. Mean [ug/mL] (cv %)	Cavgss Geo. Mean [ug/mL] (cv %)
240 mg	61.5 (44.6)	133.7 (35.0)	82.4 (38.2)
3 mg/kg	54.7 (41.9)	118.9 (31.8)	73.3 (35.6)

Nivolumab has been shown to be safe and well tolerated up to a dose level of 10 mg/kg, and the relationship between nivolumab exposure produced by 3 mg/kg and efficacy has been found to be relatively flat. Taken together, the PK, safety, and efficacy data indicate that the safety and efficacy profile of 240 mg nivolumab will be similar to that of 3 mg/kg nivolumab. As the PK of nivolumab is linear, the corresponding flat dose for Q3W and Q4W are 360 mg/kg and 480 mgs, respectively. The simulated Cminss, Cmaxss and Cavgss with 360 mg Q3W and 480 mg Q4W are less than 10 mg/kg Q2W, and hence these regimens are expected to be safe and tolerable.

The PK and safety of nivolumab have been evaluated in the Asian population. The comparison of PK parameters in global and Japanese patients suggests that the PK of nivolumab is similar in these populations. Nivolumab is shown to be safe and well tolerated in Japanese patients. The similar PK and safety profile of nivolumab between global and Japanese patients supports the use of similar dosing in the Asian population as is being used in global clinical studies.

Nivolumab in Combination with Cisplatin

In terms of safety and efficacy of combining anti-PD-1 mAb with cisplatin, administration of nivolumab in combination with high-dose cisplatin has been shown to have acceptable toxicity in a phase I clinical trial in patients with NSCLC (Rizvi 2013). A phase I clinical trial evaluating the safety of nivolumab (10 mgs/kg q3 weeks) in combination with platinum-based doublets (gemcitabine/cisplatin, pemetrexed/cisplatin, carboplatin/paclitaxel) has been completed in 43 patients with chemotherapy-naïve advanced NSCLC. Importantly, no dose limiting toxicities (DLTs) were observed across all 3 regimens. Grade 3-4 toxicity was observed in 49% of patients, and grade 3-4 toxic events likely attributable to nivolumab (pneumonitis, rash, nephritis, and colitis) were

observed in 7 (16%) patients. One death due to pneumonitis was observed. Single agent nivolumab has demonstrated clinical activity in refractory squamous NSCLC. A phase III study comparing single agent nivolumab to docetaxel in patients with metastatic NSCLC has been stopped early because of superior OS in the nivolumab arm, per a Bristol-Myers Squibb press release. Nivolumab is now FDA approved for second line use in patients with squamous lung cancer based upon these results.

Checkpoint Inhibitors and Chronic Viral Infections

PD-1/PD-L1 interactions may contribute to T cell exhaustion in the setting of chronic viral infections such as HPV. Blockade of PD-1/PD-L1 interactions has been shown to restore proliferation and cytokine secretion of functionally impaired CD8+ T cells and to restore their ability to lyse cells and decrease viral load in a model of chronic lymphocytic choriomeningitis (LCMV) infection (Barber 2006). PD-1 also has been shown to be upregulated in HIV infection and blockade enhanced HIV-specific T cell responses in vitro (Kaufmann 2008). PD-1 blockade also has been observed to result in clearance of chronic, persistent hepatitis B infection in a mouse model (Tzeng 2012). PD-1 and PD-L1 have recently been shown to be upregulated in the tumor microenvironment in a mouse model of hepatitis-C induced hepatocellular carcinoma, contributing to tumor-antigen-specific tolerance (Willimsky 2013). Preliminary studies also suggest that patients with pre-existing antibodies to tumor-specific antigens (e.g. NY-ESO-1, an antigen expressed in 30-40% of patients with advanced melanoma) have an increased response to ipilimumab (Postow 2012). Notably, approximately 70% of patients with HPV16-positive HNSCC have high titers to the E6 or E7 oncoproteins at diagnosis, indicating immune exposure to these tumor-specific antigens (Gillison 2008). Nonetheless, potential immune exhaustion of HPVE6/7-specific T cells exist, which are often driven into a terminally differentiated phenotype (Albers 2005). These data suggest that PD-1 blockade has promise for the enhancement of standard of care therapies for HPV-positive cancers as well.

Clinical trials of checkpoint inhibitors in patients with head and neck cancer

Clinical activity of checkpoint inhibitors has now been demonstrated in clinical trials for patients with platinum-refractory, recurrent and metastatic HNSCC. A phase 1b clinical trial that included 60 patients with HNSCC with PD-L1 expression ≥1% observed a clinical response rate of 18%. Grade 3-4 drug-related adverse events were experienced by 17% (Seiwert 2016). In CheckMate 141, 361 patients with recurrent, metastatic HNSCC who progressed within six months of platinum in the primary, adjuvant or recurrent, metastatic setting were randomized in a 2:1 ratio to receive nivolumab 3 mg/kg IV every 2 weeks or single-agent systemic therapy of investigator's choice (methotrexate, docetaxel or cetuximab). Patients treated on the nivoulmab arm had a significant improvement in overall survival (HR 0.71, 97.73%CI 0.51-0.96; p=0.01), had higher response rates (13.3 vs 5.8%) , reduced grade 3-4 treatment related adverse events (13.1 vs. 35.1%) and sustained physical, emotional and social functioning compared to investigator's choice therapy (Gillison ML, AACR, 2016, Ferris, ASCO, 2016). These data provide strong evidence of clinical activity for anti-PD-1 targeted therapy in patients with HNSCC.

Preliminary results of a phase II trial were reported at ASCO 2016 indicating that anti-PD-1 therapy (pembrolizumab) was safe when combined with concurrent, platinum-based chemoradiotherapy in patients with stage III-IV HNSCC. Treatment consisted of a loading dose of pembrolizumab 200 mgs IV starting 7 days prior to chemoradiotherapy followed by a total of 8 doses every 3 weeks. Chemoradiotherapy was administered to a total of 70 Gy with weekly cisplatin 40 mg/m2. A total enrollment of 39 patients is planned, and no DLTs have been observed to date with 28 patients having completed chemoRT. These data provide strong evidence that anti-PD-1 therapy can be administered safely on the therapeutic platform proposed for this trial.

Summary of Rationale

- Our analysis of RTOG 0522 inclusive of the patients who meet the eligibility criteria for this trial indicates that 40% of patients with intermediate or high-risk, local-regionally advanced HNSCC will experience disease progression within 5 years of CRT. Novel therapeutic approaches are needed to improve disease control (Ang 2010, O'Sullivan 2013).
- A randomized phase III trial has demonstrated that nivolumab improved survival for patients with platinum-refractory HNSCC in comparison to single agent therapy of investigator's choice.
- Over 50% of HPV-positive and HPV-negative HNSCC express PD-L1, and tumor infiltration by PD-1+CD8+ T cells is frequently present in HPV-positive HNSCC. We note, however, that responses to nivolumab have been observed in both PD-L1 positive and negative HNSCC (Seiwert 2014).
- Nivolumab can be safely administered with high dose cisplatin.
- Preliminary data indicate that anti-PD-1 therapy can be safely administered in combination with weekly cisplatin and radiotherapy for patients with newly diagnosed stage III-IV HNSCC.
- PD-1 blockade has demonstrated synergistic activity with radiotherapy in vivo.
- PD-1 blockade can reverse T cell exhaustion to chronic viral infections such as HPV and therefore, may be particularly effective in viral-induced tumors.
- PD-1 blockade may reverse immune escape in carcinogen-induced cancers (HPV-negative HNSCC) with a high mutational burden by enhancing the immune response to neo-antigens generated during RT-mediated tumor destruction (Stransky 2013, Yu 2014).

2.6 Study Design

2.6.1 Study Design

In Arms 1, 3, and 4 (8 evaluable patients per cohort), the nivolumab dose will start at a fixed dose of nivolumab (240 mgs q14 days) and will be de-escalated in the event of dose limiting toxicities (DLT) attributable to nivolumab to a fixed dose of 80 mgs. In Arm 2 only, the nivolumab dose after day -14 will be modified to every 3 week dosing (360 mgs) to accommodate the q21 day dosing of high-dose cisplatin. There will be at least 8 evaluable patients enrolled into each of the cisplatin-based, cetuximab-based or nivolumab monotherapy chemoradiotherapy platforms, for a minimum overall sample size of 32. Nivolumab administration will start 14 days prior to the initiation of radiotherapy concomitant with either weekly cisplatin (40 mg/m^2/week x 7), high-dose cisplatin (100 mg/m^2 q 21 days X 3) or cetuximab (400 mg/m^2 load followed by 250 mg/m^2 x 7) or as monotherapy. In all arms of the trial, nivolumab therapy will continue

for 3 months after the completion of chemoradiotherapy. Starting 3 months after completion of radiation, patients will be administered adjuvant nivolumab 480 mgs q28 days x 7 doses (this is equivalent to a total of 1 year of nivolumab administration). The feasibility of the nivolumab will be assessed in the first 8 evaluable patients. If more than 4 of 8 patients discontinue adjuvant nivolumab, then adjuvant administration will cease for all subsequently enrolled patients. The principal outcome of interest in the dose finding study is safety.

The guiding principle of the study is to evaluate the safety of the addition of nivolumab to standard of care therapy. Nivolumab is a molecularly targeted immunotherapy with minimal overlapping toxicities with molecularly-targeted cetuximab (e.g. rash, liver function abnormalities) and cisplatin (e.g. fatigue, renal). Clinical trials have not yet investigated the safety of nivolumab in combination with radiotherapy. However, the combination of ipilimumab and radiotherapy is well tolerated and preliminary data presented at ASCO 2016 indicate anti-PD-1 target therapy with pembrolizumab can be safely administered in combination with chemoradiotherapy with weekly cisplatin 40 mg/m2. Although peripheral receptor saturation is achieved at 0.3 mg/kg, a phase I single agent trial demonstrated less clinical benefit below 3 mg/kg (bioequivalent of fixed dose of 240 mgs) in patients with NSCLC and increased grade 3-4 toxicities at 10 mg/kg. Preclinical data indicate that initiation of checkpoint blockage prior to radiotherapy may result in an abscopal effect and enhanced anti-tumor immune responses and prevention of the RT induced upregulation of PDL1 on tumors. Therefore, a single dose of nivolumab will be administered 2 weeks prior to initiation of CRT. Phase I studies of single agent nivolumab in patients with refractory disease have observed sustained responses with 3-4 months of therapy. In Arms 1, 3, and 4, nivolumab dosing will start at the fixed dose bioequivalent (240 mgs) of the recommended FDA approved dose of nivolumab (3 mg/kg). In the event of a >2 in 8 dose limiting toxicity (DLT), the regimen will be considered not worthy of further study. For Arm 2 only, to accommodate the q21 day schedule of cisplatin, the nivolumab dose and schedule will be modified to 360 mgs q21 days and dose reductions will be to 120 mgs. This dose and schedule (as well as 10 mg/kg) was utilized in phase I trials of nivolumab in combination with platinum doublets in patients with NSCLC. Based on this design, it is estimated that there will be at least 8 evaluable patients per arm in each of the 4 patient subgroups, for a minimum overall sample size of 32 evaluable patients.

In this protocol, we will evaluate the feasibility of adjuvant administration of nivolumab for a total of 1 year of therapy. It should be noted that patients in the 4 arms of the trial will receive nivolumab up to three months after the end of radiation therapy. The term "adjuvant therapy" therefore refers to the 7 additional months of nivolumab therapy after this time point. Historically, the head and neck patient population has been noncompliant with adjuvant therapy, demonstrating the infeasibility of this approach. For example, compliance with a year of adjuvant therapy of single agent cetuximab was 14% in ECOG 3303 and with 9 months or more of single agent lapatinib in a phase III randomized trial, compliance was only 60%.

Therefore, our safety and feasibility evaluation will include an evaluation of adjuvant

administration (nivolumab, 480 mgs q28 days x 7). We will prospectively monitor compliance with therapy in all arms of the the trial. The period of observation for feasibility is from the start of adjuvant nivolumab through 7 months of adjuvant therapy. We will evaluate the first 8 patients. If more than 4 patients stop the adjuvant therapy before 7 months, we will consider the adjuvant therapy infeasible. Administration would then be discontinued.

2.6.2 Participating Sites

A minimum of ten institutions with prior experience with immunochemotherapeutics and phase I clinical trials for head and neck cancer will be selected to participate in the this clinical trial. Inter-institutional communication regarding accrual, enrollment, and patient safety and toxicity will be facilitated by weekly e-mail communications and bi-weekly conference calls for all investigators.

2.7 Biomarker Studies

2.7.1 Tumor PD-L1 Expression

The effect of tumor PD-L1 expression on treatment response to anti-PD-1 targeted immunotherapy is currently unclear and a matter of ongoing investigation. Identification of predictive biomarkers of response to therapy protects patients from exposure to risks of ineffective therapies and improves cost-effectiveness. Submission of formalin-fixed and paraffin embedded tumor samples (blocks or 3 mm cores) is required for all patients at the time of study enrollment. Analysis of PD-L1 expression will be performed by use of the 28-8 antibody to PD-L1 (BMS) using the Dako IHC platform (Taube 2012). PD-L1 membrane staining will be assessed by light microscopy. Either complete circumferential or partial linear plasma membrane staining will constitute positive PD-L1 staining. While cytoplasmic staining may be observed, it will not be used in the evaluation of tissue sample status.

2.7.2 Peripheral blood CD69/137+ activated-positive T cells

Activated T cells expressing markers CD69 and/or CD137 have been identified in the circulation of head and neck cancer patients but at a low level (Jie 2013, Albers 2005, Lyford-Pike, 2013). These cells would be expected to increase after anti-PD-1 therapy, reversing T cell "exhaustion" and enabling their reactivation. This detectable population will be measured at baseline and longitudinally in the control and nivolumab-treated cohorts. Within this subset of activated, circulating T cells, we will phenotype them by memory/naïve status (using markers CD45Ra and CCR7) and by oncogene specificity against HPV-16 E6 or E7 (according to the patient's HLA type). Activated T cells expressing markers CD69 and/or CD137 will be measured at baseline and longitudinally by use of flow cytometry. We will also secondarily measure memory status, HPV oncogene specificity and PD1-positivity within this population of circulating T cells using flow cytometry (Jie 2013, Albers 2005, Lyford-Pike, 2013) Pre-post comparison of these frequencies will be performed for each patient during therapy, using each patient's baseline as the control time point, and comparing these values to the control arm cohort (cisplatin/RT).

3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

Note: Exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (via the contact list on the RTOG website). For radiation therapy-related eligibility questions,

please contact ACR Core Laboratory/RTQA (via the contact list on the RTOG website).

3.1 Patient Selection Guidelines

Although the guidelines provided below are not inclusion/exclusion criteria, investigators should consider these factors when selecting patients for this trial. Investigators also should consider all other relevant factors (medical and non-medical), as well as the risks and benefits of the study therapy, when deciding if a patient is an appropriate candidate for this trial.

3.1.1 Patients must have the psychological ability and general health that permits completion of the study requirements and required follow up.

3.1.2 Women of childbearing potential and men who are sexually active must be willing and able to use medically acceptable forms of contraception during the trial.

3.1.3 Investigators should check with their site Pathology department regarding release of biospecimens before approaching patients about participation in the trial. (See details of submissions in Section 10.)

3.2 Eligibility Criteria (26Dec2017)

A patient cannot be considered eligible for this study unless ALL of the following conditions are met.

Step 1: Registration

3.2.1 Histologically or cytologically-confirmed diagnosis of HNSCC of the oral cavity, oropharynx, larynx, or hypopharynx; A histological or pathological specimen from cervical lymph nodes with a well-defined primary site documented clinically or radiologically is acceptable;

3.2.2 Intermediate-risk Group: Oropharynx cancer that is p16-positive by immunohistochemistry with smoking status

$>$ 10 Pack-years, stage T1-2N2b-N3 or T3-4N0-3OR

$\leq$ 10 pack-years, stage T4N0-N3 or T1-3N3;

OR

High-risk Group: Oral cavity, larynx, hypopharynx, or p16-negative oropharynx cancer, stage T1-2N2a-N3 or T3-4N0-3 based on the following diagnostic workup:

- Mandatory submission of H&E and p16 stained slides to the Biospecimen Bank at UCSF for central review of p16 staining is required for oropharyngeal patients and H&E stained slide and block (or punch biopsy of paraffin block) for PD-L1 expression analysis for all patients; see Section 10 for details.
- History/physical examination within 28 days prior to registration;
- Examination by Radiation Oncologist, Medical Oncologist, and ENT or Head & Neck Surgeon within 28 days prior to registration;
- Fiberoptic exam with laryngopharyngoscopy, as clinically indicated, within 28 days prior to registration;
- Diagnostic quality, cross sectional imaging of the thorax within 28 days prior to registration; 18-F-FDG-PET/CT or conventional CT are acceptable. See "Recommendations for Imaging" in Section 4 for guidance.
- Diagnostic quality CT or MRI of neck, with contrast, within 28 days prior to registration; a 18-F-FDG-PET/CT of the neck only is acceptable as a substitute if the CT is of diagnostic quality and with IV contrast.

3.2.3 Age $\geq$ 18;

3.2.4 The trial is open to both genders;

3.2.5 Zubrod Performance Status of 0-1 within 14 days prior to registration; (**Note**: Zubrod Performance Status 2 patients are eligible for the nivolumab RT only arm, Arm 4, of the study (refer to section 3.2.16), all other eligibility criteria must be met.)

3.2.6 Adequate hematologic function within 14 days prior to registration defined as follows:

- WBC $\geq$ 2000/µL;
- Absolute neutrophil count (ANC) $\geq$ 1,500 cells/mm^3;
- Platelets $\geq$ 100,000 cells/mm^3;
- Hemoglobin $\geq$ 9.0 g/dl; Note: The use of transfusion or other intervention to achieve Hgb $\geq$ 9.0 g/dl is acceptable.

3.2.7 Adequate renal function within 14 days prior to registration defined as follows:

- Serum creatinine $\leq$ 1.5 mg/dl or creatinine clearance (CC) $\geq$ 50 ml/min determined by 24-hour collection or estimated by Cockcroft-Gault formula:

$$\text{CCr male} = \frac{[(140 - \text{age}) \times (\text{wt in kg})]}{[(\text{Serum Cr mg/dl}) \times (72)]}$$

$$\text{CCr female} = 0.85 \times (\text{CrCl male})$$

Note: Patients with CrCl < 50 ml/min are eligible for the nivolumab/RT-only arm, Arm 4, of the study (refer to section 3.2.16), all other eligibility criteria must be met.

3.2.8 Adequate hepatic function within 14 days prior to registration defined as follows:

- Total bilirubin $\leq$ 1.5 x ULN (except patients with Gilbert Syndrome who can have total bilirubin < 3.0 mg/dL);
- AST or ALT $\leq$ 3 x the upper limit of normal.

3.2.9 Na, K, Cl, glucose, Ca, Mg, albumin, ALP, Amylase, lipase, TSH within 14 days prior to registration;

3.2.10 Negative serum pregnancy test within 14 days prior to registration for women of childbearing potential (see Section 4);

3.2.11 Agreement of women of childbearing potential to use highly effective contraception during receipt of study drug and up to 161 days (23 weeks) from the last dose of nivolumab and men receiving nivolumab who are sexually active with women of childbearing potential to use highly effective contraception during receipt of study drug for 31 weeks from the last dose of nivolumab;

3.2.12 Negative test for HBsAg, HCV Ab (or HCV RNA) within 14 days prior to registration;

3.2.13 All patients must provide their personal smoking history prior to registration. The calculation of pack-years will be performed by use of the same survey utilized on RTOG 1016. The survey will be administered by use of a computer assisted, self-interview (CASI) application that will be available via a web-based portal or download. See the RTOG Foundation 3504 protocol page on the RTOG website for details.

3.2.14 The patient must provide study-specific informed consent prior to study entry. Patients who lack the psychological or intellectual capacity to consent for themselves are excluded.

Step 2 Sequential assignment to arms of the trial (oropharyngeal cancer patients only)

3.2.15 For oropharyngeal cancer patients: p16 determination by immunohistochemistry (defined as greater than 70% strong nuclear or nuclear and cytoplasmic staining of tumor cells),

confirmed by central pathology review; (see Section 3.1.3 above and Section 10.1 for details). **Note**: For patients with oral cavity, laryngeal, and hypopharyngeal cancer, the site can proceed to Step 2 immediately after completing Step 1.

3.2.16 **Note:** Patients (inclusive of p16-positive oropharynx patients) who meet all of the eligibility criteria noted above, but have 1 to 4 of the following pre-existing conditions (age ≥ 70 years; Zubrod performance status 2; baseline grade ≥ 3 peripheral neuropathy; grade ≥ 2 hearing loss; renal insufficiency [CrCl < 50 ml/min]) that in the opinion of the treating physician makes them unsuitable for cisplatin, may be enrolled in the study and treated on the nivolumab/RT-alone arm, Arm 4.

3.2.17 The patient has measurable disease as defined by the presence of at least one measurable lesion per RECIST 1.1.

3.3 Ineligibility Criteria

Patients with one or more of the following conditions are NOT eligible for this study.

Step 1: Registration

3.3.1 Definitive clinical or radiologic evidence of distant (beyond cervical lymph node and neck tissue) metastatic disease;

3.3.2 Patients with oral cavity cancer are excluded from participation if resection of the primary tumor is considered technically feasible by an oral or head and neck cancers surgical subspecialist (Please consult the Surgical Oncology Co-PI, Robert Ferris, MD, PhD, if clarification is needed on an individual case).

3.3.3 Carcinoma of the neck of unknown primary site origin (even if p16-positive);

3.3.4 Absence of RECIST, v. 1.1 defined measurable disease;

3.3.5 Gross total excision of both primary and nodal disease; this includes tonsillectomy, local excision of primary site, and nodal excision that removes all clinically and radiographically evident disease. Patients with RECIST, v. 1.1 evaluable remaining cancer either in the neck or primary site remain eligible.

3.3.6 Simultaneous primary cancers or separate bilateral primary tumor sites;

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

3.3.8 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable if the criterion in Section 3.3.7 is met;

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

3.3.10 Severe, active co-morbidity defined as follows:

- Patients with active autoimmune disease, with exceptions of vitiligo, type I diabetes mellitus, hypothyroidism and psoriasis;
- Use of systemic corticosteroids (> 10 mg daily prednisone or equivalent) or other immunosuppressive medications within 14 days of study drug administration, with exception of inhaled or topical steroids;
- Known immunosuppressive disease, for example HIV infection or history of bone marrow transplant or CLL;
- Positive test for hepatitis B virus surface antigen or hepatitis C virus indicating acute or chronic infection;

- Unstable angina and or congestive heart failure requiring hospitalization in the last 6 months;
- Myocardial infarction within the last 6 months;
- Active bacterial or fungal infection requiring intravenous antibiotic at the time of registration;
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration;
- As there is potential for hepatic toxicity with nivolumab, drugs with a predisposition to hepatoxicity should be used with caution.
- History of severe hypersensitivity reaction to any monoclonal antibody.

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

3.3.12 Grade 3-4 (CTCAE, v 4) electrolyte abnormalities:

- Serum calcium (ionized or adjusted for albumin) < 7 mg/dl or > 12.5 mg/dl despite intervention to normalize levels;
- Glucose < 40 mg/dl or > 250 mg/dl ;
- Magnesium < 0.9 mg/dl or > 3 mg/dl despite intervention to normalize levels;
- Potassium < 3.0 mmol/L or > 6 mmol/L despite intervention to normalize levels;
- Sodium < 130 mmol/L or > 155 mmol/L despite intervention to normalize levels.

3.3.13 Prior allergic reaction to cisplatin or cetuximab.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP

NOTE: INSTITUTIONS ARE REQUIRED TO COMPLY WITH DATA SUBMISSION WITHIN A 14-DAY WINDOW FOR EACH ASSESSMENT INDICATED BELOW (ADVERSE EVENT REPORTING GUIDELINES HAVE SHORTER REPORTING INTERVALS, SEE SECTION 7.)

PRE-TREATMENT ASSESSMENTS (26Dec2017)

Assessments	Prior to Step 1 Registration (calendar days)	Prior to Treatment (calendar days)
Informed Consent	Within 30 days, including day of Step 1 Registration	
Mandatory tissue collection	Prior to Step 2 Registration	
History/physical exam	28	
Administration of tobacco smoking survey (via web-based portal or download)	28	
Exam by Rad Onc, Med Onc, and ENT or H&N Surgeon	28	
Fiberoptic exam with laryngopharyngoscopy (as clinically indicated)	28	
CT or MRI of neck, with contrast	28	
CT scan of chest or 18-F-FDG-PET/CT of the neck and chest	28	
Whole body 18-F-FDG-PET/CT		Recommended: 28
Performance Status	14	
CBC w/diff & ANC	14	
Total bilirubin; ALP, AST or ALT	14	
Creatinine or Creatinine Clearance	14	
Serum pregnancy test (for women of childbearing potential)	14	
Na, K, Cl, glucose, Ca, Mg, albumin, Amylase, lipase, TSH	14	
HBsAg, HCV Ab (or HCV RNA)	14	
Dental assessment		Recommended: 56
Swallowing evaluation (see note below)		Required 28
Charlson Comorbidity Index (CCI)		Required: 28
Audiogram		Recommended: 84

Nutrition/feeding tube eval		Recommended: 14
Adverse event evaluation		Required: 14
Specimen collection for banking		If patient consents: 14 See Section 10 for details.

Notes for Pre-Treatment Assessments (table above)

- The H&N exam can be done by Medical, Radiation, and/or Surgical Oncologist.
- The fiberoptic exam with laryngopharyngoscopy can be done by the treating surgeon, medical oncologist, or radiation oncologist with experience in endoscopic examinations of cancer patients.
- The dental assessment is by a physician or designee (such as a physician's assistant, nurse or nurse practitioner, or a dentist/hygienist) to assess number of teeth and overall dental health with management (refer to the study-specific guide for details);
- The swallowing assessment is a single question completed by the physician and/or research associate to describe the consistencies of foodstuff that the patient is able to swallow.
- *Recommendations for Imaging*: All CTs should be of diagnostic quality with iodinated contrast with contiguous 3 mm minimum axial slice thickness, with the same angulation and gantry tilt as performed on the initial study (where possible), with reconstructions performed in the axial and coronal planes, with the same fields of view (FOV), mA, kVP, and similar window and level settings on follow-up examinations. If there is extensive dental amalgam, a butterfly technique adjusting the gantry in two planes to minimize dental streak artifact and 1.5 T MRI with gadolinium also should be obtained to improve visualization of the tumor margins for baseline and follow up imaging. All MRIs of the head and neck ideally should include a Sagittal T1 localizer, axial and coronal T1 pre and post-gadolinium images with fat saturation, and an axial T2, DWI, and coronal STIR sequence.
- A 18-F-FDG-PET/CT of the neck only is acceptable as a substitute if the CT is of diagnostic quality (noted above) and with IV contrast. **Note**: Diagnostic quality CT scan of neck with contrast and/or 18-F-FDG-PET/CT performed for radiation planning may serve as both staging and planning tools.
- Nutritional evaluation to include the physician's evaluation for placement of prophylactic gastrostomy or other type of feeding tube; note: The decision to place a feeding tube should be individualized and is not mandated. Investigators may consider a number of factors including: prior weight loss, current nutritional status, size and location of the primary tumor (impacting high dose target volume), availability of feeding tube placement services, availability of speech and swallowing specialists, dietician counseling, and social support. Feeding tubes may be placed after start of treatment at the discretion of the clinical team. If a tube is placed, the site will document on the appropriate case report form if the tube was placed prophylactically (as a preventative measure) or therapeutically (because of nutritional compromise or other clinical indications). It is highly recommended as part of the standard of care that all patients, but particularly those who require feeding tubes, be provided with professional swallowing evaluations and counseling during and after treatment.
- The Charlson Comorbidity Index (CCI) is required. The investigator and/or research associate will collect the data by extracting information from the patient's history and/or chart.

ASSESSMENTS DURING TREATMENT (26Dec2017)
[Day -14 (14 days prior to IMRT) to 12 weeks after ChemoRT]

Assessments	Weekly (± 2 days) during radiation then prior to each dose of nivolumab/placebo	As clinically indicated
Brief history	X	
Physical exam by Rad Onc, Med Onc, or associated NP/PA	X	
CBC w/diff & ANC	X	
Creatinine or Creatinine Clearance	X	
Na, K, Cl, glucose, Ca, Mg, albumin	X	
ALT, AST, T Bili, ALP, amylase, lipase, TSH	Within 72 hours prior to each dose of nivolumab	
Whole body 18-F-FDG-PET/CT		If suspicion of tumor recurrence
CT or MRI or 18-F-FDG-PET/CT of neck, with contrast		If suspicion of tumor recurrence
Biopsy		If suspicion of tumor recurrence
Adverse Event evaluation	X	X

Notes for Assessments during Treatment (table above)

- For Arm 2, assessments will take place **q3 weeks** (rather than q 2 weeks) prior to each dose of nivolumab.

ASSESSMENTS IN FOLLOW UP (starting 3 months after end of RT) (26Dec2017)

Assessments	q28 days during adjuvant nivolumab for all arms	2 weeks after last dose of nivolumab or placebo	q3 mos. (±2 weeks) from end of RT for 2 yrs	As clinically indicated
Brief history	X	X	X	
Exam by Rad Onc or Med Onc or ENT or H&N Surgeon	X	X	X	
CT or MRI of neck, with contrast			At 3, 6, 9, and 12 mos. after RT, then q6 mos. x 1 year	
Performance Status	X	X	X	
CBC w/diff & ANC	X	X	At 3 mos. from last dose of nivolumab or placebo	
Total bilirubin; AST or ALT, ALP, amylase, lipase, TSH	X	X	At 3 mos. from last dose of nivolumab or placebo	
Na, K, Cl, glucose, Ca, Mg, albumin	X	X	At 3 mos. from last dose of nivolumab or placebo	
Whole body 18-F-FDG-PET/CT			Recommended 3 mos. after RT	If suspicion of tumor recurrence
Dental Assessment			X	
Nutrition/feeding tube eval			X	
Chest CT			At 3, 6, 9, and 12 mos. after RT, then q6 mos. x 1 year	If suspicion of tumor recurrence
Biopsy				If suspicion of tumor recurrence
Adverse event evaluation	X	X (see note below)	At each follow-up visit	
Specimen collection for banking, if the patient consents: See Section 10 for details.			3 and 6 months from end of RT	

Notes for Assessments in Follow Up (table above)

- Note: The feasibility of adjuvant administration of nivolumab will be evaluated among the first 8 evaluable patients. If more than 4 of 8 discontinue therapy before 7 months, then adjuvant administration will be discontinued in all arms of the trial.
- During the trial, adverse event evaluations performed at 2 and 4 weeks after the last radiotherapy treatment are within the window of the DLT definition. Additional adverse event evaluations are to occur at 1 and 2 months after the last dose of nivolumab but will not contribute to the DLT definition.
- Note: All adverse events occurring up to100 days after the last dose of nivolumab are required to be submitted regardless of attributions to nivolumab. For individuals not receiving the 7 months of adjuvant nivolumab, this extends to the 6-month post-radiotherapy visit. For individuals receiving adjuvant nivolumab, this extends to the 3-month visit after completion of 7 months of adjuvant nivolumab (corresponding to the 15-month post-completion of radiotherapy visit).
- The dental assessment is by a physician or designee (such as a physician's assistant, nurse or nurse practitioner, or a dentist/hygienist) to assess number of teeth and overall dental health with management (Refer to the study-specific guide for details);

Definition of Disease Assessments

Response to initial therapy at the tumor primary and/or regional involved lymph nodes is not an endpoint in this study. However, progression-free survival is an important secondary endpoint. Progression of head and neck cancer will be assessed at defined time points by radiological imaging as indicated in the Assessment Tables above. Additionally, any clinical evidence of disease progression as determined by the treating physician outside of these defined time points during treatment and in follow up should trigger confirmation by radiological imaging and biopsy, if clinically feasible and associated with acceptable risk to the patient.

The protocol will utilize RECIST, v. 1.1 for the purposes of evaluating progressive disease only. Investigators will not be required to report response or best overall response.

As described in RECIST, v. 1.1, it is strongly recommended that the imaging studies performed at baseline be performed in follow up on the same equipment with the same techniques as noted above in Recommendations for Imaging. CT neck and chest with contrast of diagnostic quality (slice thickness no greater than 3 mm) is preferred, with CT head, abdomen/pelvis added if clinically indicated. 18-F-FDG-PET/CT (inclusive of the chest) may be used as radiographic evaluation for overall cancer status.

For the purposes of this protocol, progressive disease will be defined as follows:

1. Clinical evidence of disease progression in a radiated field that is confirmed by cytology or histopathology (**see Note below**) OR
2. Progressive disease as defined by RECIST, v. 1.1 criteria (Eisenhauer 2009)
   a) At least a 20% increase in the sum of the diameters of target lesions; the sum also must demonstrate an absolute increase of at least 5 mm OR
   b) unequivocal progression of non-target lesions OR
   c) the appearance of one or more new lesions

Note: A positive biopsy at the primary site or involved nodes that occurs ≤ 20 weeks from the

end of RT will be categorized as disease persistence and > 20 weeks as progression.

It is anticipated that measurable, target lesions by RECIST, v. 1.1 for head and neck cancer would include the primary tumor and up to 4 measurable cervical lymph nodes with a short axis of ≥ 15 mm. Non-target lesions would include cervical lymph nodes > 10 mm and < 15 mm.

Local or regional progression during primary chemoradiotherapy for head and neck cancer is unusual; however, it may occur and would be defined by meeting RECIST, v. 1.1 criteria in comparison to the imaging studies performed at baseline/enrollment. Per RECIST, v. 1.1. progressive disease is defined by at least a 20% increase in the sum of the diameters of target lesions, taking as a reference the smallest sum on study. It is anticipated that the first required imaging time point after completion of chemoradiotherapy (3 months after RT) will be the reference scan for defining progression. However, further decline in measurement of target lesions may occur beyond the 3-month post RT evaluation time point, In that instance, the reference scan containing the smallest sum may occur beyond the 3-month post-RT time point.

RECIST, v. 1.1 recognizes that it can be difficult to determine progressive disease in a previously irradiated or previously treated area (e.g. after neck dissection). In the event of clinical suspicion of progressive disease within an irradiated field in the absence of meeting formal RECIST definition, investigators are strongly encouraged to perform further investigation, including:

a) Repeat CT imaging at a short interval (e.g. six weeks). If short interval imaging results in confirmation of progressive disease by RECIST, v. 1.1 definition, the date of progression will be defined by the first scan.
b) 18-F-FDG-PET/CT: Per RECIST, progressive disease would be indicated on 18-F-FDG-PETCT if a previously negative 18-F-FDG-PET/CT becomes positive at a new lesion. For this protocol, a previously negative measurable lesion that becomes positive by FDG-PET also would be considered progression. Biopsy confirmation, however, is still strongly recommended.
c) Biopsy

In addition to formal evaluation of progressive disease by RECIST, v. 1.1, investigators will be asked at the time of first progression to report whether progressive disease was local (at the primary tumor), regional (within the head and neck, including cervical lymph nodes) or distant (inclusive of brain and below the clavicles). Sites of distant disease progression should be noted. This will accommodate analysis of patterns of failure.

All images should be reviewed and reported by the local study investigators by RECIST, v. 1.1.

Case-report forms for investigator interpretation of progressive disease by RECIST, v. 1.1 are available in Medidata Rave.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

5.1 Chemotherapy/Other Agent-Based Therapy

Protocol treatment (first dose of nivolumab) must begin within 7 days after Step 2 registration.

Nivolumab (Arms 1, 3, and 4)

Starting Dose
240 mgs

Nivolumab (Arm 2 only)

Starting Dose (Day 1)
360 mgs

Cohorts of 8 patients each will be sequentially enrolled into all 4 arms of the study. The first cohort in Arms 1, 3, and 4 will receive nivolumab 240 mgs IV starting 14 days prior to the first IMRT dose and every 2 weeks for a total of 10 doses. For Arm 2 only (high-dose cisplatin 100 mg/m^2 x 3), a loading dose of 240 mgs will be given starting 14 days prior to the first IMRT dose and then nivolumab 360 mgs IV q21 days for 6 doses will be initiated on day 1 of IMRT. All treatment arms will receive adjuvant administration of nivolumab. This is defined as nivolumab 480 mgs IV q28 days starting 12 weeks after end of RT for a maximum of 7 doses (resulting in a total of 1 year of nivolumab therapy).

All patients will receive nivolumab as a 30 minute IV infusion 14 days prior to the first IMRT dose and prior to chemotherapy infusion.

For Arms 1, 3, and 4, drug will be administered every 14 days for a total of 10 doses. For Arm 2, after the first infusion on day -14, starting on day 1 of IMRT, nivolumab, 360 mgs will be administered q21 days for a maximum of 6 doses.

Drug should be administered on a Monday or Tuesday prior to the first IMRT dose and prior to chemotherapy.

Patients may be dosed no less than 12 days from the previous dose for q14 day dosing, and no less than 19 days for q21 day dosing (Arm 2 only).

There will be no intra-patient dose escalation or reductions of nivolumab.

See Section 5.1.2 for details concerning nivolumab dosing schedule. See Section 6 for Nivolumab Dose Modifications.

The period of observation for a DLT is from day -14 (first dose of nivolumab) through to 28 days after the completion of radiotherapy.

A nivolumab attributable, dose-limiting toxicity (DLT) will be defined as follows:

1) Any ≥ grade 3 adverse event (CTCAE, v. 4) 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;
4) Inability to receive an adequate dose (≥ 70%) of cisplatin (Arm 1 and 2) or cetuximab (Arm 3) due to toxicity definitely related to nivolumab.

Note: Toxcity related to nivolumab that does not affect delivery of either chemotherapy or radiotherapy is not a dose limiting toxicity unless it satisfies criteria 1 noted above.

If a dose of nivolumab is delayed, it should be added to the end of treatment for a total of 10 doses (Arms 1, 3, 4) if the patient is not to receive adjuvant nivolumab therapy. For Arm 2, this is equivalent to a total of 6 doses of nivolumab 380 mgs q21 days. For patients receiving adjuvant therapy, patients should proceed with adjuvant monthly dosing starting 3 months after radiation therapy, as specified below.

Adjuvant Nivolumab

In Arms 1, 3 and 4, adjuvant administration of nivolumab should begin a minimum of 2 and a maximum of 4 weeks after the last dose of nivolumab in the primary therapy setting. In Arm 2, adjuvant administration of nivolumab should begin a minimum of 3 and a maximum of 5 weeks after the last dose of nivolumab.

All patients will receive adjuvant nivolumab 480 mgs as a 30 minute IV infusion administered q28 days for a maximum of 7 doses. Patients may be dosed no less than 26 days from the previous dose. There will be no intra-patient dose escalation or reductions of adjuvant nivolumab.

Cetuximab and Cisplatin

Cetuximab Dose Administration (Arm 3)

Patients on the cetuximab arms will receive an initial dose of cetuximab, 400 mg/m^2, (using actual body weight for all BSA calculations) intravenously (iv) over 120 minutes 7 days following the first nivolumab dose and corresponding to 7 days prior to the first radiation dose.

The loading dose of cetuximab must precede the first radiation treatment by at least 5, but no more than 7, days (the day of the loading dose is not included in these 5 days). Patients will then receive cetuximab, 250 mg/m^2, intravenously (iv) over 60 minutes on a weekly basis once a week on Monday or Tuesday for a total of 7 doses concurrent with radiation therapy. The infusion rate of cetuximab must never exceed 5 mL/min.

Note: If a weight change of ≥ 10% occurs, the cetuximab dose should be adjusted.

Patients will receive a total of 8 doses of cetuximab over 8 weeks, including the initial loading dose and 7 doses concurrent with radiation therapy.

If a dose of cetuximab is omitted, it will not be made up or added to the end of treatment. The omitted dose and the reason for the omission should be recorded in the site's source documentation.

Cetuximab Supportive Care Guidelines

Note the black box warning for cardiopulmonary arrest in patients receiving radiation therapy in combination with cetuximab. **CAUTION: Infusion reactions may occur during or following cetuximab administration. Most infusion reactions occur with the first infusion of cetuximab, but some patients' first infusion reactions have been reported following subsequent doses. The infusion reaction may occur during the infusion or be delayed until any time after the infusion.**

Patients shall receive prior to the first dose of cetuximab: 50 mg of diphenhydramine, PO or IV.

Prior to all doses of subsequent cetuximab, patents shall receive: 25-50 mg of diphenhydramine PO or IV per physician discretion.

The use of steroids should be minimized where possible. Premedications are recommended prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine may be reduced.

It is recommended that the medical staff closely observe patients for treatment-related adverse events, especially infusion reactions (see Section 6 for management) during the cetuximab infusion per local institutional standards. In the event that a patient experiences an infusion reaction, see Section 6 for proper management.

For subsequent infusions, it is recommended that the patient be observed for 1 hour post-infusion.

Dose modifications (see Section 6) will be made based upon specific criteria defined by the type, grade and time to resolution of toxicity.

Weekly Cisplatin Dose Administration (Arm 1)

Patients on the weekly cisplatin arms will receive cisplatin 40 mg/m^2/week (using actual body weight for all BSA calculations) intravenously (iv) on a weekly basis once a week on Monday or Tuesday for a total of 7 doses concurrent with radiation therapy.

Dose modifications will be made based upon specific criteria defined by the type, grade and time to resolution of toxicity. **No substitution of carboplatin for cisplatin will be permitted**. See Section 6 for dose modifications.

Cisplatin Supportive Care Guidelines

High dose cisplatin is highly emetogenic. While this protocol is using more frequent dosing of cisplatin that is considered moderately emetogenic, investigators should be prepared to use aggressive prophylactic antiemetics and hydration. Many institutions will

have standard guidelines for the administration of cisplatin at the doses used in this study. **For purposes of this protocol, individual investigators may use these local guidelines for cisplatin administration. One possible approach is outlined below.** These guidelines may need to be modified based on local guidelines and patient related factors (e.g. the substitution of normal saline in diabetic patients). Similarly, the anti-emetic regimen is to be determined by the local investigator, although one possible approach is outlined below.

- *Low-dose Cisplatin anti-emetic administration guidelines*: 5-HT3 antagonists and decadron should be given (palonosetron 0.25 mg IV and decadron 12 mg prior to cisplatin is preferred). The use of steroids should be minimized were possible. Therefore, for prevention of delayed nausea and vomiting, use of 5-HT3 antagonist monotherapy or NK-1 antagonist is preferred over steroid monotherapy. Use of other anti-nausea meds such as aprepitant, metoclopramide, or prochlorperazine is left to the discretion of the investigator.
- *Low-dose Cisplatin pre-hydration guidelines*: Pre-hydration with 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin should be given. Mannitol 12.5 gm IV immediately prior to cisplatin may be given. Use of mannitol is left to the discretion of the investigator.
- *Low-dose Cisplatin administration*: Standard administration is cisplatin, 40 mg/m^2 over 30-60 minutes IV in 250 cc NS. Infusion rate not to exceed 2 mgs per min. See Section 6 for dose modifications. See above discussion on scheduling and number of doses concurrent with radiation.
- *Low-dose Cisplatin post-hydration guidelines*: Following the end of the cisplatin administration, an additional liter of D5½ NS with 10 meq KCL/L, 8 meq MgSO4/L, and 25 g mannitol should be infused over 2 hours. On the second and third day following cisplatin, patient should be encouraged to take at least 2 liters of fluid per day orally. Patients unable to orally self-hydrate should be considered for additional IV hydration on these days with NS. The amount of pre- and post-hydration is left to the discretion of the investigator.

High-Dose Cisplatin (Arm 2)

Patients will receive cisplatin, 100 mg/m^2, administered intravenously on days 1, 22 and 43 of the treatment course (Note: cisplatin given within 24 hours of days 1, 22 and 43 due to holidays, for example, is acceptable). Weekends count as days.

***High-Dose Cisplatin Anti-Emetic Administration Guidelines*:** High-dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting. Institutional or NCCN guidelines for highly emetogenic regimens should be followed.

***High-Dose Cisplatin Pre-Hydration Guidelines*:** A suggested regimen is prehydration with a 1 liter of D5N S over 2-4 hours and mannitol, 12.5g iv bolus immediately prior to cisplatin. Then cisplatin, 100 mg/m^2, in 500-1000 ml NS is administered over 1-2 hours followed by an additional 1 to 1.5 liters of fluid. Any pre-existing dehydration must be corrected prior to cisplatin administration. Should extravasation occur, the treating physician should follow institutional guidelines for management.

Overnight hospitalization for hydration after cisplatin should be considered if it is allowed by the patient's insurance company. Additional iv hydration and BUN/creatinine check also should be considered, if necessary, later in the week after cisplatin administration, in order to address any dehydration or severe fluid/electrolyte imbalance.

5.2 Radiation Therapy (26Dec2017)

Protocol treatment (first dose of nivolumab) must begin within 7 days after Step 2 registration.

Note: All participating institutions must be credentialed for head and neck IMRT and IGRT prior to registering patients to the study. See Section 8.2 for details.

Intensity Modulated Radiation Therapy (IMRT) and Image-Guided Radiation Therapy (IGRT) are mandatory for this study. Proton therapy is not permitted.

IMRT will be given in 35 fractions over 7 weeks, 5 fractions per week. Missed treatments due to holidays or logistical reasons can be compensated by delivering additional BID fractions, with a minimum inter-fraction interval of 6 hours, or by treating on Saturday or Sunday.

5.2.1 Treatment Technology

Megavoltage energy photon beam irradiation with a photon beam of ≥ 4 MV is required. Any treatment delivery modality that previously has been credentialed for head and neck IMRT for previous RTOG trials is acceptable. **Note**: Tomotherapy requires separate credentialing.

IGRT Instructions

Boney anatomy IGRT credentialing is required (see Section 8.2). Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (KV) images;
- Linear-accelerator mounted kV and MV cone beam CT images;
- Linear-accelerator mounted MV CT images.

The institution's procedure for registering daily treatment imaging datasets with a reference dataset should comply with the following recommendations:

- Region-of-Interest (ROI) or "clip box" for fusion should be set to encompass the high dose PTV and adjacent spinal cord; if the supraclavicular region is a part of the target volume the ROI should extend to the C6 level;
- If the fusion software allows the user to create an irregular ROI, treatment room objects seen on in-room x-rays should be excluded from the registration;
- Both manual (e.g. drag-and-drop system based on bony anatomy matching) and automatic (e.g. based on mutual information) types of registration can be used; the result of the fusion must be visually checked for the alignment of the bony anatomy, such as vertebral bodies and applicable soft tissue structures (e.g. optic nerves and/or optic chiasm).
- Following the registration, the translational and (if the appropriate technology is available) rotational corrections should be applied to the treatment couch. If all the

variances are < 2.5 mm (this typically corresponds to one half of the usual PRVmargin), the treatment can proceed without correction (however, the physician/team may elect to perform adjustments even for a variance < 2.5 mm). If one or more corrections are 2.5 to 5 mm, adjustment is necessary prior to treatment; however, reimaging is not mandatory. If one or more of the corrections are > 5 mm, the imaging must be repeated in addition to performing table/positioning adjustments. However, the use of numerous repeat IGRT studies should be avoided;

- Imaging dose to the patient may become significant if repeated studies are performed for patients with severe set up problems (e.g., requiring frequent corrections of more than 5 mm). It is recommended that patients demonstrating severe set up problems during the first 7 calendar days of treatment be re-simulated or moved to a treatment with larger margins.

5.2.2 Immobilization and Simulation

Immobilization

The use of a thermoplastic head and shoulder mask is mandatory for head and neck IMRT. Patients will be planned in the supine position with their arms at their sides, ensuring the shoulders are situated as far inferior as possible to avoid entry and exit through the shoulders.

Planning CT Scan

The treatment planning CT scan is mandatory for defining target volumes and normal organ at risk. The planning CT scan should be done with contrast (unless contraindicated). CT scan thickness should be a minimum of 0.3 cm, and the CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. All tissues receiving irradiation should be included in the CT scan limits. The scanning limits should at least encompass the orbits superiorly, and extend at least 1 cm below the suprasternal notch inferiorly.

5.2.3 Imaging for Structure Definition, Image Registration/Fusion and Follow up

A diagnostic CT or MRI for structure delineation is recommended. These may be fused to the planning CT scans to facilitate target and structure definition. When available 18-F-FDG PET/CT images may also be fused to the planning CT data set.

5.2.4 Definition of Dose Prescriptions, Target Volumes, and Margins

General

The primary tumor and involved nodes will be encompassed by PTV_7000 and will receive 2 Gy per fraction x 35 fractions, while subclinical disease sites will be encompassed by PTV_5600 which will receive 1.6 Gy per fraction x 35 fractions. Treatment of both volumes will occur at the same time using a simultaneous integrated boost (SIB) technique delivered at 5 fractions per week over 7 weeks. For regions considered to be at high risk for microscopic disease, PTV_6125 may be treated to a dose of 61.25 Gy at 1.75 Gy per fraction x 35 fractions. The treatment plan 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 planning with computerized optimization should be used.

Gross Tumor Volume (GTV) represents the region judged to contain gross primary tumor or involved node(s) based on clinical and endoscopic examinations, CT scan, and, when

applicable, other imaging techniques. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm or nodes with a necrotic center.

Clinical Target Volume (CTV) is defined as the GTV plus areas considered at risk for containing microscopic disease delineated by the treating physician. CTV_7000 represents GTV plus a margin of generally 5-10 mm, and CTV_5600 represents CTV_7000 with a margin of 10 mm, plus nodal regions to receive elective irradiation. When the tumor is infiltrative (endophytic) or when the border is ill defined, it might be desirable to deliver an intermediate dose to a volume (CTV_6125) that is slightly larger than CTV_7000. The CTV margins can be narrower when GTV is in the proximity of the spinal cord or critical normal tissues. CTV should be cropped to exclude anatomical barriers to tumor spread such as air cavities, uninvolved bone, and external body contours.

Guidelines for CT based delineation of lymph node levels for node negative patients can be found at the RTOG web site: https://www.rtog.org/CoreLab/ContouringAtlases/HNAtlases.aspx. For patients with positive neck nodes, consult Gregoire et al. (2006) for the delineation of the nodal CTV.

Planning Target Volume (PTV) represents an additional margin around CTV to compensate for the variability of treatment set-up and internal organ motion. A minimum margin of 3 mm around the CTV is required in all directions to define each respective PTV, except for situations in which the CTV is adjacent to spinal cord or other critical normal tissues. In such situations, the margin can be reduced judiciously at the discretion of the treating physician.

When expansion of a CTV results in a PTV that extends beyond the patient's body surface, the PTV should be constrained to at least 3 mm from within the external contour, while still including the CTV. The use of tissue equivalent bolus material is indicated in situations where the disease is at or just under the skin surface. The PTV should align with the skin surface when bolus is used. Other volumes such as tuning or avoidance or optimization structures, can be employed to drive the IMRT treatment planning process. Such volumes should be considered to be treatment-planning tools that are not reported or sent forward for review.

The following PTV volumes must be sent for review. When disease with appropriate margin extends to the skin surface and bolus is used or when the disease with margin is more than 8 mm from the skin surface, the PTV volume (identified as PTV_7000 in the table below) must be sent for review. For situations where the disease plus margin falls between 8 mm from the skin surface and the body surface, a special volume (identified as PTV_7000-08 in the table below) must be sent in addition to the PTV volume indicated above.

The density corrected dose distributions shall be calculated, and the dose prescription is to be based on a dose distribution corrected for heterogeneities.

5.2.5 Definition of Critical Structures and Margins

All submitted treatment plans must strictly adhere to the structure names listed below:

Standard Name	Description	Validation Required/Required when optional/Optional
GTV	Primary tumor and involved nodes	**Required**
CTV_7000	GTV + 5-10mm margin, excluding anatomic boundaries to tumor spread	**Required**
PTV_7000	CTV-to-PTV 5mm margin that can be reduced to 3mm in some situations	**Required**
CTV_5600	CTV_7000 + 1cm margin (excluding anatomic boundaries to tumor spread), plus elective nodal regions	**Required**
PTV_5600	CTV-to-PTV 5mm margin that can be reduced to 3mm in some situations	**Required**
CTV_6125	CTV_7000 plus regions at high-risk for subclinical disease	**Required when applicable**
PTV_6125	CTV-to-PTV 5mm margin that can be reduced to 3mm in some situations	**Required when applicable**
SpinalCord	Spinal Cord	**Required**
SpinalCord_05	Planning Risk Volume of 5mm margin around Spinal Cord	**Required**
BrainStem	Brain Stem	**Required**
BrainStem_05	Planning Risk Volume of 5mm margin around Brain Stem	**Required**
Parotid_L	Left Parotid	**Required**
Parotid_R	Right Parotid	**Required**
OralCavity	Oral Cavity	**Required**
Lips	Lips	**Required**
Mandible	Mandible	**Required**
Pharynx	Uninvolved posterior pharyngeal wall plus adjacent constrictor muscles	**Required**
Esophagus_Up	Upper Cervical Esophagus	**Required**
LarynxGSL	Glottic/Supraglottic (GSL)	**Required**
Submandibula_R	Right Submandibular Gland	**Required**
Submandibula_L	Left Submandibular Gland	**Required**

External	External border of patient used to define Unspecified Tissue	**Required**
PTV_7000-08	PTV_7000, not including portion of PTV near (<8 mm skin)	**Required when applicable**
NonPTV	External minus PTVs	**Required**

Definitions of Normal Tissues/Organs at Risk (OARs)

Spinal Cord: The spinal cord begins at the cranial-cervical junction (i.e. the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRV cord = spinal cord + 5 mm in each dimension. This is irrespective of the use of IGRT for margin reduction.

Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid process. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined. The PRV brainstem = brainstem + 5 mm in each dimension. This is irrespective of the use IGRT for margin reduction.

Lips and Oral Cavity: These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The definition of lips is self-explanatory. The oral cavity will be defined as a composite structure consisting of the anterior one half to two thirds of the oral tongue/floor of mouth, buccal mucosa, and palate.

Parotid Glands: Parotid glands are defined based on the treatment planning CT scan.

Pharynx: This is defined as the "uninvolved" posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level).

Cervical Esophagus (Esophagus_Up): This is defined as a tubular structure that starts at the bottom of pharynx and extends to the thoracic inlet.

Glottic/Supraglottic Larynx (LarynxGSL): The GSL begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid but not suprahyoid epiglottis.

Mandible: The mandible includes the entire bony structure from TMJ through the symphysis.

Unspecified Tissue outside of the Targets: This tissue is located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.

5.2.6 Dose to Normal Structures

Spinal Cord: The cord should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The PRV spinal cord should not exceed 50 Gy to any volume in excess of 0.03 cc. In treatment planning, the spinal cord PRV should be given the highest priority.

Brainstem: The PRV brainstem should not exceed 54 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the PRV brainstem should be given less priority than the PRV spinal cord but more priority than the other critical structures listed below.

Lips: Reduce the dose as much as possible. The mean dose ideally should be <20 Gy.

Oral Cavity: Reduce the dose as much as possible. The mean dose ideally should be <30 Gy for the non-involved oral cavity. Efforts should also be made to avoid hot spots (> 60 Gy) within the non-involved oral cavity.

Parotid Glands: In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of < 26 Gy.

Contralateral submandibular gland: If contralateral level I is not a target, aim to reduce mean contralateral submandibular gland to < 39 Gy.

Pharynx: Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the pharynx exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the pharynx exceeds 60 Gy.

Cervical Esophagus (Esophagus_Up): Reduce the dose as much as possible. Attempt to maintain mean dose < 30 Gy and max dose (defined for a volume of 0.03cc) < 60 Gy.

Glottic and Supraglottic larynx (LarynxGSL): Reduce the dose as much as possible. Attempt to maintain mean dose < 20 Gy. If whole-neck IMRT is used, under-dosage of PTV adjacent to the glottic larynx will be limited to <10% receiving 95% of the prescribed dose.

Mandible: Reduce the dose as much as possible. Hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 70 Gy

Unspecified Tissue outside of the Targets: No more than 1cc of unspecified tissue outside the targets can receive 74 Gy or more.

5.2.7 Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, ideally should not exceed 5 days at a time and 10 days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons.

Name of Structure	Per Protocol	Variation Acceptable	Deviation Unacceptable
Total RT dose to PTV_7000 (to 95% of the PTV)	70 Gy	69.3 to 70.7 excluding 70 Gy	> 70.7
Minimum dose ("cold spot" within PTV_7000-08, not including portion of PTV near (<8 mm skin) defined for a point that is 0.03 cc in size	66.5 Gy (equals 95% of prescribed dose)	< 66.5 but > 63 Gy	<= 63 Gy
Maximum dose ("hot spot" > 1cc) within PTV_7000	<= 77 Gy	> 77 but <= 82 Gy	> 82 Gy
Maximum dose to NonPTV ("hot spot" > 1cc outside the PTVs)	< 74 Gy	74-77 Gy	> 77 Gy
Total dose to PTV_6125 (to 95% of the PTV-INT)	61.25 Gy	>= 59.5 but <= 63 Gy	< 59.5 or > 63 Gy
Total dose to PTV_5600 (to 95% of the PTV)	56 Gy	< 56 Gy but > 50.4 Gy	<= 50.4 Gy
Total RT dose to Spinal Cord _05 (0.03 cc)	<= 50 Gy	>= 50 but <= 52 Gy	> 52 Gy
Total RT dose to BrainStem_05(0.03cc)	<= 54Gy	> 54Gy but <= 56Gy	> 56Gy
Overall RT treatment time	< 50 days	50-54 days (without a medically appropriate indication for delay)	> 54 days (without a medically appropriate indication for delay)
Non-Medically Indicated Treatment Interruptions (Days)	0-2	2-4	> 4

Recommended dose acceptance criteria for other normal tissue but not to be used for plan score

Structure	**Recommended dose acceptance criteria**
Parotid	Dmean <26Gy (for at least one parotid)
Lips	Dmean<20Gy
LarynxGSL	Dmean <20Gy
Pharynx	Dmean <45Gy
Submandibula_R or	Dmean <39Gy

Submandibula_L (contralateral)	
OralCavity (non-involved oral cavity)	Dmean <30Gy
Esophagus_Up	Dmean <30Gy
Mandible	Dmax <70Gy

5.2.8 Treatment Planning Priorities and Instructions

Prioritization of IMRT Planning

1. Spinal Cord
2. Brainstem
3. PTV_7000
4. PTV_6125 (if applicable)
5. PTV_5600
6. a. Pharynx
   b. Parotid gland contralateral to primary tumor site
7. a. LarynxGSL
   b. Esophagus_Up
8. a. Lips
   b. Oral Cavity
9. a. Parotid gland ipsilateral to primary tumor site
   b. Mandible
10. Unspecified tissue outside the targets

Resimulation

In cases of weight loss >10%, or significant shrinkage of lymphadenopathy during therapy, it is recommended that the immobilization mask be adjusted or remade and a new plan be performed to assess the dose distributions with the current anatomy. Whether a new IMRT plan will be generated is at the discretion of the treating physician. If a new plan is made, the targets should be the same as those used for the initial plan. The new CT contour should be used for IGRT image registration with the new plan.

5.3 General Concomitant Medication and Supportive Care Guidelines

5.3.1 Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication.

5.3.2 Prohibited Therapies

The use of amifostine or palifermin as a radioprotectant is not allowed. The use of granulocyte colony stimulating factor or erythropoietin is not allowed. Transfusion is to be performed at the discretion of the treating physician. Any exceptions must be approved by the Co-Principal Investigator, Dr. Gillison.

5.3.3 Participation in Other Trials

Patients may not participate in other clinical trials that are intended to treat the diagnosed head and neck cancer or intended to reduce toxicity of therapy.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as

specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression;
- Intercurrent illness that prevents further administration of treatment;
- Unacceptable adverse event(s);
- Patient decides to withdraw consent for participation in the study;
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator;
- New data related to the experimental agent which would suggest that continuing treatment on protocol would impose unwarranted potential risks beyond what was known at the time of treatment initiation.

6. TREATMENT MODIFICATIONS/MANAGEMENT

Nivolumab, cetuximab, and cisplatin should be delivered only if there is no indication for holding the radiation and if all other hematological and non-hematological toxicity criteria are met.

Radiation therapy may continue at the discretion of the treating physician if nivolumab, cetuximab, or cisplatin are held unless specific criteria to hold radiotherapy are met.

The treating physician may elect to continue cetuximab or cisplatin in the event that nivolumab is delayed due to toxicities related to nivolumab.

However, nivolumab therapy should be delayed in the event cetuximab or cisplatin therapy is held with the specific exceptions listed below in Section 6.1.2.

6.1 Nivolumab Dose Modifications (26Dec2017)

6.1.1 Management Algorithms for Immuno-Oncology Agents

Immuno-oncology (I-O) agents are associated with adverse events that can differ in severity and duration from adverse events caused by other therapeutic classes. Nivolumab is considered to be an immuno-oncology agent in this protocol. Management algorithms have been developed to assist investigators in assessing and managing the following groups of adverse events: Gastrointestinal, Renal, Pulmonary, Hepatic, Endocrinopathies, Skin, and Neurological; see the nivolumab Investigator Brochure (IB) for the toxicity management algorithms.

Early recognition and intervention are recommended according to the management algorithms. In addition, the nivolumab Investigator Brochure (IB) includes ophthalmologic evaluations for any visual symptoms in order to evaluate for nivolumab related uveitis. Investigators should be guided by the algorithms in the IB for immune-related events.

Note: The algorithms are guides for AE management, but the guidance provided in these algorithms should not replace the investigator's medical judgment but should complement it.

For patients expected to require more than 4 weeks of corticosteroids or other immunosuppressants to manage an adverse event, consider the following recommendations:

- Antimicrobial/antifungal prophylaxis per institutional guidelines to prevent opportunistic infections such as Pneumocystis jiroveci and fungal infections.
- Early consultation with an infectious disease specialist should be considered. Depending on the presentation, consultation with a pulmonologist for bronchoscopy or a gastroenterologist for endoscopy may also be appropriate.
- In patients who develop recurrent adverse events in the setting of ongoing or prior immunosuppressant use, an opportunistic infection should be considered in the differential diagnosis.

Additional details on the safety of nivolumab, including results from clinical studies, are available in the IB.

6.1.2 Dose Delay Criteria

Nivolumab administration should be delayed for CTCAE, v. 4 toxicities, as recommended in the treatment algorithms located in the IB, that in the opinion of the treating physician are **related to the study drug**. **Please note nivolumab therapy will not be delayed for the following:**

- Grade 2 weight loss;
- Grade 2 or 3 nausea that in the opinion of the investigator is related to cisplatin;
- Grade 3 radiation dermatitis;
- Any Grade 2-3 mucositis, dysphasia, or pharyngolaryngeal pain that in the opinion of the treating physician is related to radiation therapy for head and neck cancer;
- Grade 2 hypokalemia or hypomagnesemia that in the opinion of the investigator is related to cetuximab or cisplatin;
- Grade 2 rash that in the opinion of the investigator is related to cetuximab;
- Grade 2 or greater hearing impairment that in the opinion of the treating physician is related to cisplatin;
- Grade 3 or 4 isolated lymphopenia;
- Grade 3 isolated anemia if, in the opinion of the treating physician, the anemia is not related to the study drug (e.g. related to chronic disease, iron deficiency, radiotherapy).

6.1.3 Criteria to Resume Treatment

Patients may resume treatment with nivolumab when the drug-related AE(s) resolve to the grade specified in the management algorithms in the IB.

If the criteria to resume treatment are met, the patient should restart treatment at the next scheduled time point (two-week interval) per the protocol.

6.1.4 Discontinuation Criteria

Treatment with nivolumab should be permanently discontinued as specified in the guidelines for management in the IB. Additional criteria for discontinuation include:

- 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;
- Grade 3 drug-related uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic adverse event, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation;
- Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires

discontinuation;

- Any Grade 4 drug-related adverse event or laboratory abnormality, with the exception of those noted below:
  - 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;
  - 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.
  - Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality not associated with underlying organ pathology that does not require treatment except for electrolyte replacement OR hormone/steroid replacement **does not** require treatment discontinuation.
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the patient with continued nivolumab dosing;
- A delay in nivolumab treatment of > 6 weeks.

6.1.5 Treatment of Nivolumab -Related Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, it is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

All Grade 3 or 4 infusion reactions should be reported as an SAE if criteria are met. Infusion reactions should be graded according to CTCAE, v. 4 guidelines.

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

For Grade 1 symptoms (Mild reaction; infusion interruption not indicated; intervention not indicated): Remain at bedside and monitor patient until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or 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 [e.g. antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for 24 hours): Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the patient with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor patient until resolution of symptoms. Corticosteroid or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor patient closely. If symptoms recur then no further nivolumab will be administered at that visit. Administer

diphenhydramine 50 mg IV, and remain at bedside and monitor the patient until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF). The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325 to 1000 mg should be administered at least 30 minutes before additional nivolumab administrations. If necessary, corticosteroids (recommended dose: up to 25 mg of IV hydrocortisone or equivalent) may be used.

For Grade 3 or Grade 4 symptoms (Severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]). Grade 4: (life threatening; pressor or ventilatory support indicated): Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and treat the patient as follows. Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1,000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Patient should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms. In the case of late-occurring hypersensitivity symptoms (eg, appearance of a localized or generalized pruritis within 1 week after treatment), symptomatic treatment may be given (eg, oral antihistamine, or corticosteroids).

6.2 Cetuximab Dose Modifications

Note: If adverse events prevent the administration of chemotherapy, the patient may continue to receive radiation therapy.

In the event of cetuximab treatment delay, there will be no reloading cetuximab infusion. Resume at the appropriate dose as indicated below.

6.2.2 Cetuximab Dose Modifications for Hematologic Adverse Events

Cetuximab will not be dose reduced or held for hematologic adverse events, such as neutropenia, neutropenic fever, or thrombocytopenia.

6.2.3 Cetuximab Dose Modifications for Non-Hematologic Adverse Events

See Section 6.2.5 for instructions for rash.

Toxicity Grade (CTCAE, v. 4)	**Cetuximab Dose** [a]
Renal-Calculated Creatinine Clearance	
≥ 50 mL/min	Maintain dose levels
< 50 mL/min	Maintain dose levels
Fatigue (Asthenia) ≥ Grade 3	Maintain dose levels
Nausea/Vomiting ≤ Grade 2 with maximal	Maintain dose levels

medical management ≥ Grade 3 with maximal medical management	Hold drug until ≤ grade 2, then resume at same dose level
Other Non-hematologic Adverse Events [a, b]	
Grade 3- 4, if possibly related to cetuximab, or likely to be exacerbated by continuation of cetuximab, e.g. diarrhea, except for weight loss or mucositis	Hold drug until < grade 3, then resume at same dose level
Any grade 1-2	Maintain dose levels

a. With the exception of infusion reaction;
b. For depressed K or Mg, administer replacement therapy. Chemotherapy should continue at the discretion of the treating physician (see table below for management of hypomagnesemia).

Hypomagnesemia

CTCAE, v. 4 Grade	Serum Magnesium		Guidelines for management	Action
	mg/dL	mmol/L		
1	< LLN – 1.2	< LLN – 0.5	Consider replacement with IV magnesium sulfate 2-5 g in normal saline or D5W. Infusion schedule based on institutional guidelines.	Maintain dose and schedule
2	< 1.2 – 0.9	< 0.5 – 0.4	As above for grade 1 and consider prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g. magnesium oxide) if grade 2 of higher hypomagnesemia persists. Note that magnesium oxide is an osmotic laxative. Consider use of combined magnesium oxide plus aluminum oxide preparations to avoid inducing diarrhea with PO magnesium supplementation	Maintain dose and schedule

3	< 0.9 – 0.7	< 0.4 – 0.3	As above for grades 1 and 2	Hold cetuximab until recovery to ≤ grade 2, then resume at same dose level
4	< 0.7	< 0.3	As above for grades 1 and 2	Hold cetuximab until recovery to ≤ grade 2, then resume at same dose level

6.2.4 Cetuximab Infusion Reaction Management

CTCAE, v. 4 Adverse Event Grade	**Treatment Guidelines[a]**
Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated	For mild infusion reactions, slow the infusion rate for cetuximab by 50% when the drug is restarted. For reactions manifesting only as delayed drug fever, consider administering prophylactic antihistamine medications for subsequent doses. Maintain the cetuximab dose. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in patients.
Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for ≤ 24 hrs	For moderate infusion reactions, slow the infusion rate for cetuximab by 50% when the drug is restarted and consider administering antihistamine medications and/or steroidal medications. Maintain the cetuximab dose. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in patients.
Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	**NO FURTHER CETUXIMAB.** Severe infusion reactions **require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab.** Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

Grade 4: Life-threatening consequences; urgent intervention indicated	**NO FURTHER CETUXIMAB.** Life threatening infusion reactions **require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab.** Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms.

a. Cetuximab Retreatment Following Infusion Reactions guidance: Institutional guidleines for cetuximab infusion rates will apply. In general, it is recommended that once a cetuximab infusion rate has been decreased due to an infusion reaction, it will remain decreased for all subsequent infusions. If the patient has a second infusion reaction > grade 2 with the slower infusion rate, the infusion should be stopped, and the patient should receive no further cetuximab treatment. If a patient experiences a Grade 3 or 4 infusion reaction at any time, the patient should receive no further cetuximab treatment. If there is any question as to whether an observed reaction is an infusion reaction of Grades 3 or 4, the Study Chair or Medical Oncology Co-Chair should be contacted immediately to discuss and grade the reaction.

6.2.5 Cetuximab Special Instructions

Weekly cetuximab will be held if radiation therapy is being held. If cetuximab is omitted for more than four consecutive infusions for adverse events due to cetuximab, or for an intercurrent illness (e.g., infection) requiring interruption of therapy, the patient should be discontinued from further cetuximab therapy. If adverse events prevent the administration of cetuximab, the patient may continue to receive nivolumab and radiation therapy.

If a dose of cetuximab is held, it will not be made up or added to the end of treatment, unless it is being held because radiation treatment is being held, and not because of cetuximab related AEs. In that case, cetuximab will be administered for up to a total of 8 doses (including the loading dose prior to radiation initiation). The omitted dose and the reason for the omission should be recorded in the site's source documentation. There will be NO reloading dose if cetuximab is held.

Treatment of Isolated Drug Fever

In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology.

If a patient experiences isolated drug fever, for the next dose, pre-treat with acetaminophen or non-steroidal anti-inflammatory agent (investigator discretion), repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses.

If a patient experiences recurrent isolated drug fever following pre-medication and post-dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the investigator

should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.

Cetuximab-related Rash

- Manifestations: Rash associated with EGFR-inhibitors is a relatively new dermatologic condition. It appears to be "acneiform" but it is NOT considered a form of acne; rather, it is a form of folliculitis. Skin changes may be manifested in a number of ways: erythema; follicle based papules, which may ulcerate; pain; itching; cosmetic disturbance; and/or nail disorders. The rash may become infected and transform into cellulitis.
- Grading of Cetuximab-induced Rash: According to physician judgment, if a patient experiences ≥ grade 3 rash (according to either the "outside of the radiation field" or the "inside of the radiation field" definitions below), cetuximab treatment adjustments should be made according to the Cetuximab Dose Modification table that follows. In patients with mild and moderate skin adverse events, cetuximab should continue without adjustment.

NOTE: Rash intensity (i.e., the size and number of papules or the level of discomfort and extent of erythema) may be an important consideration. However, the absolute number of lesions, **without associated physical discomfort**, does not necessarily constitute a basis for a dose reduction or delay. Rash considered "intolerable" (because of pain, itching, or appearance) or that has failed to respond to symptomatic management may be considered grade 3 and thus prompt dose reduction or delay of cetuximab. **The clinical judgment of the treating physician is critical to grading and will ultimately dictate dose modification.**

- Acute Skin Changes:
  - Rash Occurring Outside of the Radiation Field: Should be graded using the following CTCAE, v. 4 terms. A rash complicated by secondary infection or cellulitis should be graded per additional CTCAE terms (see table below).
  - Rash Occurring Inside the Radiation Field: Acute radiation dermatitis may be exacerbated by cetuximab or chemotherapy. The severity of such rash should be graded using CTCAE, v. 4 criteria for radiation dermatitis (see table below).
  - Late Skin Changes: A potential late change of interest is consequential scarring/pock marking in or out of the radiation field. This may be reported by using the MedDRA code, "Skin and subcutaneous tissue disorders - Other, specify", with the following protocol-specific grading scale as guidance:
    - Grade 1: Mild (seen only on close inspection)
    - Grade 2: Moderate (scarring, intervention or cosmetic coverage/intervention indicated)
    - Grade 3: Severe (significant disfigurement, deep scarring, or ulceration)
    - Grade 4: Deep cratering/scarring, skin necrosis, or disabling

Rash Occurring Outside of the Radiation Field				
	1	2	3	4
Pruritus*	Mild or localized	Intense or widespread	Intense or widespread and interfering with ADL	-
Rash/acneiform*	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADLI	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self - care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences
Paronychia*	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-

*Onset of grade 3 will require modification. See the table below, Cetuximab Dose Modification Guidelines for Dermatologic Changes.

Rash Occurring Inside the Radiation Field				
	1	2	3	4
Radiation recall reaction (dermatologic); Dermatitis radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated

Cetuximab Dose Modification Guidelines for Dermatologic Changes (≥ Grade 3)			
	Cetuximab	Outcome	Cetuximab Dose Modification
	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Resume at 250 mg/m^2
		No Improvement; remains grade 3	Continue to hold cetuximab for up to 4 weeks If cetuximab is held for four consecutive infusions for adverse events the patient should be discontinued from further cetuximab therapy

Drug Related Rash Management: Patients developing dermatologic adverse events while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Below are suggestions for managing cetuximab-induced rash*:

- **Antibiotics**: The benefit of routine antibiotics in uncomplicated (uninfected) rash is unclear. Some clinicians have used oral minocycline (Minocin), mupirocin (Bactroban), or topical clindamycin (Cleocin). Rash complicated by cellulitis should be treated with appropriate antibiotics based on clinical judgment or microbial sensitivity analysis.
- **Antihistamines**: Benadryl or Atarax may be helpful to control itching.
- **Topical Steroids**: The benefit of topical steroids is unclear.
- **Retinoids**: No data to support use. Use is not advised.
- **Benzoyl peroxide**: Should NOT be used--may aggravate rash.
- **Makeup**: Rash can be covered with makeup; this should not make it worse (use a dermatologist-approved cover-up, e.g., Dermablend, or any other type of foundation). Remove makeup with a skin-friendly liquid cleanser, e.g., Neutrogena, Dove, or Ivory Skin Cleansing Liqui-Gel.

- **Moisturizers**: Use emollients to prevent and alleviate the skin dryness, e.g., Neutrogena Norwegian Formula Hand Cream or Vaseline Intensive Care Advanced Healing Lotion.
- **Sunlight**: It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.
- **Over-the-counter medications**: Over-the-counter acne vulgaris medications (e.g., benzoyl peroxide) are not advised. This rash is not like acne vulgaris and these treatments could make it worse.

*Adapted from Perez-Soler R, Delord J, Halpern A, et al. HER1/EGFR inhibitor-associated rash: Future directions for management and investigation outcomes from the HER1/EGFR Inhibitor Rash Management Forum. *The Oncologist*. 10:345–356, 2005.

6.3 Cisplatin Dose Modifications

6.3.1 Weekly Cisplatin Dose Modifications during Concurrent Radiation

Note: Substitution of carboplatin for cisplatin during adverse events is NOT allowed.

Patients will be examined and graded for subjective/objective evidence of developing toxicity weekly according to CTCAE, v. 4 while receiving concurrent cisplatin with radiotherapy. If adverse events prevent the administration of cisplatin, the patient may continue to receive nivolumab and radiation therapy

Treatment interruptions are allowed if there is symptomatic mucositis or skin reaction that, in the judgment of the clinician, warrants a break. For chemotherapy-attributable AEs requiring a break in treatment, resumption of concurrent cisplatin may begin when AEs have recovered to the levels specified below. Chemotherapy should be discontinued in the event of more than 2 events requiring dose reduction (e.g. if grade 3 or greater non-hematologic or hematologic event occurs at the reduced dose of cisplatin, at 23 mg/m^2/week).

If an AE does not resolve to the levels specified in the sections below prior to the calendar week of the last radiation treatment (See Section 5.1 for details concerning parameters for timing of last allowable concurrent cisplatin dose), then chemotherapy should be discontinued.

There will be no dose re-escalation for concurrent cisplatin.

Chemotherapy dosage modifications are based upon lab values obtained within the 24 hours prior to cisplatin and interim non-hematologic toxicities during the week prior to a particular cisplatin dose.

6.3.2 Weekly Cisplatin Dose Modifications for Hematologic Adverse Events during Concurrent Radiation

Starting Dose	Dose Level -1	Dose Level -2
40 mg/m^2	30 mg/m^2	23 mg/m^2

Chemotherapy must not be administered until the ANC is ≥ 1,000 mm^3 and platelets are ≥ 75,000 mm^3. If not, delay 7 days. Cisplatin should be held every week until the above ANC and platelet parameters are met. Dose reductions when cisplatin is resumed after delay for low ANC or platelets will be as follows, based upon counts at time cisplatin was held.

ANC		Platelets	Reduction
< 1000 mm3	or	< 75,000	One dose level

Note: Hematologic growth factors for neutropenia or anemia are not allowed during concurrent cisplatin and radiation treatment.

Neutropenic Fever: Grade 3 (CTCAE, v 4) neutropenic fever (ANC < 1000/mm^3 with a single temperature of > 38.3 degrees C [101 degrees F] or a sustained temperature of ≥ 38 degrees C [100.4 degrees F] for more than 1 hour) is an expected potential complication of concurrent chemotherapy and radiotherapy or chemotherapy alone. If neutropenic fever is noted, the chemotherapy dose reduction will be determined by the weekly blood counts. See above.

6.3.3 Weekly Cisplatin Dose Modifications for Non-Hematologic Adverse Events during Concurrent Radiation

Renal Adverse Events: Dose will be modified based on the serum creatinine prior to each cisplatin dose. If the serum creatinine is ≤ 1.5 mg/dL, creatinine clearance is not necessary for treatment with full dose. If the serum creatinine is > 1.5 mg/dL, a creatinine clearance should be obtained by urine collection or nomogram calculation (valid only if serum creatinine is not changing rapidly).

Cisplatin must not be administered until creatinine is ≤ 1.5 or creatinine clearance ≥ 50. Once the creatinine has met the above parameters, cisplatin may be restarted with the below modifications based on the creatinine at the time the cisplatin was held: In general, cisplatin should be held for weekly intervals (rather than restarting cisplatin later in the same week that a dose limiting AE is seen).

Cisplatin dose modifications for creatinine during concurrent radiation			
Creatinine (mg/dL)		Creatinine clearance, measured or calculated ml/min	Cisplatin dose reduction
≤ 1.5	or	> 50	No change
> 1.5	and	40-50	One dose level
		< 40	Hold drug

Neurologic (neuropathy) Adverse Events:

Grade (CTCAE, v. 4)	Dose Reduction
0-1	None
2	One dose level
3-4	Hold drug

Ototoxicity: Should patients develop clinical evidence of ototoxicity, further audiometric evaluation is required. A neurologic deficit should be distinguished from a conductive loss from obstruction of the Eustachian tube leading to a middle ear effusion. Because no AE scale, including the CTCAE, v. 4, has been validated in terms of correlation with clinically relevant hearing loss, there are no protocol mandates requiring dose reduction for audiogram-determined sensorineural hearing loss without an analogous clinical high grade hearing loss. However, for clinical grade 3 or higher hearing loss, cisplatin should be held and for grade 2 clinical hearing loss, one dose level reduction should be implemented.

All Other Non-Hematologic Adverse Events Attributable to Cisplatin during Concurrent Radiation: For all other non-hematologic adverse events in which toxicity is ≥ grade 2 (CTCAE v. 4), investigators are advised to evaluate and manage correctable issues promptly to prevent worsening of toxicity. For these events in which toxicity is ≥ grade 3, investigators should hold cisplatin, with weekly re-evaluation until AE grade falls to 0-1, then restart cisplatin at one lower dose level. Note: Grade 3 mucositis is commonly experienced by head and neck cancer patients; the investigator generally would not hold the cisplatin dosing in this case, unless there is unusual concern for progression to grade 4 mucositis.

6.3.4 High-Dose Cisplatin Dose Modifications, Days 22 and 43 for Arm 2 only

Neutropenia: If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1200, hold treatment until ANC ≥ 1200, then treat at 100% dose. Neutropenic fever will require permanent 25% dose reduction. Per CTCAE, v. 3.0, febrile neutropenia is fever of unknown origin without clinically or microbiologically documented infection; ANC < 1.0 x 10e9L, fever > 38.5°C.

Thrombocytopenia: If on the day of scheduled treatment with cisplatin the platelet count is < 75,000, hold treatment until platelets are ≥ 75,000, then treat at 100% dose. Thrombocytopenia that results in bleeding will require a 25% dose reduction.

Neurotoxicity: If any signs of grade 3 or greater neurotoxicity occur, discontinue cisplatin. Continue RT

Renal Adverse Events: Cisplatin should be administered on the scheduled day of treatment using the following guidelines:

Note: If creatinine is > 1.2 mg/dl, clearance must be done in order to make dose adjustment. If the calculated nomogram is 50 mL/min or above, a 24-hour urine collection is not needed, but if the nomogram calculation is less than 50 mL/min, a 24-hour urine collection is mandated.

Creatinine Clearance	**Cisplatin Dose**
> 50 ml/min.	100 mg/m^2
40-50 ml/min.	50 mg/m^2

< 40 ml/min.	Discontinue

Other Adverse Events:

- Mucositis: Grade 4 will require a 25% dose reduction
- Ototoxicity: For new clinical hearing loss not requiring a hearing aid or for tinnitus that interferes with activities of daily living, treat at 50% dose reduction. For hearing loss requiring a hearing aid, discontinue cisplatin. Continue RT (Arm 1).
- If the physician is unsure about the severity of the hearing loss, an audiogram is encouraged.

If the second dose of cisplatin is delayed more than 21 days because of hematologic or renal adverse events, then the third dose will be omitted.

If a weight change of ≥ 10% occurs, the cisplatin dose should be adjusted.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agent

The investigational agent administered in RTOG 3504, nivolumab, is being made available by the RTOG Foundation and distributed by a third party drug distributor. For nivolumab, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in Section 7.4 of the protocol.

Commercial Agents

The commercial agents in RTOG 3504 are cisplatin and cetuximab.

7.1.1 Adverse Events for Investigational Study Agents

Investigators must obtain the current version of the BMS-936558 (nivolumab) Investigator Brochure (IB) for comprehensive pharmacologic and safety information. The IB can be accessed on the RTOG Foundation 3504 protocol page of the RTOG website, www.rtog.org. Sites must use their username and password to access the protocol page and the IB.

7.1.2 Adverse Events for Commercial Study Agents

Refer to the package inserts for cisplatin and cetuximab for detailed pharmacologic and safety information

7.2 Adverse Events (AEs)

This study will use the Common Terminology Criteria for Adverse Events (CTCAE) version 4 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.

7.2.1 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not 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 (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of related or unrelated). (International Conference on Harmonisation [ICH], E2A, E6).

For multi-modality trials, adverse event reporting encompasses all aspects of protocol treatment including radiation therapy, surgery, device, and drug.

AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1). All nonserious adverse events (not only those deemed treatment-related) are to be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment. Follow up also is required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate. All identified nonserious AEs must be recorded and described on the nonserious AE page of the CRF.

The following laboratory test result abnormalities should be captured on the nonserious AE CRF page and SAE Report Form, if they meet seriousness criteria:

- Any laboratory test result that is clinically significant or meets the definition of an SAE;
- Any laboratory test result abnormality that required the subject to have study drug discontinued or interrupted;
- Any laboratory test result abnormality that required the subject to receive specific corrective therapy.

It is expected that wherever possible, the clinical rather than laboratory term would be used by the reporting investigator (eg, anemia versus low hemoglobin value).

Definition of Immune-Mediated Adverse Events (IMAES)

IMAEs include events, regardless of causality, occurring within 100 days of the last dose. IMAEs are specific events (that include pneumonitis, diarrhea/colitis, hepatitis, nephritis/renal dysfunction, rash, and endocrine [adrenal insufficiency, hypothyroidism/thyroiditis, hyperthyroidism, diabetes mellitus, and hypophysitis]) for which subjects received immunosuppressive medication for treatment of the event, with the exception of endocrine events (hypothyroidism/thyroiditis, hyperthyroidism, hypophysitis, diabetes mellitus, adrenal insufficiency), which are included regardless of treatment since these events are often managed without immunosuppression. The table below provides a summary of the IMAEs category and their respective preferred terms.

Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions	
IMAE Category	**PTs included under IMAE Category**
Pneumonitis	Pneumonitis, Interstitial lung disease
Diarrhea/Colitis	Diarrhea, Colitis, Enterocolitis
Hepatitis	Hepatotoxicity, Hepatitis, Hepatitis acute, Autoimmune hepatitis, AST increased, ALT increased, Bilirubin increased, ALP increased
Adrenal insufficiency	Adrenal insufficiency

Preferred Terms Included in Analysis of IMAEs to Support Warnings and Precautions	
Hypothyroidism/Thyroiditis	Hypothyroidism, Thyroiditis Thyroiditis acute (collapsed with thyroiditis for frequency), Autoimmune thyroiditis (collapsed with thyroiditis for frequency)
Hyperthyroidism	Hyperthyroidism
Hypophysitis	Hypophysitis
Diabetes mellitus	Diabetes mellitus, Diabetic ketoacidosis
Nephritis and renal dysfunction	Nephritis, Nephritis allergic, Tubulointerstitial nephritis, Acute renal failure, Renal failure, Increased creatinine
Rash	Rash, Rash maculopapular

NOTE: If the event is a Serious Adverse Event (SAE) (see next section), further reporting will be required. Reporting AEs only fulfills Data Management reporting requirements.

7.3 Serious Adverse Events (SAEs)

Serious Adverse Events that meet expedited reporting criteria defined in the table below will be reported via the SAE report form in Rave. SAEs that require 24h notification are defined in the expedited reporting table.

Definition of an SAE: Any adverse drug event (experience) occurring at any dose that results in any of the following outcomes:

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

Due to the risk of intrauterine exposure of a fetus to potentially teratogenic agents, the pregnancy of a study participant must be reported in an expedited manner.

7.4 Serious Adverse Event (SAE) Reporting Requirements

It is the responsibility of the investigator to document all adverse events which occur during the study. All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the RTOG SAE Report Form in RAVE. RTOG will report SAEs to Bristol-Myers Squibb within 24 hours of awareness. RTOG will report unexpected and related SAEs to the FDA and Bristol-Myers Squibb

via the MedWatch Form 3500A per the requirements set forth in the Code of Federal Regulations, Section 312.32.

7.4.1 Reporting SAEs

Following the patient's written consent to participate in the study, all SAEs, whether related or not related to study drug, must be collected, including those thought to be associated with protocol-specified procedures. **All SAEs must be reported per the reporting table below that occur from time of consent and within 100 days of the last dose of study drug.** Patients, who are randomized and never receive treatment, must have SAEs collected for 30 days from the date of randomization. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (e.g. a follow-up skin biopsy).

The investigator should report any SAE that occurs after these time periods and that is believed to be related to study drug or protocol-specified procedure.

An SAE report should be completed for any event where doubt exists regarding its seriousness. If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.

The SAE report should comprise a full written summary, detailing relevant aspects of the SAE in question. The SAE summary also must include the investigator's assessment of relatedness to all components of protocol treatment. Amend the SAE report with follow-up information, when it becomes available, In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to RTOG Operations Office by phone,215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

SAEs that occur during the follow-up period beginning 100 days after end of treatment and are considered by the investigator to be related to protocol treatment must be reported expeditiously via the SAE Report Form.

All SAEs must be reported in Rave within the designated timeframe outlined in the reporting table below. RTOG will complete a preliminary review of the SAE details and will contact the site with queries as needed. RTOG will report the SAE to Bristol-Myers Squibb within 24 hours of notification of the event. RTOG will report to the FDA per 21 CFR 312.

Pregnancy

Patients who become pregnant during the study should discontinue the study immediately. Investigators should report the pregnancy, including a male participant's impregnation of his partner, expeditiously as a grade 3 SAE coded in the CTCAE v.4 as "pregnancy, puerperium and perinatal conditions, other—pregnancy" on the SAE Report Form (in RAVE) and submit the Pregnancy Report Form in Rave within 14 days of

notification. RTOG will report the pregnancy to Bristol-Myers Squibb within 24 hours of notification of the event. Patients should be instructed to notify the investigator if it is determined after completion of the study that they become pregnant (including a male participant's impregnation of his partner) either during the treatment phase of the study or within 100 calendar days after the end of treatment. The pregnancy outcome for patients on study should be reported to RTOG. RTOG will report the status to Bristol-Myers Squibb.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 100 Days of the Last Administration of the Investigational Agent/Intervention [1, 2]

FDA REPORTING REQUIREMENTS FOR SERIOUS ADVERSE EVENTS (21 CFR Part 312)

NOTE: Investigators **MUST** immediately report to the sponsor (NCI) **ANY** Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64)

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

1) Death
2) A life-threatening adverse event
3) An adverse event that results in inpatient hospitalization or prolongation of existing hospitalization for ≥ 24 hours
4) A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions
5) A congenital anomaly/birth defect.
6) Important Medical Events (IME) that may not result in death, be life threatening, or require hospitalization may be considered serious when, based upon medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. (FDA, 21 CFR 312.32; ICH E2A and ICH E6).

ALL SERIOUS adverse events that meet the above criteria MUST be immediately reported to RTOG HQ within the timeframes detailed in the table below.

Hospitalization	Grade 1 and Grade 2 Timeframes	Grade 3-5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days	24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required	

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report.
- "10 Calendar Days" - A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.

[1]Serious adverse events that occur more than 100 days after the last administration of investigational agent/intervention and are considered related to protocol treatment require reporting as follows:

Expedited 24-hour notification followed by complete report within 5 calendar days for:

- All Grade 3, 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

[2]For studies using 18-F-FDG-PET/CT or SPECT IND agents, the AE reporting period is limited to 10 radioactive half-lives, rounded UP to the nearest whole day, after the agent/intervention was last administered. Footnote "1" above applies after this reporting period.

Specific Protocol Exceptions to Expedited Reporting (SPEER):
The following adverse events are specific protocol exceptions to expedited reporting. Report the following AEs in an expedited manner only if they exceed the grade (CTCAE, v. 4) in parentheses next to the AE: diarrhea (grade 2), fatigue (grade 2), pruritus (grade 2), rash maculo-papular (grade 2), lymphocyte count decrease (grade 4), anemia (grade 4), WBC decrease (grade 4), mucositis oral (grade 3), radiation dermatitis (grade 3), thromboembolic event (grade 3).

Additional Protocol-Specific Inclusions to Expedited Reporting Requirements
Hemophagocytic lymphohistiocytosis is an ***inclusion*** to expedited reporting. Hemophagocytic lymphohistiocytosis is a rare but potentially fatal disease of normal but overactive histiocytes and lymphocytes. It is a manifestation of cytokine release syndrome. Occurring at any grade, hemophagocytic lymphohistiocytosis must be reported in an expedited manner as a serious adverse event.

8. REGISTRATION AND STUDY ENTRY PROCEDURES

8.1 Regulatory Requirements

Please refer to the study-specific guide for investigators and research staff for detailed procedures regarding requirements for regulatory collection. **The study-specific guide is available on the RTOG Foundation 3504 protocol page on the RTOG website, www.rtog.org**.

8.2 RT Registration Requirements

All sites will be IMRT and IGRT credentialed prior to registering patients to the study. Please refer to the MD Anderson Dosimetery Lab website (http://rpc.mdanderson.org/mdadl/RTOG_Foundation/RTOG_3504.htm), for details regarding RT registration requirements.

8.2.1 Digital RT Data Submission to RTOG Using TRIAD

TRIAD is the image exchange application used by the RTOG Foundation. **See the study-specific guide on the RTOG Foundation 3504 protocol page on the RTOG website, www.rtog.org, for details of TRIAD.**

8.3 Patient Enrollment

See the study-specific guide on the RTOG Foundation 3504 protocol page on the RTOG website, www.rtog.org, for details of patient enrollment.

9 DRUG INFORMATION

9.1 Investigational Study Agent

Nivolumab, IND# 129841
To supplement the toxicity information contained in this document, investigators must obtain the current version of the BMS-936558 (nivolumab) Investigator Brochure (IB), for comprehensive pharmacologic and safety information. Also see Appendix I.

The IB can be accessed on the RTOG Foundation 3504 protocol page of the RTOG website, www.rtog.org. Sites must use their username and password to access the protocol page and the IB.

Table	Product Description				
Product Description and Dosage Form	**Potency**	**Primary Packaging (Volume) / Label Type**	**Secondary Packaging (Qty) /Label Type**	**Appearance**	**Storage Conditions (per label)**
Nivolumab BMS-936558 Solution for Injection[a]	100 mg (10 mg/mL)	10 mL vial	5-10 vials per carton/ Open-label	Clear to opalescent colorless to pale yellow liquid. May contain particles	2° to 8°C; protect from light, freezing, and shaking

*Nivolumab may be labeled as BMS-936558 Solution for Injection

If stored in a glass front refrigerator, vials should be stored in the carton. Recommended safety measures for preparation and handling of nivolumab include laboratory coats and gloves.

For additional details on prepared drug storage and use time of nivolumab under room temperature/light and refrigeration, please refer to Appendix I and the BMS-936558 (nivolumab) Investigator Brochure section for "Recommended Storage and Use Conditions".

9.1.1 Availability/Supply

Bristol-Myers Squibb will supply nivolumab free of charge to patients on study in the U.S. and Canada. An on-site unblinded pharmacist will be responsible for mixing placebo per instructions provided in Appendix I, "Nivolumab Pharmacy Reference Sheet". The drug will be distributed by a third-party vendor under contract to RTOG. Drug accountability records must be maintained at all sites according to good clinical practices.

See the study-specific guide on the RTOG Foundation 3504 protocol page of the RTOG website, www.rtog.org, for details of drug shipment.

9.2 Commercial Agents

Cetuximab and Cisplatin

Sites must refer to the package insert for detailed pharmacologic and safety information.

9.2.1 Availability/Supply

Please see Section 5 for administration instructions. Please refer to the current FDA-approved package insert provided with each drug and the site-specific pharmacy for toxicity information and instructions for drug preparation, handling, and storage.

10. PATHOLOGY/BIOSPECIMENS

10.1 p16 Immunohistochemistry for Oropharynx Cancers

Tumor p16 status is an established clinical surrogate of tumor HPV status. p16 status is an integral biomarker, as tumor p16 status is a stratification factor. Evaluation of tumor p16 status may be performed locally, but the assay is to be performed by use of a mouse monoclonal antibody to p16 (CINtec E6H4, MTM Laboratories, Heidelberg, Germany)

visualized with the Ventana XT autostainer (or equivalent) using the 1-view secondary detection kit (Ventana) (or equivalent) as described by Jordan, et al. (2012). Other acceptable p16 antibody types include 16P04 and JC8. Pathological interpretation of tumor p16-status may be performed locally and reviewed centrally per Jordan et al (2012). Central review of local p16 IHC results by Dr Richard Jordan will be required for oropharyngeal patients prior to randomization.

10.2 Tissue/Specimen Submission

In this study, it is **required** that tissue be submitted to the Biospecimen Bank at UCSF for the purpose of p16 central review for patients with oropharyngeal carcinomas and for PD-L1 expression analysis for all patients. It is highly recommended (but optional for the patient) that if any tissue remains after analysis, it will be stored at the Biospecimen Bank at UCSF for future research.

In addition, it is highly recommended (but optional for the patient) that peripheral blood specimens be submitted for the test described in Section 10.4 (Peripheral blood CD69/137+ activated T cells and phenotype) and for banking for future translational research.

Tissue from a biopsy or surgical specimen will be obtained from formalin fixed and paraffin embedded (FFPE) in tissue blocks. Institutions must ship FFPE tissue as outlined in Section 10.2 to the Biospecimen Bank at UCSF by overnight courier.

Submission of H&E and p16 stained slides to the Biospecimen Bank at UCSF for central review of p16 staining is **required** for oropharyngeal patients and submission of the H&E and block (or punches) is **required** for all patients for PD-L1 expression analysis. The FFPE samples must have sufficient tumor material for both analyses.

See the table below.

Central review of p16 for patients with oropharyngeal carcinomas will be conducted with rapid turnaround (1-2 business days from receipt of the slides) coordinated by Dr. Richard Jordan at the Biospecimen Bank. Specifics of type and source of p16 antibody and testing method will be requested (although not required) at the time of specimen submission. Every effort should be made to obtain and submit this information at the time of specimen transmission, in order to ensure the fastest possible resolution should there be any questions about staining technique.

Note: Due to potential delays in customs, Canadian sites will be permitted to submit an Aperio digital image of the H&E and p16 stained slide for remote central review by Dr. Jordan. Prior approval for this must be obtained from the Biospecimen Bank at UCSF. In cases in which Dr. Jordan determines that the image quality or staining is inadequate, the site will be required to send the original slides to the Biospecimen Bank directly. H&E slides will still have to be submitted by Canadian sites along with the FFPE block as per section 10.2 for the PDL expression analysis.

H&E stained slides will be used to confirm presence of tumor in the sample and to aid in

assay interpretation and must be submitted with blocks. The primary reviewer will be the Pathology Co-Chair, Richard Jordan, DDS, PhD, with secondary analysis by the Pathology Co-Chair, Christina Kong, MD. Interpretation of each p16 immunostained slide will be performed using the H-score method described by Jordan, et al. (2012) that has been validated as a reliable, reproducible, and accurate method to score p16 in squamous cell carcinoma of the head and neck. p16 IHC will be scored as evaluable if strong and diffuse positivity was observed in the tissue mounted on each slide. The highest intensity of p16 staining present in the tumor will be scored on an ordinal score of 0-3, relative to the intensity of the positive (score 3) and negative (score 0). The percent of tumor staining at the highest intensity also will be estimated within 5% increments. The H score is derived from the cross product of the intensity score (0 to 3), and the percent of tumor staining at the highest intensity (0-100%). An optimal H-score cut-point of 60 on a scale of 0-300 yields an average sensitivity of 91.6% and specificity of 90.4% for HR-HPV oncogene expression and thus an H-score cut-point of 60 indicates that a tumor with diffuse low-intensity nuclear and cytoplasmic p16 staining in the majority of the tumor is a true positive (Jordan 2012). High agreement on inter-rater interpretation has been reported (Schlecht 2011, Thavaraj 2011), indicating the familiarity of pathologists with interpretation of IHC assays. Similarly, comparable assay performance for p16 to that observed here has also been previously reported (Schlecht 2011, Thavaraj 2011). The most common p16 monoclonal antibody in use is E6H4 (CINtec). Other acceptable p16 antibody types include 16P04 and JC8. If a different p16 antibody is used, discussion with the Pathology Co-Chairs is strongly encouraged.

In cases in which a major discrepancy arises between the primary evaluator and the central reviewer (Dr. Jordan), the p16 stained slide and the associated probe and testing specifics will be sent to a secondary central reviewer, Dr. C. Kong at Stanford University, to resolve the disagreement. If p16 staining cannot be established as positive through the central review process, the patient is not considered eligible.

Ship FFPE biospecimens for mandatory central review and PD-L1 expression, and for optional banking to:
(do not ship fresh peripheral blood to this address)
Biospecimen Bank at UCSF
2340 Sutter Street, Room S341 (Box 1800)
San Francisco, CA 94115
415-476-7864; RTOG@ucsf.edu

Ship all fresh peripheral blood to:
Ferris Laboratory
Attn.: Sandra Poveda Gibson
University of Pittsburgh Cancer Institute
Room 2.26 Hillman Research Pavilion
5117 Centre Avenue
Pittsburgh, PA 15213
For questions: 412-623-7738 or 412-443-8673; povedas@upmc.edu

Alternatively, contact Dr. Ferris: 412-298-7002; ferrisrl@upmc.edu

See the tables below for mandatory and optional specimen collection and Appendix III for further details.

See further details of specimen collection/processing/shipping on the RTOG web site, http://www.rtog.org/LinkClick.aspx?fileticket=1SFlEVxSui4%3d&tabid=281.

10.3 Mandatory Studies (26Dec2017)

Mandatory Study #1: Specimen Collection for Central p16 Confirmation for Oropharyngeal Cancer Patients			
The specimens are being collected for confirmation by central review. Institutions must screen oropharyngeal patients by immunohistochemistry prior to registration • Required Forms: ST form and pathology reports with accession number, date of procedure, and p16 staining result; any other personal health information (PHI) should be redacted. • Shipping costs: Submitting site pays cost of shipping. • Residual Material: p16 slides will be retained unless return is requested by the submitting site; sites should submit a return request form with a return air bill. H&E slide will be retained for all cases. **Ship central review specimens to:** **Biospecimen Bank at UCSF** **2340 Sutter Street, Room S341** **San Francisco, CA 94115** For questions, contact: Biospecimen Bank at UCSF; RTOG@ucsf.edu; 415-476-7864/FAX 415-476-5271			
Specimen Type	**Collection Time Points**	**Collection Information and Requirements**	**Shipping**
One H&E slide One p16 stained IHC slide Note: Both slides must be from the same block. The H&E can be a duplicate cut slide.	Pre-Treatment	Enrolling institution, using a CLIA certified laboratory, screens patient with p16 testing by IHC. Then Biospecimen Bank does central review.	Slides shipped ambient to the UCSF Biospecimen Bank
Mandatory Study #2: Tumor PD-L1 Expression for All Patients			
Specimens are being collected to determine if patients with PD-L1 positive tumors will have an improved PFS when treated with nivolumab in comparison to patients with PD-L1 negative tumors (see Section 2.7 for further details). • FFPE blocks and punches must have sufficient tumor cells present in the sample			

being submitted for PDL1 testing.

- Required Form: ST form and pathology reports with accession number, date of procedure; any other personal health information (PHI) should be redacted.
- Shipping costs: Return labels are provided for frozen biospecimens only.

Ship specimens to:
Biospecimen Bank at UCSF
2340 Sutter Street, Room S341
San Francisco, CA 94115

For questions, contact:
Biospecimen Bank at UCSF; RTOG@ucsf.edu; 415-476-7864/FAX 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Representative H&E stained slides of the primary tumor or metastatic lymph node. Can be a duplicate cut slide, does not have to be the diagnostic slide.	Pre-treatment	H&E stained slide (can be the same one submitted for central review, if applicable)	Slide shipped ambient to the UCSF Biospecimen Bank
A corresponding paraffin-embedded tissue block or one to two 3 mm punches of the primary tumor or metastatic lymph node taken before initiation of treatment	Pre-treatment	Paraffin-embedded tissue block or punch biopsies from the block. If embedded punches are submitted the H&E from the punch block must also be sent	Block or punches shipped ambient (ship with a cold pack during hot weather) to the Biospecimen Bank

10.4 Optional Specimen Collection for RTOG 3504 Research and Banking

Optional Study #1: Peripheral blood CD69/137+ activated T cells and phenotype

Patients must be offered the opportunity to consent to optional specimen collection. If the patient consents to participate, the site is required to submit the patient's specimens as specified in the protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.

Specimens are being collected to determine if activated, CD69+ or CD137+ T cells will increase in the circulation of nivolumab-treated patients (see Section 2.7 for further details) and to correlate their phenotype, and co-stimulatory/co-inhibitory receptors with clinical response.

- Required Form: Study specific ST form for peripheral blood
- Shipping days: Monday-Wednesday (U.S. sites); Monday-Tuesday (Canada and Non-North American).
- Shipping labels will be provided with kits for peripheral blood from the UCSF Biospecimen Bank.

Ship specimens to:
Ferris Laboratory
Attn.: Sandra Poveda Gibson
Room 2.26 Hillman Research Pavilion
5117 Centre Avenue
Pittsburgh, PA 15213

For questions, contact: Sandra Gibson (Ferris Lab), 412-623-7738 or 412-443-8673; povedas@upmc.edu
Sites should email the Ferris lab tracking information before shipping the samples.

Alternatively, contact Dr. Ferris: 412-298-7002; ferrisrl@upmc.edu

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
Peripheral Blood Mononuclear Cells (PBMC) – four 10 ml or five 8 ml green top (heparin) tubes	• Pre-treatment (day -14) • Post-treatment: 3 and 6 months after RT	See Appendix IV for processing and shipping information	Ship fresh at room temperature overnight for morning delivery to the Ferris Laboratory

11. SPECIAL STUDIES (NON-TISSUE)

Not Applicable

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

The Radiation Oncology Co-Chair, Loren Mell, MD will perform ongoing remote RT Quality Assurance Review after cases enrolled have been received at RTQA.

The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of radiotherapy treatment data as specified in Section 13.1. The scoring mechanism is: Per Protocol, Variation Acceptable, and Deviation Unacceptable.

12.2 Drug Quality Assurance Reviews

The Co-Principal Investigator/Medical Oncology, Maura Gillison, MD, PhD and Medical Oncology Co-Chair, A. Dimitrios Colevas, MD, will perform a Chemotherapy Assurance Review of all patients who receive or are to receive drug therapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of drug treatment data as specified in Section 13. The scoring

mechanism is: Per Protocol/Acceptable Variation, Unacceptable Deviation, and Not Evaluable. A report is sent to each institution once per year to notify the institution about compliance for each case reviewed in that year.

Drs. Gillison and Colevas will perform a Quality Assurance Review after RTOG Headquarters has received complete data for the first 20 cases enrolled. Drs. Gillison and Colevas will perform the next review after RTOG Headquarters has received complete data for the next 20 cases enrolled. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as RTOG Headquarters has received complete data for all cases enrolled, whichever occurs first.

12.3 Surgical Quality Assurance Reviews

Patients with oral cavity cancer are excluded from participation if resection of the primary tumor is considered technically feasible by an oral or head and neck cancers surgical subspecialist. Co-Principal Investigator/Surgical Oncology, Dr. Robert Ferris MD, PhD, will review individual cases as they arise to document appropriateness for accrual and reason(s) for deeming cases unresectable.

Drs. Ferris also will review cases after RTOG Headquarters has received complete data for the first 5 such oral cavity cases enrolled, and after each 5 cases thereafter. The final cases will be reviewed within 3 months after this study has reached the target accrual or as soon as RTOG Headquarters has received complete data for all cases enrolled, whichever occurs first.

13. DATA AND RECORDS

This study will utilize Medidata Rave. See the Data Collection/RAVE Data Forms Guide in the study-specific guide on the RTOG Foundation 3504 protocol page of the RTOG website, www.rtog.org, for further details.

13.1 Summary of Dosimetry Digital Data Submission (Submit to RTOG via TRIAD; see the study-specific guide on the RTOG Foundation 3504 protocol page of the RTOG website, www.rtog.org, for details of data submission and TRIAD.) (26Dec2017)

Item		Due
DICOM Items	DICOM CT Image	**Within 1 week of start of RT**
	DICOM Structure	
	DICOM Dose	
	DICOM RT Plan	
All required structures must be labeled per the table in Section 5.2.5.		
DVH Analysis Worksheet (optional) to be submitted via TRIAD with RT Digital Data listed above: https://www.rtog.org/ClinicalTrials/RTOGFoundationStudies/RTOGFoundationStudy3504/RTOG3504Forms.aspx		

Upon submission of the digital data via TRIAD, complete an online **Digital Data Submission Information Form (DDSI)**: https://www.rtog.org/Corelab/TRIAD.aspx	
NOTE: ALL SIMULATION AND PORTAL FILMS AND/OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.	

14. STATISTICAL CONSIDERATIONS

14.1 Study Design

14.1.1 Total Accrual

40 (minimum) to have 8 evaluablepatients per arm.

14.2 Study Endpoints (26Dec2017)

Primary Endpoints:

- Dose limiting toxicity for the addition of nivolumab (anti PD-1 immunotherapy) to chemoradiotherapy with weekly cisplatin (40 mg/m^2/week x 7) for patients with intermediate- or high-risk head and neck squamous cell carcinoma (HNSCC);
- Dose limiting toxicity for the addition of nivolumab to chemoradiotherapy with high-dose cisplatin (100 mg/m^2 q 21 days x 3) for patients with intermediate- or high-risk head and neck squamous cell carcinoma (HNSCC);
- Dose limiting toxicity for the addition of nivolumab to chemoradiotherapy with weekly cetuximab (400 mg/m^2 load, 250 mg/m^2/week x 7) for patients with intermediate- or high-risk head and neck squamous cell carcinoma (HNSCC);
- Dose limiting toxicity for the addition of nivolumab to radiotherapy for patients with intermediate- or high-risk head and neck squamous cell carcinoma (HNSCC) with one to four of the following: age $\geq$ 70 years; Zubrod Performance Status 2; baseline grade $\geq$ 3 neuropathy; grade $\geq$2 hearing loss; CrCl < 50 ml/min.

Secondary Endpoint: To evaluate the safety, feasibility and patient compliance with adjuvant administration of single agent nivolumab for a maximum of 1 year of therapy (Nivolumab, 480 mgs q28 days x 7).

Also to be evaluated at the completion of this trial will be the ability of patients to tolerate the planned treatment per protocol. A patient will be considered to have tolerated protocol therapy if the following criteria are met:

i) Radiation therapy was delivered within 8 weeks;
ii) Patient was administered $\geq$70% of the nivolumab dose per protocol (excluding adjuvant therapy);
iii) Patient was administered $\geq$70% of the cetuximab dose per protocol, where applicable;
iv) Patient was administered $\geq$70% of the cisplatin dose per protocol, where applicable.

14.3 Primary Objectives Study Design

14.3.1 Sample Size and Power Calculations

Patients will be sequencially enrolled into Arms 1, 2 and 3. The goal of Arm 1 is to confirm the safety of anti-PD-1 therapy administered in combination with weekly

cisplatin-based chemoradiotherapy. Arms 1, 3, and 4 will start at the fixed-dose bioequivalent (240 mgs) of the FDA-approved dose and schedule of nivolumab (3 mgs/kg q14 days). For any arm, in the event of 0-2 DLT events, the regimen will be considered worthy of additional study. If >2 of 8 DLTs occur, the regimen will be considered too toxic for further study. Observation of the last patient for the period of DLT (28 days post-completion of RT) is mandatory. A DLT will be defined as: (1) Any ≥ grade 3 adverse event (CTCAE, v. 4) 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; or (4) Inability to receive an adequate dose (≥ 70%) of cisplatin (Arm 1 and 2) or cetuximab (Arm 3) due to toxicity definitely related to nivolumab. With a cohort of 8 patients, the probability of the nivolumab arm being judged to be too toxic when the true toxicity rate is 45% or higher is at least 78%. If the true toxicity rate is 20% or lower, the probability that the therapy will be safe is 80%. The period of observation for DLT is from the start of nivolumab through 28 days post-completion of radiotherapy.

We will accrue 10 patients per cohort to get 8 evaluable patients, if more than 8 patients are evaluable, we will analyze data from the first 8 patients. All patients who receive at least one dose of nivolumab are considered evaluable for DLT, should a DLT occur. In the absence of DLT, patients must have received at least one fraction of radiation therapy, at least one dose of cisplatin or cetuximab (where applicable), and have completed the DLT observation period to be evaluable for DLT. Patients considered inevaluable may be replaced to ensure a minimum of 8 evaluable patients per arm. Therefore, the total number of patients enrolled into any one arm of the study may exceed 10. Analysis results will be reviewed by the RTOG Foundation DMC.

In this trial, we will evaluate the feasibility of 7 months of adjuvant nivolumab. We will prospectively monitor compliance with therapy in all 4 arms of the the trial. The period of observation for feasibility is from the start of adjuvant nivolumab through 7 months of therapy. We will evaluate the first 8 patients from all 4 arms. If more than 4 patients stop the adjuvant therapy before 7 months, we will consider the adjuvant therapy infeasible. Evidence of infeasibility would include: patient refusal; discontinuation due to drug related toxicity; physician decision that therapy is no longer in the best interests of the patient in the absence of disease progression. In that event, administration of adjuvant nivolumab would be discontinued. With a cohort of 8 patients from all 4 arms, the probability of the nivolumab arm being judged to be infeasible when the true noncompliance rate is 70% or higher is at least 81%. If the true noncompliance rate is 40% or lower, the probability that the therapy will be feasible is 83%.

14.4 Accrual/Study Duration Considerations

All non-Arm 4 patients will be registered to Arm 1 initial dose until the sample size is reached, then to Arm 2 initial dose, then to Arm 3 initial dose. Arm 4 will be open concurrently with Arms 1/2/3. The accrual time for the 4 cohorts in phase I will take approximately 5 months (10 sites). The study time will be approximately 12-18 months.

14.5 Dose Level Guidelines

See Section 5.1.1.

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APPENDIX I: NIVOLUMAB (BMS-936558) PHARMACY REFERENCE MANUAL

1 OBJECTIVE

The objective of this procedure manual is to provide the study site with clear and detailed information for the storage, handling, preparation and administration of Nivolumab used in the RTOG 3504/CA209-410 study

2 BMS CLINICAL PRODUCT CONTACT

If concerns regarding the quality or appearance of the study drug, or questions regarding administration arise, do not dispense the study drug and contact the Bristol-Myers Squibb immediately:

Questions with regard to drug preparation and pharmacy manual content:

Peter Trimboli, RPh
Pharmacy Services, Drug Supply Management
Bristol-Myers Squibb Research and Development
Telephone: 609-252-4862
Email: pharmacyservices@bms.com

3 NIVOLUMAB INJECTION

3.1.1 Description

Product Name	Nivolumab Injection (BMS 936558), 100 mg/vial (10 mg/mL)
Product description and Packaging	*Packaging:* Vials assembled into white dispensing boxes containing 100 mg vials. *Vials:* 10 cc Type I glass vial. 20 mm stopper and seal, respectively. *Appearance:* Clear to opalescent, colorless to pale yellow liquid, light (few) particulates may be present.
Product Ingredients	Each vial contains 100 mg Nivolumab

3.1.2 Handling and Dose preparation

As with all injectable drugs, care should be taken when handling and preparing Nivolumab. Whenever possible, Nivolumab infusions should be prepared in a laminar flow hood, glovebox, or safety cabinet using standard procedures for the safe handling of intravenous agents applying aseptic techniques. Gloves are required. If nivolumab solution comes in contact with the skin or mucosa, immediately and thoroughly wash with soap and water.

Dose Preparation and administration

Visually inspect drug product solution for particulate matter and discoloration prior to

APPENDIX I (continued)

administration. Nivolumab is a clear to opalescent, colorless to pale yellow solution. Discard the vial if the solution is cloudy, discolored, or contains extraneous particulate matter other than a few translucent-to-white, proteinaceous particles. Do not shake the vial.

Preparation

- Withdraw the required volume of Nivolumab and transfer into an intravenous container.
- Dilute Nivolumab with either 0.9% Sodium Chloride Injection, USP or 5% Dextrose Injection, USP to prepare an infusion with a final concentration ranging from 1 mg/mL to 10 mg/mL (see example below)
- Mix diluted solution by gentle inversion. Do not shake.
- Discard partially used vials or empty vials of Nivolumab.

Storage of Infusion

The product does not contain a preservative. After preparation, store the Nivolumab infusion either:

- at room temperature for no more than 4 hours from the time of preparation. This includes room temperature storage of the infusion in the IV container and time for administration of the infusion

or

- under refrigeration at 2°C to 8°C (36°F to 46°F) for no more than 24 hours from the time of infusion preparation.

  Do not freeze.

Administration

Administer the infusion over 30 minutes through an intravenous line containing a sterile, non-pyrogenic, low protein binding in-line filter (pore size of 0.2 micrometer to 1.2 micrometer). Do not coadminister other drugs through the same intravenous line. **Flush the intravenous line at end of infusion with appropriate amount of diluent (e.g. 15-20 ml) to ensure that the total dose is administered. Total infusion and flush time should equal to 30.**

Dose selection for Nivolumab should be assigned per subject as outlined in the clinical protocol study drug dosing section of the clinical protocol. *The examples below use a total volume of 60 ml to allow for a practical administration rate, however other volumes may be used for Nivolumab preparation so as long as the final concentration remain between 1 - 10 mg/ml (e.g. 100 ml).*

NOTE: When Nivolumab Placebo is required, placebo shall be considered an equal volume of drug diluent alone (NS, D5W) which is standard to site practice for mixing active Nivolumab (60 ml, or 100 ml) and should be infused at the same rate (30 minutes).

Preparation example 240 mg dose;

Nivolumab 240 mg (24 ml Nivolumab 10mg/ml solution, local rounding rules applicable) may be mixed with 36 ml NS or D5W to a total volume = 60 ml which can be infused over 30 minutes at 2 ml/min followed by flush.

Preparation example 480 mg dose;

Nivolumab 480 mg (48 ml Nivolumab 10mg/ml solution, local rounding rules applicable) may be mixed with 12 ml NS or D5W to a total volume = 60 ml which can be infused over 30 minutes at 2 ml/min followed by flush.

3.1.3 Product Storage and Stability

Nivolumab 100 mg vials for injection should be refrigerated at 2°C to 8°C (36°F to 46°F). Protected from light and **should not be frozen**. Do not use beyond the expiration date on the vial. Protect the vials from light by storing in the original package until time of use. Vials do not contain preservative and thus are intended for single use only and should be discarded after use and product reconciliation.

Nivolumab should not be infused concomitantly in the same intravenous line with other agents. No physical or biochemical compatibility studies have been conducted to evaluate the co-administration of Nivolumab with other agents.

4 SITE TEMPERATURE EXCURSIONS AND TRANSIT

Drug must be stored under the proper conditions as listed on the clinical supply label. If any temperature excursions are encountered during on site storage, please report these to BMS for assessment as outlined in the Bristol-Myers Squibb, "Investigational Medicinal Product (IMP) handling at Investigational Sites: Shipment, Receipt, Storage, Use Date Extension and Return/Destruction" guideline using the Temperature Excursion Response Form. See Form 1

Proper storage conditions must be maintained during movement of inventory within an investigational site. Storage conditions for medications requiring storage at 2ºC to 8ºC (36ºF-46ºF) must be maintained throughout the transport with documentation maintained within the site files. Where controlled storage conditions (for example, temperature, relative humidity, light, etc.) are required during transit, the necessary environmental controls must be in place to ensure that the drug product remains within the acceptable temperature range. Temperature monitoring devices such as min max device must be implemented during transit.

5 PRODUCT RECEIPT, ACCOUTABILITY, AND DESTRUCTION

Drug Receipt

Shipment Inspection Instructions

1. Open box **immediately** upon receipt.
2. Carefully inspect kits ensuring all of the supplies were received in good condition, correct quantity received, and all of the container ID #s were received as noted on packing slip.
3. Sign and date (date of receipt) packing slip and file with study-specific documents.

4. Log in all supplies in each shipment on the appropriate Inventory log Form

Accountability

It is the responsibility of the investigator to ensure that a current disposition record of investigational product accountability and reconciliation is maintained at each study site where study drug is inventoried and dispensed.

In addition, records or logs must comply with local regulations and guidelines for the conduction and handling of clinical supplies should include but not limited too:

- Amount received and placed in storage area
- Amount currently in storage area
- Label ID number or batch number
- Amount dispensed to and returned by subject, including unique subject identifiers
- Amount transferred to another area/site for dispensing or storage
- Non-study disposition (e.g. lost, wasted)
- Amount destroyed at study site, if applicable
- Amount returned to the Sponsor, if applicable
- Dates and initials of person responsible for Investigational Product (IP)
- Dispensing/accountability, as per the Site Signature and Delegation Log.

Study Drug Destruction

Study drugs can be destroyed on site if local policies allow to do so. It is the Investigator's responsibility to ensure that arrangements have been made for the disposal, procedures for proper disposal have been established according to applicable regulations, guidelines and institutional procedures, and appropriate records of the disposal have been documented.

Form 1

Bristol-Myers Squibb

Temperature Excursion Response Form for Investigational Medicinal Products

Section A. To be completed by the site at the time of Site Storage Temperature Excursion:

Protocol Number:	**Site Number/Investigator Name/Country:**
Description of Drug Products involved in Excursion:	
Batch number (s) printed on label:	**Container numbers:**
Description of Excursion (temperature highs/lows and duration):	
Below label storage lower limit …..°C Duration:…… Low extreme t°: …..°C **Above label storage upper limit ….. °C Duration:…….. High extreme t°: …..°C**	
Reason for excursion:	
Has the issue been resolved?	
Have these specific containers been involved in a previous excursion? NO ☐ YES ☐ **If yes, please provide:**	

Batch number (s):	**Container numbers:**	**Temperature highs/lows and duration**

When is the next planned patient visit when these supplies may be dispensed?

Excursion information submitted by: _____ **Date:** _____

Print/Signature/Title of site staff

Section B. Usage Decision to be made by Bristol-Myers Squibb:

Temperature excursion details for the products listed above have been evaluated. Usage decision is based on the temperature data that were made available by the investigational site.

Conclusion (and comments):

☐ **All products are suitable for continued use**

_____

_____

☐ **All products are NOT suitable for further dispensation. Please remove supplies from available inventory and work with your Site Manager/Site Monitor to have supplies destroyed and IVRS updated if applicable.**

_____

_____

Assessment completed by: _____ **Date** _____

Print/Signature/Title

Templates as provided via separate attachment or below may serve as a sample for dosage calculations and may be printed out and used to document any calculations and infusion times as required by the clinical study team. Content in this attachment may be added or omitted.

Drug Dose and Volume Calculator for IV Infusion	
Drug Product :	
Protocol number	
Patient name or ID:	
Preparation date and time:	
Drug Strength (mg/mL)	
Subject body weight (kg)	
[1]Dose in mg	
Volume of Drug (mL)	
Total Volume of infusion (mL)	
Volume of Diluent (mL) NS or D5W	
Infusion duration (min)	
Infusion Rate (mL/min)	
Infusion hang time	
Infusion completion time	

Note: If required, flush line with separate volume of same diluent (e.g. 15-20 ml) as outlined in the study pharmacy manual

APPENDIX II: BIOSPECIMEN BANK AT UCSF: BIOSPECIMEN COLLECTION, PROCESSING, AND SHIPPING INSTRUCTIONS FOR FFPE

- **FFPE Specimens:**
  - Slides should be shipped in plastic slide holder/slide box. Place a small wad of padding in top of the container. If you can hear slides shaking they can break during shipping.
  - FFPE Blocks can be shipped in a plastic block holder or wrapped with paper or placed in a paper envelope, and placed in a cardboard box with padding. Do not wrap blocks with bubble wrap or gauze. Place padding in top of container so that if you shake the container the blocks are not shaking. If you can hear blocks shaking they may break during shipping. During warm weather months the use of cold packs is recommended to prevent wax from melting.
  - Slides, Blocks, or Plugs can be shipped ambient or with a cold pack either by United States Postal Service (USPS) to the USPS address (94143) or by Courier to the Street Address (94115). **Do NOT ship on Dry Ice**.
  - Urgent overnight shipments (central review) should always be sent by Courier.
  - If patients consented to banking DO NOT ship FFPE specimens with a return request. We cannot accept or bank samples that we cannot keep. Always send what can be banked (duplicate H&Es, Blocks or punches or unstained as specified in the protocol). We can punch and return blocks if noted in the protocol. Punch kits can be requested from us by email (RTOG@ucsf.edu) for sites that wish to punch the block themselves.

- **For Questions regarding collection/shipping please contact the Biospecimen Bank at UCSF by e-mail: RTOG@ucsf.edu or phone: 415-476-7864 or Fax: 415-476-5271.**

Shipping Instructions for FFPE: (See Appendix III for processing and shipping information for peripheral blood)

US Postal Service Mailing Address: **Use only for non-urgent ambient specimens- FFPEs, slides, blocks:**	**Courier Address (FedEx, UPS, etc.):** **For Frozen, Urgent or Trackable Specimens:**
Biospecimen Bank at UCSF **UCSF- Box 1800** **2340 Sutter St, room S341** **San Francisco, CA 94143-1800**	**Biospecimen Bank at UCSF** **University of California San Francisco** **2340 Sutter St, room S341** **San Francisco, CA 94115**

- Include all required specimen paperwork in pocket of biohazard bag.
- Check that the Specimen Transmittal (ST) Form has been completely filled out
- Check that all samples are labeled with the study and case number, and include date of collection as well as collection time point (e.g., pretreatment, post-treatment).

Note: See Appendix III for processing and shipping information for peripheral blood.

APPENDIX III: FERRIS LABORATORY: PREPARATION, PROCESSING AND SHIPPING OF PERIPHERAL BLOOD

Kit Contents for each timepoint:
Four 10 ml or five 8 ml Heparin Blood (green top) draw tubes
Tube holder
Outer box for tube holder
Secondary plastic bag with absorbent
Study specific ST Form
Fed Ex Clinical Pak with labels and stickers
Instructions how to pack and ship the samples

Processing:

1. Sites should only draw blood samples on Monday-Wednesdays and only ship Monday-Wednesdays.
2. Draw blood in four 10 ml or five 8 ml green top (heparin) tubes.
3. Mix gently.
4. Place tubes in styrofoam tube holder and outer box provided with Kit.
5. Seal up tube holder box and place in secondary plastic bag with absorbent. Use of ambient gel packs with insulated packs are encouraged during cold winter and hot summer months.
6. Place ST form in pouch of bag.
7. Place bag with tube box in the Fed Ex Clinical Pak provided.
8. Place provided fed ex label in shipping pouch, and stick to Fed Ex envelope.
9. Place "keep away from heat" and "perishable" Stickers provided with kit on envelope

   Ship the blood at room temperature for overnight delivery same day to Dr Ferris's lab. Label is provided on the Clinical Pak.
10. If sites draw the blood sample late in the day, the site should refrigerate the sample until it is shipped and note the storage conditions on the ST form.

Shipping Address: Note: Do NOT ship peripheral blood to Biospecimen Bank at UCSF.
Ferris Laboratory
Attn.: Sandra Poveda Gibson
Room 2.26 Hillman Research Pavilion
5117 Centre Avenue
Pittsburgh, PA 15213

For questions, contact: Sandra Gibson (Ferris Lab), 412-623-7738 or 412-443-8673; povedas@upmc.edu

Alternatively, contact Dr. Ferris: 412-298-7002; ferrisrl@upmc.edu