NRG ONCOLOGY

NRG-HN005
(ClinicalTrials.gov NCT #03952585)(04-NOV-2020)

A RANDOMIZED PHASE II/III TRIAL OF DE-INTENSIFIED RADIATION THERAPY FOR PATIENTS WITH EARLY-STAGE, P16-POSITIVE, NON-SMOKING ASSOCIATED OROPHARYNGEAL CANCER

This trial is part of the National Clinical Trials Network (NCTN) program, which is sponsored by the National Cancer Institute (NCI). The trial will be led by NRG Oncology with the participation of the network of NCTN organizations: the Alliance for Clinical Trials in Oncology; ECOG-ACRIN Medical Group; and SWOG.

Coordinating Center:
NRG Oncology, Four Penn Center; 1600 JFK Blvd; Suite 1020; Philadelphia, PA 19103

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Protocol Agent

Agent	Supply	NSC #	IND #	IND Sponsor
Nivolumab	CTEP/PMB	748726		DCTD, NCI
Cisplatin	Commercial	119875		

Participating Sites (04-NOV-2020)
☒ U.S.
☒ Canada
☐ Approved International Member Sites

Document History

	Version Date
Amendment 4	**August 21, 2023**
Amendment 3	April 19, 2023
Amendment 2	February 16, 2021
Amendment 1	November 04, 2020
Initial	May 29, 2019

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<table>
<tr><td colspan="3">CONTACT INFORMATION (21-AUG-2023)</td></tr>
<tr><td>For regulatory requirements:</td><td>For patient enrollments:</td><td>For data submission:</td></tr>
<tr><td>Regulatory documentation must be submitted to the Cancer Trials Support Unit (CTSU) via the Regulatory Submission Portal.

(Sign in at https://www.ctsu.org, and select the Regulatory > Regulatory Submission.)

Institutions with patients waiting that are unable to use the Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

Contact the CTSU Regulatory Help Desk at 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org for regulatory assistance.</td><td>Refer to the patient enrollment section of the protocol for instructions on using the Oncology Patient Enrollment Network (OPEN). OPEN is accessed at https://www.ctsu.org/OPEN_SYSTEM/ or https://OPEN.ctsu.org.

Contact the CTSU Help Desk with any OPEN related questions by phone or email : 1-888-823-5923, or ctsucontact@westat.com.</td><td>Data collection for this study will be done exclusively through Medidata Rave. Refer to the data submission section of the protocol for further instructions.</td></tr>
<tr><td colspan="3">The most current version of the study protocol and all supporting documents must be downloaded from the protocol-specific Web page of the CTSU Member Web site located at https://www.ctsu.org.

Permission to view and download this protocol and its supporting documents is restricted and is based on person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the CTSU members' website.</td></tr>
<tr><td colspan="3"><u>For clinical questions (i.e. patient eligibility or treatment-related)</u> Contact the Study Data Managers of the Lead Protocol Organization</td></tr>
</table>

For non-clinical questions (i.e. unrelated to patient eligibility, treatment, or clinical data submission) Contact the CTSU Help Desk by phone or e-mail: CTSU General Information Line – 1-888-823-5923, or ctsucontact@westat.com. All calls and correspondence will be triaged to the appropriate CTSU representative.
For imaging data submission questions: **IROCimagearchive@acr.org; please include trial number in the email subject line** **For TRIAD access and installation support:** **TRIAD-Support@acr.org** **Triadhelp.acr.org** **TRIAD Software Installation:** **https://triadinstall.acr.org/triadclient/**

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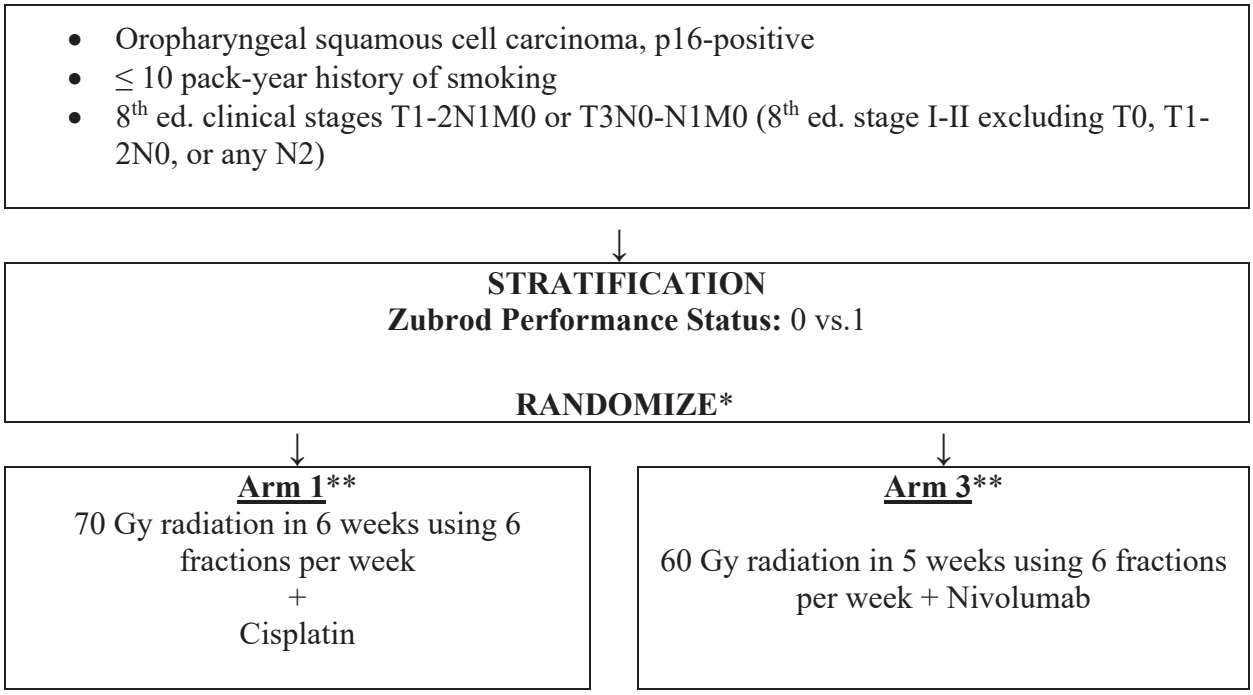
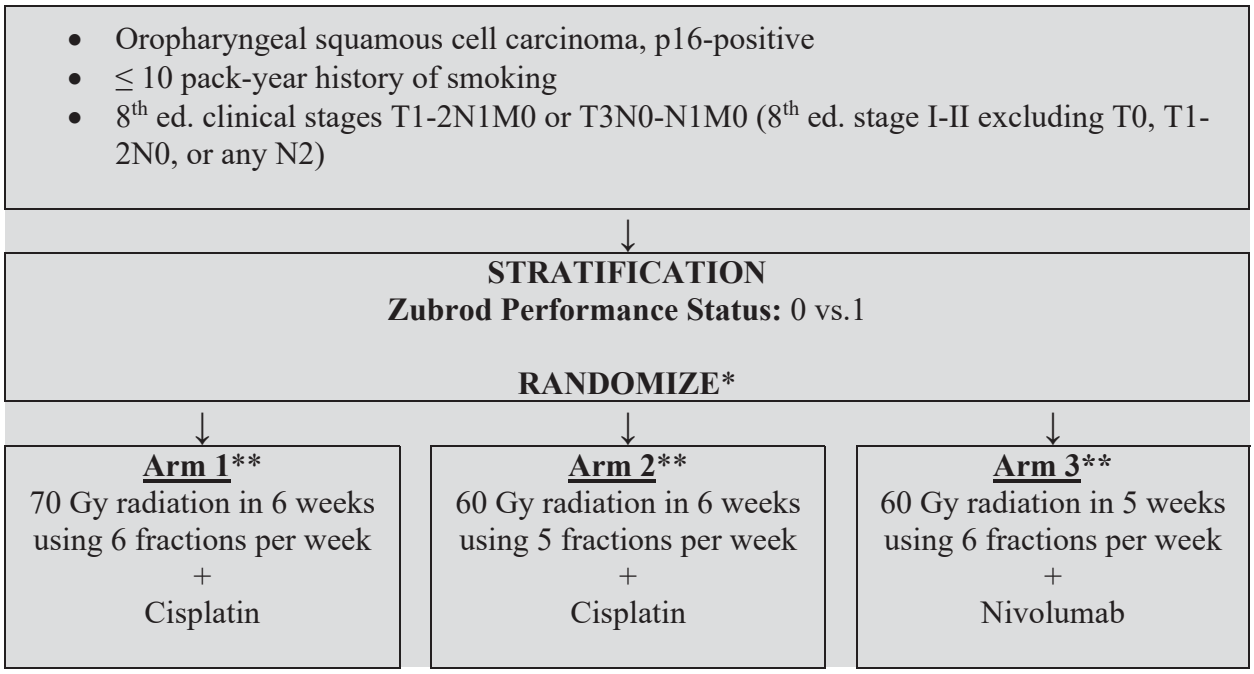
Effective with Amendment 3



*Randomization is 1:1
**See Section 5 for radiation and systemic therapy treatment details.
Note: Arm 2 (see prior schema) eliminated after phase II interim futility analysis.

PRIOR PHASE II SCHEMA (19-APR-2023)

For patients enrolled prior to amendment 3; closed to accrual 03-FEB-2023



*Randomization is 1:1:1.
**See Section 5 for radiation and systemic therapy treatment details.

1. OBJECTIVES

1.1 Primary Objective (19-APR-2023)

1.1.1 Phase II

To demonstrate non-inferiority in terms of progression-free survival (PFS) of concurrent reduced-dose radiation therapy (RT) with cisplatin* or concurrent reduced-dose radiation therapy with nivolumab to the current standard of care (standard-dose RT with cisplatin).

***Arm 2 (concurrent reduced-dose RT with cisplatin) was dropped after interim futility analysis in phase II.**

1.1.2 Phase II (REVISED)

To demonstrate non-inferiority in terms of progression-free survival (PFS) of concurrent reduced-dose radiation therapy (RT) with nivolumab to the current standard of care (standard-dose RT with cisplatin).

1.1.3 Phase III

To demonstrate co-primary endpoints of non-inferiority of PFS and superiority of quality of life (QOL) as measured by the MDADI of concurrent reduced-dose radiation with cisplatin* or concurrent reduced-dose radiation with nivolumab to the current standard of care (standard-dose RT with cisplatin).

***Arm 2 (concurrent reduced-dose RT with cisplatin) was dropped after interim futility analysis in phase II.**

1.1.4 Phase III (REVISED)

To demonstrate co-primary endpoints of non-inferiority of PFS and superiority of quality of life (QOL) as measured by the MDADI of concurrent reduced-dose radiation with nivolumab to the current standard of care (standard-dose RT with cisplatin).

1.2 Secondary Objectives (19-APR-2023)

1.2.1 To compare patterns of failure (local and regional relapse versus distant) and overall survival between the experimental arm and the control arm;
1.2.2 To assess long term PFS, overall survival, and toxicity between the experimental arm and the control arm;
1.2.3 To determine acute and late toxicity profiles as measured by the CTCAE;
1.2.4 To explore the symptomatic adverse events (AEs) for tolerability of each treatment arm as measured by the PRO-CTCAE;
1.2.5 To compare changes in patient-reported outcomes (HHIA-S, EORTC-QLQ30) between the experimental arm and the control arm;
1.2.6 To assess the association of FDG-PET/CT at baseline with locoregional control and PFS;
1.2.7 To estimate the negative predictive value of the 12-14 weeks post-RT FDG-PET/CT in terms of locoregional control rates and PFS rates at 1 and 2 years.

1.3 Exploratory Objectives (19-APR-2023)

1.3.1 To collect blood and tissue specimens for future translation research;
1.3.2 To optimize radiotherapy treatment plan quality assurance methodology for radiotherapy

planning and imaging;
1.3.3 To compare changes in patient-reported outcomes (EQ-5D-5L) between the experimental arm and the control arm;
1.3.4 To collect Modified Barium Swallow (MBS) data for future review and analysis.

2. BACKGROUND

2.1 Rationale for Approach to De-Intensification for HPV-Associated Oropharyngeal Cancer

Major Network groups, including NRG Oncology and GORTEC, long ago established the standard of care for curative chemoradiation for oropharyngeal cancer to be a combination of 70 Gy of large-field radiation therapy with concurrent platinum-based chemotherapy (Ang 2010; Bourhis 2012). These approaches are associated with a high level of short- and select long-term toxicities (Trotti 2007; Machtay 2008) which is a concern in patients anticipated to have long survivorship.

In an RTOG 0129 recursive partitioning analysis of oropharyngeal cancer patients, the HPV-positive group with ≤ 10 pack years of smoking was found to be at "low risk" for death. The 3-year rates of overall survival were 93.0% in the low-risk group; 70.8% in the intermediate-risk group; and 46.2% in the high-risk group (Ang 2010). Intensive ongoing data analysis from accrued and maturing trials within the NRG Oncology group identified benchmark PFS estimates that were used to establish eligibility for NRG-HN002, a completed phase II study of reduced-dose radiation therapy (60 Gy to gross disease, 48-54 Gy to elective neck). While NRG-HN002 was in progress, the Universities of North Carolina and Florida reported a phase II study for HPV/p16+ T0-3 N0-N2c (7^{th} ed.) oropharyngeal cancer patients who received 60 Gy of radiation with concurrent cisplatin at 30 mg/m^2 per week. At planned short-term (6-14 weeks) surgical sampling of the primary site and nodal dissection, the pathologic complete response rate was 86% and at mature follow-up of 44 patients, the 3-year locoregional control and survival were 100% and 95% (Chera 2015; Chera 2018). Other reduced-dose radiation single-arm phase II study results, as well as continued large-scale data accumulation within NRG Oncology, now form the basis for continued investigation of de-intensification. Our current proposed goal is to conduct a randomized phase III study to establish that reduced-dose radiation programs are equivalent to the current standard of care (SOC).

The recently reported results of RTOG 1016, which compared concurrent cisplatin and concurrent cetuximab given with a modestly accelerated radiation course, confirmed that cisplatin remains the standard of care for the treatment of HPV-associated oropharyngeal cancer (Gillison 2018). In that study, cisplatin was administered at 100 mg/m^2 for 2 cycles every 3 weeks with 70 Gy of radiation therapy delivered over 6 weeks coinciding with the two cycles. The accelerated radiation course was the practical and biological justification for delivery of only two cycles of concurrent cisplatin.

This trial begins with a randomized phase II comparison of three arms: (1) control arm based on RTOG 1016: 70 Gy of radiation therapy over 6 weeks, with concurrent cisplatin at 100 mg/m^2 every 3 weeks x 2 cycles; (2) experimental arm: 60 Gy of radiation therapy over 6 weeks, with concurrent cisplatin at 100 mg/m^2 every 3 weeks x 2 cycles; (3) experimental arm: 60 Gy of radiation therapy over 5 weeks, with concurrent nivolumab 240 mg every 2 weeks for 6 cycles (starting 1 week prior to radiation and continuing for 12 weeks; includes 3 cycles of continued nivolumab therapy post-RT). The experimental arm(s) found to be non-inferior in terms of PFS

in phase II will continue in a phase III comparison against the control, with a co-primary endpoint of PFS and QOL.

The importance of this trial is three-fold: (1) to establish safety and efficacy of reduced-dose radiation therapy with either cisplatin or nivolumab in comparison to the current SOC; (2) to study patient-reported outcomes and toxicities of these de-intensified treatment regimens compared to the current SOC; and (3) to study long-term immunologic effects resulting from cisplatin or nivolumab with reduced-dose radiation therapy in comparison to the current SOC. The phase III component of this trial may establish a new equivalent SOC with superior QOL and non-inferior PFS compared to the current SOC (70 Gy with cisplatin) in place at present.

2.2 Rationale for Reduced-Dose Radiation Therapy in Oropharyngeal Cancer Treatment

The toxicities of a high-dose radiation therapy approach are pertinent in this context, associated with lasting multiple functional and quality-of-life effects. In particular, increasing radiation doses to the pharynx and larynx have proportionately been associated with higher risks of dysphagia or difficulty in swallowing (Vlacich 2014; Caglar 2008; Caudell 2010; Frowen 2013; Schwartz 2010; Wopken 2014; Petkar 2016). Dysphagia is a major, dose-limiting side effect of radiotherapy for patients with head and neck cancer, including those with oropharyngeal cancer (Hutcheson 2017). In a study of 81 patients with oropharyngeal cancer, a steep dose-effect relationship was observed: the probability of dysphagia increased 19% with every additional 10 Gy (Levendag 2007). Researchers who conducted a prospective study of patients with oropharyngeal cancer observed a similar association between the mean radiation dose to higher swallowing organs and the worsening of swallowing 2 years after treatment (Eisbruch 2011). For this reason, dysphagia was considered an important patient-reported outcome both in RTOG 1016 and NRG-HN002. In keeping with the importance of this endpoint, in both the phase II and phase III components of this trial, dysphagia will be assessed from the patient's perspective and acceptable patient-reported outcome is necessary for viability of any study arm. In addition, because this is the first comparative randomized dose-reduction study in this unique population, an objective functional assessment of dysphagia will be offered as an exploratory substudy, to provide an objective correlate to the endpoint of the patient's experience.

Other long-term side effects of radiation therapy also have a relationship to higher radiation dose. For example, even low or intermediate-level doses of radiation to the salivary glands, thyroid gland, and brachial plexus have been associated with xerostomia (Gabryś 2017; Beetz 2014), hypothyroidism (Chyan 2014; Bhatia 1996), and late neuropathy (Galecki 2006; Johansson 2000; Chen 2014; Olsen 1993; Bajrovic 2004). For this reason, the related organs at risk are considered important avoidance structures that are contoured in a standard head and neck cancer radiation treatment planning process. Furthermore, while neck and shoulder fibrosis are underreported and difficult to quantify (Deng 2016; Moloney 2015), following current standard of care treatments to the entire neck, there are reports of chronic spasm, pain, and shoulder dysfunction related to neurologic or musculature effects (Gelblum 2016; Ghosh 2015). This trial, as the first comparator trial of the standard of care regimen to a dose-reduced regimen, will set the stage in the future, if one or more of the experimental arms is successful, to aim at the further improvement of these and other known long-term side effects of radiation therapy.

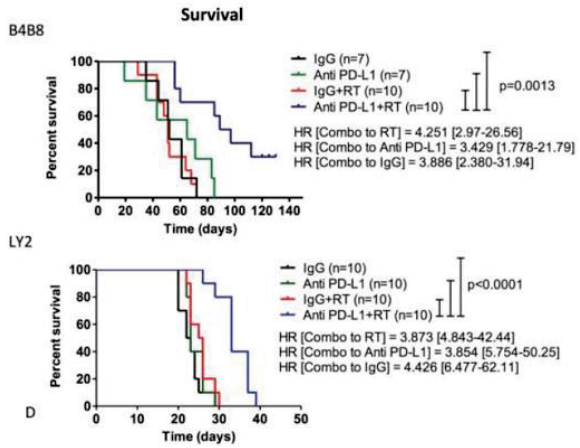
2.3 Rationale for Introduction of Immunotherapy for Oropharyngeal Carcinoma Patients

The very long-term immune effects of radiation therapy, particularly given in conjunction with myelosuppressive chemotherapy have clinical implications. Head and neck radiotherapy delivers high radiation doses to multiple lymph node chains, abundant lymphoid tissue, and major blood vessels containing large volumes of hematologic cells (Hodge 2008). In studies of peripheral blood, nonspecific immune system responses are suppressed for years in patients receiving head and neck radiotherapy (Gray 1985; Kuss 2004) and effects are seen in CD4+ and CD8+ T cell subsets that last longer in patients irradiated to the head and neck than in patients irradiated to pelvic or brain tumors. In one study, patients remained lymphopenic up to 60 months after radiotherapy, and low lymphocyte levels predisposed to tumor recurrence (Verastegui 2003). These data raise the question of how best to modulate the systemic immunologic effects of radiation therapy for the greatest long-term therapeutic advantage in head and neck cancer patients.

In response to radiation, increased expression of MHC-I and MHC-II molecules, CD80, adhesion molecules, stress ligands, Hsp70 and death receptors on tumor cell surfaces are observed. Immune-activating chemokines, cytokines, exosomes and danger signals are released, resulting in activation of dendritic cells (DCs). These DCs are activated by the released danger signals and by taking up tumor peptides derived from irradiated cells, initiate innate and adaptive immune responses including the activation of T cells (Derer 2016). This process of T cell activation is controlled by the immune checkpoint inhibitory pathways. However, tumors exposed to ionizing radiation also acquire an immunosuppressive phenotype characterized by expression of PD-L1, secretion of TGF-β, infiltration of regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC) into the tumor, and induction of immunosuppressive apoptosis. During and after radiation, radioresistant cancer stem cells are selected, as well as Langerhans cells that generate immunosuppressive Treg (Frey 2016). Fractionated head and neck chemoradiation increases circulating CD-8+ T-effector cells, myeloid-derived suppressor cells, regulatory T cells, and checkpoint receptor-expressing T cells, particularly PD-1+ T cells (Sridharan, Margalit, Curreri 2016).

Preclinical evidence indicates that the abrogation of checkpoint blockade acts synergistically to overcome these immunosuppressive effects. Sharabi et al. (2015) used an in vivo flank tumor model (B16-OVA) which was irradiated and the draining lymph nodes were harvested on day 4. Radiation to the primary tumor resulted in antigen-specific T cell activation and proliferation in the draining lymph nodes, and dendritic cells in the draining lymph nodes expressed the MHC-OVA complex, indicative of cross-presentation against the tumor in the specifically unirradiated lymph nodes. Of note, radiation-induced Treg increased in the tumor microenvironment but not in the unirradiated lymph nodes. Furthermore, the combination of radiation and PD-1 blockade uniquely increased the proportion of tumor-specific CD8+ T cells with an effector memory phenotype, indicating that limiting the extent of the radiation stimulated and enabled the full effect of checkpoint inhibitor therapy.

It has been observed in preclinical studies that p16+ oropharyngeal cancers arise in immune-privileged sites (Lyford-Pike 2013). While response rates of recurrent/metastatic head and neck cancer (R/M SCCHN) patients are relatively low (13%-18%) in response to single-agent checkpoint blockade, the biology of heavily pretreated R/M SCCHN is likely very different from initially presenting tumors receiving radiation. Immunohistochemical expression of PD-L1, a potential biomarker of response to clinical immunotherapy, is higher in initially presenting head and neck cancers than metastatic cancers and higher in HPV-related head and neck cancer (Zandberg 2014). Preclinical data supports that this pathway may offer an opportunity for therapeutic benefit. In a longitudinal profiling study of circulating T-cell subsets among patients receiving seven weeks of fractionated head and neck radiation, lymphopenia was commonly seen as an effect of chemotherapy, while the radiation therapy induced increases in circulating T-cells expressing the exhaustion marker of PD-1 in up to 10% and 20% of CD8+ and CD4+ T cells, an indication that counteracting exhaustion during the several weeks of fractionated radiation would be beneficial (Sridharan et al 2016). In a preclinical head and neck cancer mouse model, tumor immunogenicity was enhanced by radiation therapy, which resulted in higher expression of H2Kd, CD80, and PD-L1 on tumor cells as well as increased IFNγ+ CD8+ T cells in tumors and draining lymph nodes. IFNγ inducible chemokines CXCL9 and CXCL10 were increased with RT, indicating radiation-related effects on the upregulation of PD-L1 and transforming the tumor to an inflamed and responsive phenotype. Survival of the mice was enhanced by the combination of PD-L1 blockade with radiation therapy (see figure) (Oweida 2017).



2.4 Clinical Data for Nivolumab in Head and Neck Cancer

Nivolumab (BMS-936558, MDX-1106, and ONO-4538) is a fully human monoclonal immunoglobulin G4 antibody that is specific for human programmed death-1 (PD-1, cluster of differentiation 279) cell surface membrane receptor (Investigator Brochure, 2014). PD-1, a 55-kDa type 1 transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors that include Ig super family member CD28, CTLA-4, inducible co-stimulator (ICOS), and B and T lymphocyte attenuator (BTLA) (Investigator Brochure, 2014). PD-1 is transiently but highly expressed on activated T cells functioning to limit immune effectors at the site of activation. Chronic stimulation may prevent the re-methylation of the PD-1 gene leading to continuous expression and characterizes a state of "exhausted" T cells that lose function and proliferative capacity while enhancing a suppressive tumor microenvironment.

In vitro, nivolumab bound specifically to PD-1 (and not to related members of the CD28 family such as CD28, ICOS, CTLA-4, and BTLA) with a dissociation constant (K_d) = 3.06 nM. In intravenous (IV) repeat-dose toxicology studies in cynomolgus monkeys, nivolumab alone was well tolerated (Investigator Brochure, 2014).

The clinical use of monoclonal antibodies to T-cell inhibitory receptors has provided new insights

into the relationship of the immune system and cancer. In a phase 1 (1, 3, and 10 mg/kg nivolumab doses) dose-escalation study the 3 mg/kg dose was chosen for expanded cohorts. Among 236 patients, objective responses (ORs) (complete or partial responses [CR or PR]) were seen in non-small cell lung cancer, melanoma, and renal cell carcinoma. ORs were observed at all doses (Sznol 2013). The phase III trial Checkmate 141 also tested an advanced R/M SCCHN population of 361 patients (54.5% had received ≥ 2 lines of prior therapy) with nivolumab administered at 3 mg/kg every 2 weeks compared to single-agent therapy (methotrexate, docetaxel, or cetuximab). The overall median survival was significantly longer in nivolumab-treated patients (superior to chemotherapy or cetuximab) and the 1-year survival was 36% with nivolumab vs 16.6% with standard therapy. Importantly, the survival advantage of nivolumab was maintained among both the p16+ and p16- groups of patients. This benefit was prolonged with the 2-year update resulting in OS 16.9% vs. 6.0% in patients treated with nivolumab compared to chemotherapy or cetuximab (Ferris 2018).

In the Checkmate 141 study, grade 3 or 4 toxicities occurred in 13.1% of nivolumab patients. However, an analysis of quality of life showed that patient-reported measures of physical, role, and social functioning, pain, sensory problems, and social contact were stable or improved in the nivolumab group but were worse in the standard therapy group receiving single-agent chemotherapy (Ferris 2016); the superior quality of life with immunotherapy was confirmed in a subsequent detailed report, with significant and clinically meaningful differences at weeks 9 and 15 in favor of nivolumab for role functioning, social functioning, fatigue, dyspnea, and appetite loss on the EORTC QLQ-C30 and pain and sensory problems on the EORTC QLQ-H&N35 (Harrington 2017). In the end, nivolumab-treated patients had superior survival but significantly improved QOL compared to patients receiving single-agent chemotherapy.

Combinations of PD-1/PD-L1 inhibition with radiation therapy are becoming a more common concept. RTOG 3504 reported initial safety evaluations of 20 patients receiving nivolumab combined with 70 Gy radiation and cisplatin followed by adjuvant nivolumab; this study included p16-negative patients or p16+ oropharyngeal cancer patients with high smoking history or T4 or N3 stage. Among evaluable patients, all received protocol-prescribed radiation therapy, 15/17 completed 200 mg/m^2 of cisplatin, and 14/17 stayed on nivolumab (Gillison 2018). A new phase III study, NRG-HN004, randomizes newly diagnosed cisplatin-ineligible patients, including p16+ oropharyngeal cancer patients, to either cetuximab or durvalumab with 70 Gy of standard radiation.

2.5 Rationale for the Duration of Nivolumab Before, Concurrently, and After Radiation Therapy

The strongest data clearly supporting extended administration of post-radiation immunotherapy (1-year adjuvant treatment) was issued for the PACIFIC non-small cell lung cancer trial (Antonia 2018), but for this trial's population where toxicity reduction and cost-effectiveness are critical, extended therapy in this manner is not a viable proposition. The schedule of priming, concurrent, and short-duration adjuvant nivolumab was developed based on preclinical evidence summarized briefly here. It is consistent with, although shorter than, the schedule developed for the more heterogenous and higher-risk population in NRG-HN004, where one arm includes durvalumab given before, during, and after 70 Gy of radiation therapy.

- Radiation therapy alone causes increases in PD-L1 expression in tumor and myeloid cells and Tregs via TGFb. However, when radiation therapy is administered in the setting of PD-1 inhibition, it upregulates MHC complexes, enhances antigen cross-presentation in draining nodes, and increases T-cell infiltration into tumors (Sharabi 2015).
- Combining anti-PD1 antibodies with radiation generates CD8+ T cell responses and tumor antigen-specific memory immune response. Three different schedules were tested starting on day 1 or day 5 of radiation therapy versus 7 days after completion of radiation; survival was best for the earlier concurrent schedules (Dovedi 2014).
- Because radiation causes transient increases in PD-L1 expression and Treg, stopping PD-1 during or at the end of radiation would enable these mechanisms to suppress the effector T cell response. In vivo mechanistic experiments conducted by Twyman-Saint Victor et al. showed that similar responses were seen in animals who received radiation given before or concurrently with anti-CTLA4, but the failure of the majority to respond was associated with a low CD8+CD44+ to Treg ratio. In these treatment-resistant tumors, the failure of the CD8+CD44+ T cell population to expand was associated with a high level of T cell exhaustion markers. Reinvigoration of the T cells, marked by an increase in the proliferation marker Ki67 and the cytotoxic protein GzmB within the exhausted T-cell pool, was only seen with slightly extended administration of anti-PD-L1 or anti-PD1 blockade, and this corresponded to markedly improved survival and complete response rates. Blockade antibodies were administered before, during and after radiation therapy (Twyman-Saint Victor 2015).
- The eventual clinical response to immunotherapy is determined by the balance between tumor cell burden and T cell reinvigoration. This effect appears to peak after the initial administration of PD-1 inhibition (at only a few to several weeks) but then starts to fall off. The major anti-PD-1-mediated T-cell reinvigoration appears to occur within a relatively short window of a few cycles of therapy, indicating the potential efficacy of a relatively short adjuvant administration assuming eradication of the major tumor burden by radiation therapy (Huang 2017).

2.6 Rationale for Patient-Reported Dysphagia-Related Outcome in HPV-Associated Oropharyngeal Cancer Patients

Oncologists now accept that quality of life is a critical clinical endpoint in the design of clinical trials for patients with locally advanced cancers. Although clinician-reported toxicity can identify adverse events, patient-reported outcomes (PROs) are essential because they directly measure patients' perception of symptom burden from treatment and its impact on quality of life (QOL) without clinician bias. As the treatment of human papillomavirus (HPV)-positive oropharyngeal cancer evolves, a high rate of acute and late-normal tissue complications from definitive radiation-based treatment may not be acceptable, if alternative treatments evolve with similar rates of cure and improved QOL.

Measuring PROs and QOL in the proposed study is particularly important because it is a novel treatment paradigm, and no data exist on the outcomes of these regimens in this population. The oncologic and long-term QOL outcomes of the targeted patient group may improve decision making in future clinical practice and research. The purpose of collecting PRO and QOL data in this phase II/III clinical trial is to evaluate the potential reduction in the burden of toxicity from

the patient perspective among different treatment arms. Clinicians involved in cancer care may find these results of great value in selecting the least toxic treatment arm - from the patient perspective - to achieve better QOL while maintaining desirable progression-free survival (PFS). Dysphagia-related QOL will thus be a co-primary endpoint in this trial.

2.7 Rationale for Stratification by Zubrod Performance Status

Based on NRG-HN002 data, preliminary results from Cox models with potential stratification factors for NRG-HN005 suggest that N stage and T stage did not have a significant effect on PFS or OS ($p>0.1$). Zubrod performance status had a significant effect for PFS ($p <0.1$) and for OS ($p<0.05$). Looking at the breakdown of all combinations of the possible stratification factors, there are several cells that have < 2% of patients which creates a problem about empty cells in this study. Since the distributions are highly imbalanced for T stage and N stage and neither has an impact on OS or PFS, we will stratify patients by Zubrod performance status (0 vs. 1) in this study.

3. ELIGIBILITY AND INELIGIBILITY CRITERIA

Note: Per NCI guidelines, exceptions to inclusion and exclusion criteria are not permitted. For questions concerning eligibility, please contact the Biostatistical/Data Management Center (see protocol cover page). For radiation therapy-related eligibility questions, please contact RTQA (see protocol cover page).

3.1 Eligibility Criteria (19-APR-2023) *A patient cannot be considered eligible for this study unless ALL of the following conditions are met.*

3.1.1 Pathologically (histologically or cytologically) proven diagnosis of squamous cell carcinoma (including the histological variants papillary squamous cell carcinoma and basaloid squamous cell carcinoma but not neuroendocrine phenotype) of the oropharynx (tonsil, base of tongue, soft palate, or oropharyngeal walls); cytologic diagnosis from a cervical lymph node is sufficient in the presence of clinical evidence of a primary tumor in the oropharynx. Clinical evidence should be documented, may consist of palpation, imaging, or endoscopic evaluation, and should be sufficient to estimate the size of the primary (for T stage).

3.1.2 Patients must have clinically or radiographically evident measurable disease at the primary site or at nodal stations. Simple tonsillectomy or local excision of the primary without removal of nodal disease is permitted, as is excision removing gross nodal disease but with intact primary site. Limited neck dissections retrieving ≤ 4 nodes are permitted and considered as non-therapeutic nodal excisions.

3.1.3 P16-positive based on local site immunohistochemical tissue staining (defined as greater than 70% strong diffuse nuclear or nuclear and cytoplasmic staining of tumor cells). Fine needle aspiration (FNA) biopsy specimens may be used as the sole diagnostic tissue. Centers are encouraged to contact the pathology chair for clarification.

Note: Institutions must screen patients, whose tumors must be p16-positive by immunohistochemistry (IHC) in order to be eligible for the trial using a Clinical

Laboratory Improvement Amendments (CLIA)-certified laboratory. A rigorous laboratory accreditation process similar to the U.S. CLIA certification, such as the provincial accreditation status offered by the Ontario Laboratory Accreditation (OLA) Program in Canada, the College of American Pathologists (CAP), or an equivalent accreditation in other countries, is acceptable. The p16-positive results must be reported on the pathology report being submitted.

Note: If p16 result is equivocal, positive HPV DNA test of tumor specimen is acceptable and fulfills the eligibility criteria.

3.1.4 Clinical stage T1-2, N1, M0 (AJCC, 8th ed.) or T3, N0-N1, M0 (AJCC, 8th ed.) including no distant metastases based on the following diagnostic workup:

- General history and physical examination within 56 days prior to registration;
- Exam with laryngopharyngoscopy (mirror or in office direct procedure acceptable) within 70 days prior to registration;
- One of the following imaging studies is required within 56 days prior to registration:
  a) FDG-PET/CT of the neck and chest (with or without contrast); FDG-PET/CT scan is strongly preferred and highly recommended to be used for eligibility
  OR
  b) Chest CT (with or without contrast)
- One of the following imaging studies is required within 28 days prior to registration:
  a) A diagnostic CT scan of neck (with contrast and of diagnostic quality)
  OR
  b) an MRI of the neck (with contrast and of diagnostic quality)

  Note: A diagnostic quality CT or MRI with contrast or FDG-PET/CT scan of neck performed for the purposes of radiation planning may serve as both staging and planning tools.

3.1.5 Patients must provide their personal smoking history prior to registration. The lifetime cumulative history cannot exceed 10 pack-years. The following formula is used to calculate the pack-years during the periods of smoking in the patient's life; the cumulative total of the number of pack-years during each period of active smoking is the lifetime cumulative history.

Number of pack-years = [Frequency of smoking (number of cigarettes per day) × duration of cigarette smoking (years)] / 20

Note: Twenty cigarettes is considered equivalent to one pack. The effect of non-cigarette tobacco products on the survival of patients with p16-positive oropharyngeal cancers is undefined. While there are reportedly increased risks of head and neck cancer associated with sustained heavy cigar and pipe use (Wyss 2013), such sustained use of non-cigarette products is unusual and does not appear to convey added risk with synchronous cigarette smoking. Cigar and pipe tobacco consumption is therefore not included in calculating the lifetime pack-years. Marijuana consumption is likewise not considered in this calculation. There is no clear scientific evidence regarding the role of chewing tobacco-containing products in this disease, although this is possibly more concerning given the proximity of

the oral cavity and oropharynx. In any case, investigators are discouraged from enrolling patients with a history of very sustained use (such as several years or more) of non-cigarette tobacco products alone.

3.1.6 Zubrod Performance Status of 0-1 within 14 days prior to registration.

3.1.7 Age ≥ 18.

3.1.8 Normal organ and marrow function within 14 days prior to registration defined as follows:

- Absolute neutrophil count ≥ 1,500/mcL
- Platelets ≥ 100,000/mcL
- Hemoglobin ≥ 8.0 g/dL (Note: use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dL is acceptable)
- Total bilirubin ≤ 1.5× institutional upper limit of normal (ULN)
- AST(SGOT) or ALT(SGPT) ≤ 3.0 × institutional ULN
- Serum creatinine ≤ 1.5× ULN

OR

- Creatinine clearance (CrCl) ≥ 50 mL/min (if using the Cockcroft-Gault formula below):

$$\textit{Female}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 0.85}{72 \times \text{serum creatinine in mg/dL}}$$

$$\textit{Male}\ \text{CrCl} = \frac{(140 - \text{age in years}) \times \text{weight in kg} \times 1.00}{72 \times \text{serum creatinine in mg/dL}}$$

3.1.9 Human immunodeficiency virus (HIV)-infected patients on effective anti-retroviral therapy with undetectable viral load within 6 months are eligible for this trial.

3.1.10 For patients with evidence of chronic hepatitis B virus (HBV) infection, the HBV viral load must be undetectable on suppressive therapy, if indicated.

Note: Known positive test for hepatitis B virus surface antigen (HBV sAg) indicating acute or chronic infection would make the patient ineligible unless the viral load becomes undetectable on suppressive therapy. Patients who are immune to hepatitis B (anti-Hepatitis B surface antibody positive) are eligible (e.g. patients immunized against hepatitis B).

3.1.11 Patients with a history of hepatitis C virus (HCV) infection must have been treated and cured. For patients with HCV infection who are currently on treatment for the hepatitis, they are eligible if they have an undetectable HCV viral load.

Note: Known positive test for hepatitis C virus ribonucleic acid (HCV RNA) indicating acute or chronic infection would make the patient ineligible unless the viral load becomes undetectable on suppressive therapy.

3.1.12 For women of childbearing potential (WOCBP), negative serum or urine pregnancy test within 24 hours prior to registration.

- Women of childbearing potential (WOCBP) is defined as any female who has experienced menarche and who has not undergone surgical sterilization (hysterectomy or bilateral oophorectomy) or who is not postmenopausal. Menopause is defined clinically as 12 months of amenorrhea in a woman over 45 in the absence of other biological or physiological causes. In addition, women under the age of 55 must have a documented serum follicle stimulating hormone (FSH) level less than 40 mIU/mL.

3.1.13 Women of childbearing potential (WOCBP) and men who are sexually active with WOCBP must be willing to use an adequate method of contraception during and after treatment (see Section 9.0).

3.1.14 The patient or a legally authorized representative must provide study-specific informed consent prior to study entry.

3.1.15 Only English, Spanish, or French speaking patients are eligible to participate as these are the only languages for which the mandatory dysphagia-related patient reported instrument (MDADI) is available.

3.2 Ineligibility Criteria (04-NOV-2020)

Patients with any of the following conditions are NOT eligible for this study.

3.2.1 Clinical stages T0; T4; T1-2, N0; or any N2 (AJCC, 8th ed);

3.2.2 Recurrent disease.

3.2.3 Definitive clinical or radiologic evidence of metastatic disease or adenopathy below the clavicles.

3.2.4 Cancers considered to be from an oral cavity site (oral tongue, floor mouth, alveolar ridge, buccal or lip), or the nasopharynx, hypopharynx, or larynx, even if p16-positive, or histologies of adenosquamous, verrucous, or spindle cell carcinomas.

3.2.5 Carcinoma of the neck of unknown primary site origin (T0 is ineligible, even if p16-positive).

3.2.6 Radiographically matted nodes, defined as 3 abutting nodes with loss of the intervening fat plane.

3.2.7 Supraclavicular nodes, defined as nodes centered below the level of the cricoid cartilage.

3.2.8 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. In other words, to participate in this protocol, the patient must have clinically or radiographically evident gross disease for which disease response can be assessed.

3.2.9 Patients with simultaneous primary cancers or separate bilateral primary tumor sites are excluded with the exception of patients with bilateral tonsil cancers.

3.2.10 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 1095 days (3 years) (of note, the exclusion applies only for invasive cancers such that carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

3.2.11 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable.

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

3.2.13 Prior treatment with an anti-PD-1, anti-PD-L1, anti-PD-L2, anti-CTLA-4 antibody, or any other antibody or drug specifically targeting T-cell co-stimulation or immune checkpoint pathways.

3.2.14 History of severe hypersensitivity reaction to any monoclonal antibody.

3.2.15 Severe, active co-morbidity defined as follows:

- Unstable angina and/or congestive heart failure requiring hospitalization within the last 6 months.
- Transmural myocardial infarction within the last 6 months.

- Acute bacterial or fungal infection requiring intravenous antibiotics 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.
- Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects.
- Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition with immune compromise greater than that noted in Section 3.1.9; note, however, that HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.
- Condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of registration. Inhaled or topical steroids and adrenal replacement doses < 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
- Patients with active autoimmune disease requiring systemic treatment (i.e. disease modifying agents, corticosteroids, or immunosuppressive drugs) should be excluded. These include but are not limited to patients with a history of immune related neurologic disease, multiple sclerosis, autoimmune (demyelinating) neuropathy, Guillain-Barre syndrome, myasthenia gravis; systemic autoimmune disease such as SLE, rheumatoid arthritis, connective tissue diseases, scleroderma, inflammatory bowel disease (IBD), Crohn's, ulcerative colitis, hepatitis; and patients with a history of toxic epidermal necrolysis (TEN), Stevens-Johnson syndrome, or phospholipid syndrome should be excluded because of the risk of recurrence or exacerbation of disease.

  Note: Patients are permitted to enroll if they have vitiligo, type I diabetes mellitus, residual hypothyroidism due to autoimmune condition only requiring hormone replacement, psoriasis not requiring systemic treatment, or conditions not expected to recur in the absence of an external trigger (precipitating event).

3.2.16 Patients who are pregnant, nursing, or expecting to conceive or father children (see Section 9.0).

3.3.17 Prior allergic reaction to cisplatin.

4. REQUIREMENTS FOR STUDY ENTRY, TREATMENT, AND FOLLOW-UP (19-APR-2023)

ASSESSMENTS: PRE-TREATMENT (See section 3.1 for details)

Timepoint	*Procedure/Test*	*Notes*
Prior to registration	☐ Pathologically (histologically or cytologically) proven diagnosis of squamous cell carcinoma of the oropharynx ☐ Smoking history	
70 days prior to registration	☐ Exam with laryngopharyngoscopy	
56 days prior to registration	☐ History/physical examination* ☐ FDG-PET/CT of the neck and chest (w/ or w/o contrast) **OR** Chest CT (w/or w/o contrast)**	*For patients with evidence of CHF, MI, cardiomyopathy, or myositis, a cardiac evaluation including lab tests and cardiology consultations as clinically indicated including EKG, CPK, troponin, ECHO cardiogram. **FDG-PET/CT scan is strongly preferred and highly recommended for eligibility.
28 days prior to registration	☐ Diagnostic neck CT (w/contrast and of diagnostic quality)* **OR** Diagnostic neck MRI (w/ contrast and of diagnostic quality)	*Radiation planning CT with contrast qualifies if acquired at diagnostic quality level with contrast.
14 days prior to registration	☐ CBC + Diff ☐ CMP ☐ Zubrod performance status	CBC to include ANC, platelets, Hgb CMP to include total bilirubin, AST(SGOT) or ALT (SGPT), serum creatinine
24 hours prior to registration	☐ Serum or urine pregnancy test	If female of child bearing potential

Prior to treatment	☐ Adverse Event Evaluation ☐ PRO-CTCAE* ☐ Patient-Reported Outcomes: MDADI, HHIA-S, EORTC QLQ-C30, EQ-5D-5L* ☐ Modified Barium Swallow (MBS) (if institution routinely performs) ☐ Specimen submissions for biobanking (optional)** ☐ Dental Assessment***	*This study uses Medidata Patient Cloud ePRO. Remember to register the patient to the Patient Cloud ePRO. For instructions on registering the patients, please refer to Appendix I. Baseline questionnaires will be completed on paper. Patients that consent to Medidata Patient Cloud ePRO will complete all questionnaires electronically using personal electronic device except baseline. The study-specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled "NRG-HN005 NCI PRO-CTCAE Item Library". **See Section 10.1 for details ***The study-specific Dental Assessment may be completed by the local investigator or a designee (such as a physician's assistant, nurse or nurse practitioner, or a dentist/hygienist) to assess number of teeth and overall dental health. This form can be found on the forms section of the CTSU protocol webpage. Please also refer Appendix III.

ASSESSMENTS: ON TREATMENT

Drug dose modifications found in Section 6.0 of protocol; Radiation Therapy per Section 5.2.		
Timepoint	***Procedure/Test/Treatment***	***Notes***
Arms 1 and 2 (Arm 2 closed to accrual 03-FEB-2023)		
Cycle 1 (Days 1 and 22)	☐ CBC + Diff* ☐ BMP*, Mg* ☐ Physical exam/ Zubrod Performance Status* ☐ Adverse Event Evaluation* ☐ Premedications** ☐ Cisplatin 100 mg/m^2 IV, given over 60 min***	CBC to include ANC, platelets, Hgb BMP to include serum creatinine, Na, K, Cl, glucose *Assess weekly during RT **Recommended premedications per section 5.1.2 ***Cisplatin should start +/- 24 hours of the first scheduled radiation treatment
Arm 3		
Cycles 1-6 (Day 1 of Weeks -1, 2, 4, 6, 8, and 10)	☐ Nivolumab 240 mg IV, given over 30 min* ☐ CBC + Diff** ☐ CMP ☐ TSH ☐ Physical exam/Zubrod Performance Status** ☐ Adverse Event Evaluation**	*Nivolumab is given every 2 weeks for 6 cycles starting 1 week (+/- 2 days) prior to radiation All labs are within 72 hours prior to nivolumab dose CBC to include ANC, platelets, Hgb CMP to include total bilirubin, AST or ALT, serum creatinine, BUN, Ca, Na, K, Cl, glucose

		TSH with reflex to free T4; T3 as clinically indicated **Prior to each nivolumab dose and weekly during radiation
All Treatment Arms		
Week 2 or 3 of RT (obtained after 20 Gy RT but before 28 Gy)	☐ Specimen submissions for biobanking (optional)	See Section 10.1 for details
During Week 2 of RT	☐ PRO-CTCAE	
End of Radiation (weeks 5-6)	☐ PRO-CTCAE ☐ Patient-Reported Outcomes: MDADI, HHIA-S, EORTC QLQ-C30, EQ-5D-5L ☐ Adverse Event Evaluation	
After completion - within 4 weeks from end of all treatment	☐ Specimen submissions for biobanking (optional)	See Section 10.1 for details

ASSESSMENTS: FOLLOW-UP

Assessments from end of radiation therapy		
Timepoint	***Procedure/Test/Treatment***	***Notes***
After radiation therapy (per institution's standard of care, recommended at approximately 8 weeks)	Diagnostic CT or MRI of head and neck with contrast (unless contraindicated)	Follow-up imaging is of the primary site in full, but does not require brain or orbit imaging.
At 12-14 weeks from end of radiation therapy	FDG-PET/CT of whole body and dedicated neck	A post-therapy FDG-PET/CT scan is highly recommended. If a post-therapy FDG-PET/ CT scan is taken, the site is required to submit the patient's post-treatment PET/CT scan.
q3 months from end of radiation therapy for years 1-2 (+/- 2 weeks)	☐ Physical Exam/Zubrod Performance Status* ☐ Adverse Event Evaluation* ☐ Chest CT or Chest FDG-PET/CT** ☐ PRO-CTCAE*** ☐ Patient-Reported Outcomes: MDADI, HHIA-S, EORTC QLQ-C30, EQ-5D-5L*** ☐ Modified Barium Swallow (MBS) (if institution routinely performs)**** ☐ Dental Assessment*****	*A brief history and physical examination including adverse event evaluation by a Radiation or Medical Oncologist or an ENT or Head & Neck Surgeon **As clinically indicated (recommended yearly) ***At 3, 6, 12, and 24 months from end of radiation therapy ****At 12 and 24 months from end of radiation therapy *****q12 months

q6 months for years 3-5 (+/- 4 weeks)	☐ Physical Exam/Zubrod Performance Status* ☐ Adverse Event Evaluation* ☐ Dental Assessment**	*A brief history and physical examination including adverse event evaluation by a Radiation or Medical Oncologist or an ENT or Head & Neck Surgeon **q12 months
Yearly for years 6-lifetime (+/- 8 weeks)	☐ Physical Exam/Zubrod Performance Status* ☐ Adverse Event Evaluation* ☐ Dental Assessment**	*A brief history and physical examination including adverse event evaluation by a Radiation or Medical Oncologist or an ENT or Head & Neck Surgeon **q12 months

Definition of Disease Assessments

- Response versus "Tumor Clearance" versus Cancer Progression
  Response and confirmation of local (primary site) or regional (neck) "tumor clearance" are not endpoints in this study. Clinical or radiographic evidence of progressive local-regional disease beyond 20 weeks should be documented in the clinical record and ideally confirmed by local or regional biopsy, neck dissection, or salvage surgery. CT or MRI (of head and neck region, with Chest CT), or PET/CT (including chest anatomy) may be used as radiographic evaluation of overall cancer status. The primary, neck and chest portions of the scans should be evaluated and reported separately. The CT portion of a PET/CT may serve as sufficient radiographic evaluation of the chest. If CT or MRI is used for evaluation of the head and neck region, CT of chest will be needed to rule out distant disease or second primaries at the designated evaluation intervals.
- Local or Regional Progression
  Local (primary site) or regional (neck) progression is defined as clinical or radiographic evidence of progressive disease at the primary site or neck. The location of progressive disease should be separately distinguished (local vs. neck) to document the precise pattern of failure if possible. Progression of local or regional disease should be confirmed by biopsy when possible but may be clinically assessed and documented in the clinical record at the judgment of the treating clinicians. Suspicion of disease progression exclusively on the basis of indeterminate or positive PET/CT scan should be confirmed with continued clinical follow-up or pathologically.
- Distant Metastasis

Clear evidence of distant metastases (lung, bone, brain, etc.); biopsy is recommended where possible. A solitary, spiculated lung mass/nodule is considered a second primary neoplasm unless proven otherwise.

- Second Primary Neoplasm
  Tumor reappearing with the initial and immediate adjoining anatomical region of the primary will be considered local recurrence. Multiple lung nodules/masses are considered distant metastases from the index cancer unless proven otherwise.

5. TREATMENT PLAN/REGIMEN DESCRIPTION

Protocol treatment must begin within 14 days after randomization.

5.1 Systemic Therapy (04-NOV-2020)

5.1.1 Cisplatin

Intravenous Cisplatin Administration Concurrent with Radiation

Cisplatin: 100 mg/m^2/day, every 3 weeks (on day 1 and 22) during radiation. Dose should be based on actual body weight. **The first cisplatin infusion should be started within 24 hours before or after the first scheduled radiation treatment**. Cisplatin is administered concurrent with radiation therapy. Doses of cisplatin that are not given or which are held for toxicities may be made up.

Cisplatin should be administered on Mondays or Tuesdays to maximize overlap of daily radiation with cisplatin exposure.

Administration on Wednesday prior to that day's radiation dose is acceptable but not preferred.
Cisplatin should be administered before or after radiation. Investigators should strive to administer cisplatin on schedule, but if the dose is not being held for toxicity reasons, a variance of 1 day is acceptable for vacations, holidays, etc. If radiation treatments are held for toxicity, cisplatin dosing should also be held.

5.1.2 Cisplatin Concurrent with Radiation Administration Guidelines

High-dose cisplatin is highly emetogenic and can cause both acute and delayed nausea (occurring > 24 hours after chemotherapy administration). 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 their local guidelines for cisplatin administration.** The anti-emetic and hydration regimen and schedule is to be determined by the local investigator. Administration of mannitol is likewise determined by the local investigator.

- All patients receiving cisplatin chemotherapy should be offered a combination of anti-emetics. Examples of appropriate anti-emetic choices are provided.
  - Neurokinin 1 (NK_1) receptor antagonist
    - Aprepitant 125 mg PO on day of cisplatin and 80 mg PO on days 2 and 3, or
    - Fosaprepitant 150 mg IV on day of cisplatin
  - Serotonin (5-HT_3) receptor antagonist
    - Granisetron 1 mg IV on day of cisplatin, or
    - Ondansetron up to 16 mg IV on day of cisplatin, or

        - Palonosetron 0.25 mg IV on day of cisplatin
    - Steroid
        - Dexamethasone up to 20 mg IV on day of cisplatin
    - Olanzapine
        - 10 mg PO on day of cisplatin
- Dexamethasone (up to 8 mg PO daily) and olanzapine may be continued on days 2 to 4 of cisplatin administration to prevent delayed nausea.
- A 5-HT_3 receptor antagonist may also be used as needed for delayed nausea.
- *Cisplatin pre-hydration guidelines*: Pre-hydration with 1 liter D5 ½ NS and 40 meq KCL/ liter x 1 liter prior to cisplatin. Mannitol 12.5 gm IV immediately prior to cisplatin.
- *Cisplatin administration*: Cisplatin, 100 mg/m^2 over 30-60 minutes IV in 250 cc NS. Infusion rate not to exceed 2 mg/min. See Section 6.2 for dose modifications. See above discussion on scheduling and number of doses concurrent with radiation.
- *Cisplatin post-hydration guidelines*: Following the end of the cisplatin administration, an additional liter of ½ 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 normal saline.

5.1.3 Nivolumab

Intravenous Nivolumab Administration Before, Concurrently, and After Radiation Therapy

Nivolumab 240 mg fixed dose administered as a 30-minute IV infusion (+/- 5 minutes or per institutional standard of care) will be given every two weeks (+/- 2 days) for 6 cycles (starting 1 week (+/- 2 days) prior to radiation and continuing for 12 weeks; includes 3 cycles of nivolumab therapy post-RT). Patients may be dosed no less than 12 days from the previous dose of drug. There will be no dose modifications allowed, although delayed doses are allowed to be made up. No premedications are required prior to nivolumab infusion. Steroids, such as dexamethasone, are strictly prohibited with nivolumab infusions.

	Week of IMRT								
	-1	1	2	3	4	5	6	8	10
IMRT (60 Gy)		X	X	X	X	X			
Nivolumab 240 mg IV	X		X		X		X	X	X

5.2 Radiation Therapy (19-APR-2023)

Note: All participating institutions must be credentialed for head and neck IMRT and IGRT prior to registering patients to the study (see Section 8 for details).

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

Radiation Therapy Schema

Effective with Amendment 3

- **Phase II/III (Arms 1 and 3)**

Arm 1: 70 Gy radiation in 6 weeks using 6 fractions per week + cisplatin every 3 weeks (Days 1 and 22)
Arm 3: 60 Gy radiation in 5 weeks using 6 fractions per week + nivolumab every 2 weeks x 6 cycles

For patients enrolled prior to amendment 3
Arm 2 closed to accrual 03-FEB-2023 after phase II interim futility analysis.

- **Phase II (Arms 1, 2, 3)**

Arm 1: 70 Gy radiation in 6 weeks using 6 fractions per week + cisplatin every 3 weeks (Days 1 and 22)
Arm 2: 60 Gy radiation in 6 weeks using 5 fractions per week + cisplatin every 3 weeks (Days 1 and 22)
Arm 3: 60 Gy radiation in 5 weeks using 6 fractions per week + nivolumab every 2 weeks x 6 cycles

5.2.1 Treatment Technology

Megavoltage energy photon beam irradiation with energy ≥ 4MV is required (6MV energy is preferred). Proton therapy is not allowed. IMRT techniques including static field IMRT, helical IMRT (Tomotherapy), and VMAT are allowed. Matched conventional anterior neck field is not allowed. MRIdian is allowed (only modality that allows Co-60 energy). Treatment machine must be equipped to provide daily MRI, kV, or MV image guidance. The minimum requirements for image guidance are given in Section 5.2.10.

Table 5.2.1A: Treatment Technology

Treatment Technology	Requirements and Recommendations
Beam Modality	Photons (protons are not allowed)
Beam Energy	≥ 4MV (6MV preferred), with the exception of the MRIdian Co-60 delivery)
Treatment Technique	Static field and helical IMRT, VMAT, and MRIdian are allowed. Matched conventional anterior neck field is not allowed.

IGRT	Treatment machine must be equipped to provide daily MRI, kV, or MV image guidance. The minimum requirements for image guidance are given in Section 5.2.10.

5.2.2 Immobilization and Simulation

Immobilization

Proper immobilization is critical for this protocol. Patient setup reproducibility must be achieved using appropriate clinical devices. Patients will be treated supine and must have a secure head and neck immobilization (e.g. aquaplast mask) made prior to the treatment planning CT scan. Intraoral immobilization devices may be utilized for tongue position control or immobilization and should be considered when the targets involve the pharyngeal axis. It is strongly encouraged that the participating centers also include the shoulders in the immobilization to further ensure accurate patient set-up on a daily basis.

Simulation Imaging

The treatment planning CT scan is mandatory for defining target volumes and normal organs at risk. The planning CT scan should be performed with intravenous contrast (unless contraindicated). CT scan should be acquired with the patient in the same position and using the same immobilization device as for treatment. CT scan thickness should be ≤ 3 mm. 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. Metal artifact reduction technique in CT scanner can be used for cases with dental filling or other high- density objects. For patients in whom contrast is contraindicated, FDG-PET/CT and MRI based imaging should be used to guide tumor and normal organ volume definition.

A diagnostic CT or MRI may be fused to the planning CT scans to facilitate target and structure definition. All image sets used for structure delineation must be submitted with the RT digital data.

5.2.3 FDG-PET/CT Imaging

FDG-PET/CT imaging is strongly preferred as part of staging in all eligible patients.

Many institutions will have standard guidelines for acquisition of FDG-PET/CT. For purposes of this protocol, individual investigators may use these local guidelines. One possible approach is outlined below which is suggested to optimize acquisition.

Recommended FDG-PET/CT Imaging Sequence and Details
• Serum glucose must be measured (ideally within 1 hour of FDG administration).
• If the serum glucose concentration is found to be > 200 mg/dL, the study should be rescheduled. The referring physician or primary physician will be contacted to optimize blood glucose control.

• It is recommended that the PET/CT scan begin 60 minutes +/- 10 minutes after FDG injection.
• It is recommended that patients be imaged from the orbits through the upper thigh.
• A dedicated head and neck imaging acquisition (orbits to upper thorax) with the patient's arms down is recommended given the higher sensitivity of this exam. The remainder of the body is to be scanned with the patient's arms raised over the patient's head. If patients cannot tolerate these positions for the PET/CT scan, investigators can use different patient positioning.
• A low-dose CT scan is required for attenuation correction and anatomical localization of findings in the PET scan.
• The acquisition parameters for the dedicated head and neck CT, low-dose CT scan should be approximately as follows: kV = 120; effective mAs = 90-150 (patient dependent, auto current modification acceptable); gantry rotation time < 0.5 sec; maximum reconstructed slice width = 2.5 mm (overlap acceptable); standard reconstruction algorithm, maximum reconstruction diameter = 30 cm; and without iodinated contrast.
• The acquisition parameters for the low-dose CT scan for attenuation correction should be approximately as follows: kV = 120; effective mAs = 30-80 (patient dependent, auto current modification acceptable); gantry rotation time < 0.5 sec; maximum reconstructed width = 3-5 mm without overlap; standard reconstruction algorithm, minimum reconstruction diameter = outer arm to outer arm; and without iodinated contrast.
• The axial field of view of the CT scan for attenuation correction should range from the mid thighs to the base of the skull. Arm positioning will be the same as for the PET scan (see above).
• The CT scan will be performed during the patient's normal breathing. No respiratory gating is needed.
• After the CT scan, a PET scan covering the same axial field of view should be performed. This scan will start at the upper thighs. The number of bed positions and the acquisition time per bed position will be scanner specific. Typical parameters are 6 bed positions and an acquisition of 2 to 5 minutes per bed position. The dedicated head and neck PET/CT will typically follow the body exam. Two bed positions will often suffice for orbits to upper thorax (top of aortic arch), and acquisitions must be at a minimum of 6 minutes per bed position and be reconstructed into a 30 cm field of view (FOV) with a 256 x 256 matrix.
• Additional diagnostic-quality CT of the neck should be performed with contrast if needed to fulfill requirements for anatomic post-treatment imaging.

FDG-PET/CT Image Reconstruction

The PET/CT data will be corrected for dead time, scatter, randoms, and attenuation using standard algorithms provided by the scanner manufacturers. For the dedicated head and neck views, a post-filter with a full-width at half maximum (FWHM) in the range of 5 mm is recommended.

5.2.4 Definition of Target Volumes and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.
Resubmission of data may be required if labeling of structures does not conform to the standard DICOM names listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Arm 1

Table 5.2.4A: Definition of Target Volumes and Margins for Arm 1

Standard Name	Description	Validation **Required/Required when applicable/Optional**
GTV_7000	Primary tumor and involved nodes	**Required**
CTV_7000	GTV_7000 + 5 mm margin, excluding anatomic boundaries to tumor spread	**Required**
PTV_7000	CTV_7000 + 3 mm margin	**Required**
PTV_Eval_7000	PTV_7000 minus high risk OARs (subtract 5 mm from skin if needed)	**Required when applicable**
CTV_5600	• CTV_7000 + 5 mm • first echelon nodes • node levels including involved nodes • 2 cm inferior/superior margin for gross nodal disease covering the fat of nodal chain • suspicious nodes < 1 cm + 5 mm	**Required**
PTV_5600	CTV_5600 + 3 mm margin	**Required**
CTV_5250	• Lower risk nodal levels that are not first echelon nodes and are not adjacent to levels containing grossly involved nodes • See Table 5.2.4C for details	**Required**
PTV_5250	CTV_5250 + 3 mm margin	**Required**
CTV_6650* or CTV_6020*	Original extent of the grossly involved tumor site, for isolated tumor or nodal sites that have been excised with focally positive microscopic or clearly negative margins	**Required when applicable**

PTV_6650* or PTV_6020*	CTV_6650 or CTV_6020 + 3mm margin	**Required when applicable**
PTV_Eval_6650* or PTV_Eval_6020*	PTV_6650 or PTV_6020 minus high risk OARs (subtract 5mm from skin if needed)	**Required when applicable**

***Note: For Arm 1 only**

In the rare case that a primary tumor or pathologically involved lymph node is excised surgically for diagnostic purposes obtaining clearly negative or focally positive microscopic margins, it is acknowledged that there may be some risk of long-term wound healing if the doses prescribed in Arm 1 are given to the surgical bed. Therefore, for these unique situations, the original extent of the grossly involved tumor site may be delineated as a CTV_6650 prescribed to 6650 cGy (at 190 cGy/fraction) over 35 fractions for a case of microscopically/focally positive margins or alternatively as a CTV_6020 (at 172 cGy/fraction) over 35 fractions for a situation of an excision with clearly negative margins. The usual PTV expansions would then apply to create the corresponding PTV_6650 or PTV_6020.

It should be noted that any residual gross primary tumor and/or any grossly involved lymph nodes which are radiologically or clinically evident should be treated to the standard dose required in Arm 1, e.g. 7000 cGy. **Furthermore, the presence of extant gross tumor is required for the eligibility of any patient on this study. Therefore, GTV_7000, CTV_7000, and PTV_7000 are required target volumes for any patient on Arm 1.**

For Arm 3 (Arm 2 closed to accrual 03-FEB-2023), if the primary tumor or a lymph node is excised, the prescribed doses should not be changed regardless of the extent of removal, meaning that the surgical bed would be treated to the required dose of CTV_6000. Likewise, for Arm 3 (Arm 2 closed to accrual 03-FEB-2023), the presence of extant gross tumor is required for eligibility.

Investigators are encouraged to contact the Principal Investigator to discuss these unusual situations and/or seek clinical guidance on these matters.

Arm 3 (Arm 2 closed to accrual 03-FEB-2023)

Table 5.2.4B: Definition of Target Volumes and Margins for Arm 3 (Arm 2 closed to accrual 03-FEB-2023)

Standard Name	Description	Validation **Required/Required when applicable/Optional**
GTV_6000	Primary tumor and involved nodes	**Required**
CTV_6000	GTV_6000 + 5 mm margin, excluding anatomic boundaries to tumor spread	**Required**
PTV_6000	CTV_6000 + 3 mm margin	**Required**
PTV_Eval_6000	PTV_6000 - high risk OARs (subtract 5 mm from skin if needed)	**Required when applicable**
CTV_5400	• CTV_6000 + 5 mm • first echelon nodes • node levels including involved nodes • 2 cm inferior/superior margin for gross nodal disease covering the fat of nodal chain • suspicious nodes < 1 cm + 5 mm	**Required**
PTV_5400	CTV_5400 + 3 mm margin	**Required**
CTV_4800	• Lower risk nodal levels that are not first echelon nodes and are not adjacent to levels containing grossly involved nodes • See Table 5.2.4C for details	**Required**
PTV_4800	CTV_4800 + 3 mm margin	**Required**

Detailed Specifications

Setup margin (SM): Daily IGRT is required for this trial; therefore, the SM will be 3 mm in all directions.

GTV_7000 (Arm 1) or GTV_6000 (Arm 3) (Arm 2 closed to accrual 03-FEB-2023): The primary tumor and clinically positive lymph nodes seen on clinical and endoscopic examinations, planning CT (> 1 cm short axis diameter) or pre-treatment PET scan (SUV > 3) will constitute the GTV. Grossly positive lymph nodes are defined as any lymph nodes > 1 cm or nodes with a necrotic center.

CTV_7000 (Arm 1) or CTV_6000 (Arm 3) (Arm 2 closed to accrual 03-FEB-2023): The CTV is defined to be the GTV plus a 0.5 cm to 1 cm margin as appropriate to account for microscopic tumor extension. 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 5600 or CTV 5400) that is slightly larger than CTV 7000 or CTV 6000. 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 on the NRG Oncology website: https://www.nrgoncology.org/ciro-head-and-neck. For patients with positive neck nodes, consult Gregoire et al. (2014) for the delineation of the nodal CTV.

PTV_7000 (Arm 1) or PTV_6000 (Arm 3) (Arm 2 closed to accrual 03-FEB-2023): The PTV is created from the CTV with additional margins to compensate for the variability of treatment setup 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.
- the 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.

PTV_Eval_7000 (Arm 1) or PTV_Eval_6000 (Arm 3) (Arm 2 closed to accrual 03-FEB-2023): PTV volume minus impinging high priority OARs created for dosimetric evaluation. In cases where PTV overlaps with critical organs, such as the brainstem and spinal cord, the PTV_Eval_7000 and the PTV_Eval_6000 should be created to limit the dose to the OARs (subtract 5 mm from the skin if needed). 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 for review.

CTV_5600 (Arm 1) or CTV_5400 (Arm 3) (Arm 2 closed to accrual 03-FEB-2023): High-risk subclinical sites are defined as areas of:

- potential subclinical tumor infiltration beyond the primary site CTV_7000 or CTV_6000,
- the first echelon node levels to the primary site irrespective of gross nodal involvement,
- all node levels containing gross nodes.
- In the event of a node excision (≤ 4 per protocol) that occurred at time of diagnosis, the nodal levels that contained grossly involved adenopathy should be included, even if there is no residual post-excision adenopathy.

A CTV_5600 or CTV_5400 would specifically include the following:

- 5 mm isotropic expansion of CTV_7000 or CTV_6000.

- 1st echelon node levels based on standard anatomic definitions. In most cases 1st echelon would be ipsilateral level II, but in cases of midline primary site involvement this should include bilateral level II. In cases with soft palate or posterior pharyngeal wall involvement, this should include the lateral retropharyngeal lymph nodes.
- All node levels containing a CTV_7000 or CTV_6000 that have been assigned to involved nodes (all grossly involved nodal levels).
- At least a 2 cm margin covering the fat of the cervical nodal chain superior and inferior to the node levels that contain/contained gross nodal disease.
- Other high-risk subclinical sites may include nodes < 1 cm not thought to harbor gross disease yet thought to be at risk of containing more than subclinical disease based on their location relative to the primary site. In such cases of clinical concern that do not meet the above criteria, a 5 mm expansion on these nodes can be added to the CTV_5600 or CTV_5400 at the discretion of the treating clinician.

PTV_5600 (Arm 1) or PTV_5400 (Arm 3) (Arm 2 closed to accrual 03-FEB-2023): The PTV is created from the CTV with additional margins to compensate for the variability of treatment setup 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.
- the 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.

CTV_5250 (Arm 1) or CTV_4800 (Arm 3) (Arm 2 closed to accrual 03-FEB-2023): The CTV will be defined to treat node levels without evidence of gross disease yet at risk of microscopic spread and not contained in CTV_5600 or CTV_5400. These levels are defined anatomically according to published Intergroup consensus guidelines (Gregoire 2014). The levels to be treated will depend on the site and extent of the primary tumor and any grossly involved lymph nodes and are indicated in Table 5.2.4C.

Table 5.2.4C: Nodal Levels to Receive Prophylactic Microscopic Dose (CTV_5250 or CTV_4800)*

CTV_5250 or CTV_4800*	Ipsilateral Neck	Contralateral Neck**
N0	• Ib (for primary oral cavity extension), • II-III • RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate	• II-III • RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate
N1	• Ib • II-IV	• II-III • RP (lateral retropharyngeal LN) for primary extension to

	• RP (lateral retropharyngeal LN including retrostyloid space) for primary extension to posterior pharyngeal wall or soft palate	posterior pharyngeal wall or soft palate
N1 with node ≥ 3 cm or multiple nodes	• Ib, II, III, IV, V, RP including retrostyloid space	• II-III • RP (lateral retropharyngeal LN) for primary extension to posterior pharyngeal wall or soft palate

*Applies to neck levels not included in CTV_5600 or CTV_5400.
** The contralateral neck may be omitted according to guidelines defined below.

Contralateral Neck
The use of unilateral radiation techniques should remain optional, in deference to the established practice and clinical judgment of the enrolling investigator, though 3 groups of patients with respect to neck irradiation are defined below.

Unilateral radiotherapy is recommended (see guidelines below) if it is the institution's established practice, if the primary tumor originates in the tonsillar fossa, and is well-lateralized, with less than 1 cm of involvement of the soft palate or base of tongue, no posterior pharyngeal wall involvement, and with minimal nodal disease burden (single node ≤ 3 cm) as assessed by clinical exam and staging radiology studies. For patients who share these characteristics but have larger nodal disease or multiple nodes confined to ipsilateral level II of the neck, unilateral radiotherapy is optional. Due to the imperative to maintain high PFS for this trial and the lack of prospectively collected data on this controversial subject, for patients with characteristics that fall outside these categorizations, bilateral treatment is required.

Groups of Patients with Regards to Unilateral or Bilateral Neck Irradiation

Group 1: Unilateral treatment is recommended
T1 to T3 tonsillar fossa primaries with < 1 cm clinical or radiographic extension into tongue base and/or soft palate, no posterior pharyngeal wall extension, N0-N1 (single node ≤ 3 cm and no extranodal extension).

Group 2: Unilateral treatment is optional
T1 to T3 tonsillar fossa primaries with < 1 cm clinical or radiographic extension into tongue base and/or soft palate, no posterior pharyngeal wall extension, N0-N1 (multiple nodes, all nodes ≤ 3 cm and no extranodal extension) with involved adenopathy confined to ipsilateral level II of the neck.

Group 3: Bilateral treatment is mandatory
Tongue base, soft palate, or posterior pharyngeal wall primaries or tonsil primaries with > 1 cm soft palate and/or tongue base extension or any posterior pharyngeal wall extension; patients with any extranodal extension or with involved adenopathy outside of ipsilateral level II of the neck.

PTV_5250 (Arm 1) or PTV_4800 (Arm 3) (Arm 2 closed to accrual 03-FEB-2023): The PTV is created from the CTV with additional margins to compensate for the variability of treatment setup 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.
- the 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.

5.2.5 Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required when applicable" must be contoured and submitted when applicable.
Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

Table 5.2.5A: Definition of Critical Structures and Margins

Standard Name	Description	Validation **Required/Required when applicable/Optional**
SpinalCord	Spinal Cord	**Required**
SpinalCord_PRV05	Spinal Cord with 5 mm expansion for Planning Risk Volume	**Required**
BrainStem	Brainstem	**Required**
BrainStem_PRV03	Brainstem with 3 mm expansion for Planning Risk Volume	**Required**
Parotid_R	Right Parotid Gland	**Required**
Parotid_L	Left Parotid Gland	**Required**
Larynx_SG	Glottic and Supraglottic Larynx	**Required**
Pharynx	Uninvolved posterior pharyngeal wall plus adjacent constrictor muscles	**Required**
Esophagus_S	Upper Cervical Esophagus	**Required**
Cavity_Oral	Uninvolved Oral Cavity	**Required**
Bone_Mandible	Mandible	**Required**
Lips	Lips	**Required**
Glnd_Submand_R	Right Submandibular Salivary Gland	**Required**

Glnd_Submand_L	Left Submandibular Salivary Gland	**Required**
BrachialPlexus_R	Right Brachial Plexus	**Required when gross disease extends below cricoid cartilage**
BrachialPlexus_L	Left Brachial Plexus	**Required when gross disease extends below cricoid cartilage**
Cochlea_R	Right Cochlea	**Required gross disease extends to skull base**
Cochlea_L	Left Cochlea	**Required gross disease extends to skull base**
Thyroid	Thyroid Gland	**Required**
E-PTV	Unspecified tissue, External minus all PTVs	**Required**
External	External border of the patient	**Required**

Detailed Specifications

SpinalCord: 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 volume will be defined at approximately T3-4 (i.e., 2-3 cm below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan.

SpinalCord_PRV05: Planning Risk Volume (PRV) spinal cord defined as SpinalCord + 5 mm in all directions.

BrainStem: The most inferior portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purpose of this study, the most superior portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan.

BrainStem_PRV03: Planning Risk Volume (PRV) brainstem defined as Brainstem + 3 mm in all directions.

Parotid_R/L: Parotid glands will be defined in their entirety (superficial and deep lobes) based on the treatment planning CT scan. The parotid gland is an irregular shaped gland wedged between the ramus of the mandible and the mastoid process. The superior border is the zygomatic arch, inferiorly, the gland extends to the angle of the mandible. The anterior border is the masseter muscle; in 20% of cases the parotid gland extends anteriorly over the surface of the masseter muscle, and posteriorly, to the anterior border of the sternocleidomastoid. Laterally, it extends to the platysma and medially, to the posterior belly of the digastric muscle, styloid process and parapharyngeal space. The retromandibular vein is included in the parotid gland contour.

Larynx_SG: This will be defined as the glottic and supraglottic larynx, including the tip of the epiglottis, the epiglottis, the aryepiglottic folds, arytenoids, false cords, and true cords, up to but not including the medial border of the thyroid cartilage, and including the cricoid cartilage to the inferior edge of the arytenoid cartilage, but not the hypopharynx. Posteriorly, the contour extends to the anterior edge of the pharyngeal wall.

Pharynx: This will be defined as the pharyngeal mucosa and wall plus adjacent constrictor muscles deemed not to require treatment (external to PTVs). This extends from the superior constrictor region (level of the inferior pterygoid plates) to the cricopharyngeal inlet (inferior level of the posterior cricoid cartilage). The posterior border is the pre-vertebral muscle.
See Figure 5.2.5.1 or
https://www.sciencedirect.com/science/article/pii/S0167814009005659#bib14 for more details.

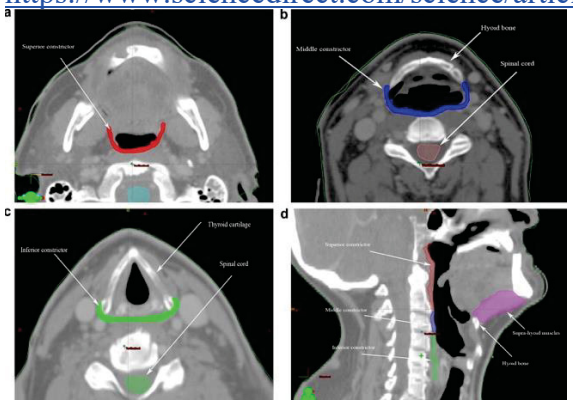


Figure 5.2.5.1. From Bhide et al (2009): Each of the pharyngeal constrictors was outlined as an arch-shaped structure with concavity facing anteriorly, in line with the mucosa (a-c). Posterior border of each of the muscles was the pre-vertebral muscle. Pharyngeal mucosa lining the muscles was included in outlines as it is quite thin and difficult to exclude with great accuracy with currently available CT images. Superior constrictor was outlined from the base of the skull up to the superior end of hyoid. Middle constrictor was outlined from the superior end to the inferior end of the hyoid bone. Inferior constrictor was outlined from the inferior aspect of hyoid to inferior end of cricoid cartilage. A sagittal view of all of the outlined pharynx is shown (d).

Esophagus_S: This will be defined as the cervical or superior (S) esophagus, a tubular structure that starts at the bottom of pharynx (cricopharyngeal inlet) and extends to the thoracic inlet.

Cavity_Oral: The oral cavity will be defined as a composite structure posterior to lips consisting of the anterior 1/2 to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and superiorly the palate, and inferiorly to the plane containing the tip of the mandible (external to PTVs).

Bone_Mandible: This includes the entire bony structure of the mandible from TMJ through the symphysis. It is recognized that for oral cavity cancers, this may overlap with PTVs.

Lips: The lip contour extends from the inferior margin of the nose to the superior edge of the mandibular body. The lateral border is at the lateral commissure. The lip contour should include the inner surface of the lips. Lips will be defined in their entirety (upper and lower) based on the treatment planning CT scan.

Glnd_Submand_R/L: Submandibular glands will be defined in their entirety based on treatment planning CT scan. The submandibular glands are paired salivary glands composed of a large superficial lobe and a smaller deep process that are continuous with each other around the posterior border of the mylohyoid muscle. The superior border is the mylohyoid muscle and medial pterygoid muscle. Inferiorly, the gland abuts fatty tissue. Anteriorly, the gland is adjacent to the lateral surface of the mylohyoid muscle and posteriorly it abuts the parapharyngeal space and sternocleidomastoid. The lateral border is platysma and the mandibular surface. The medial border is the lateral surface of the mylohyoid muscle and the anterior belly of the digastric. The submandibular gland is often hypodense on CT and can be distinguished from surrounding structures.

BrachialPlexus_R/L: Please follow the RTOG Atlas definition: https://www.rtog.org/CoreLab/ContouringAtlases/BrachialPlexusContouringAtlas.aspx.
To contour the brachial plexus use a 5-mm diameter paint tool. Start at the neural foramina from C5 to T1; this should extend from the lateral aspect of the spinal canal to the small space between the anterior and middle scalene muscles. For CT slices where no neural foramen is present, contour only the space between the anterior and middle scalene muscles. Continue to contour the space between the anterior and middle scalene muscles; eventually the middle scalene will end in the region of the subclavian neurovascular bundle. Contour the brachial plexus as the posterior aspect of the neurovascular bundle inferiorly and laterally to one to two CT slices below the clavicular head. The first and second ribs serve as the medial limit of the OAR contour. See Figure 5.2.5.2 and https://www.redjournal.org/article/S0360-3016(08)00416-1/fulltext for more details.

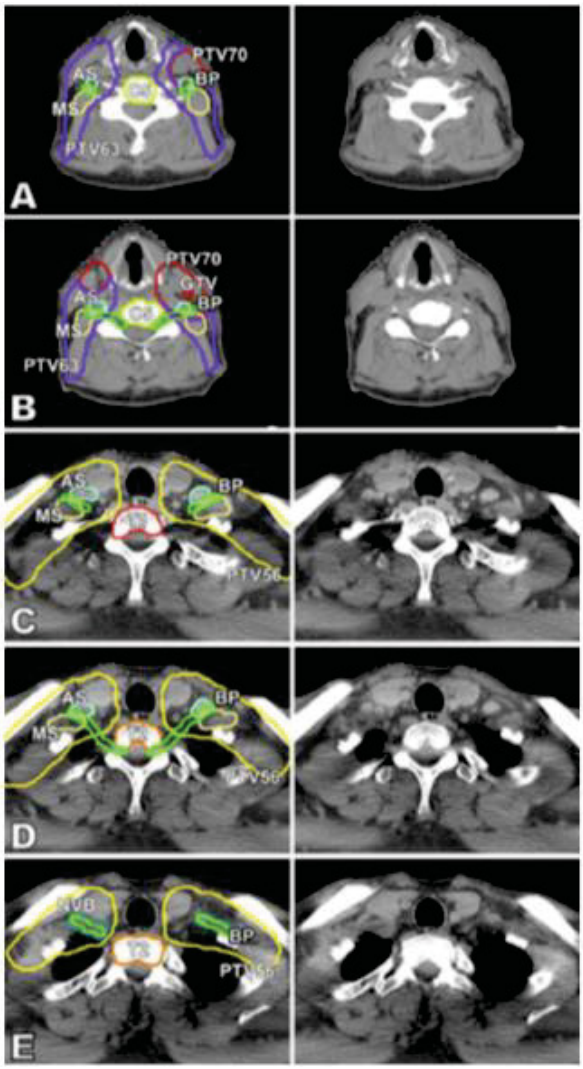


Figure 5.2.5.2 From Hall et al (2008): Major anatomic landmarks (Anterior and Middle Scalene muscles, and the neurovascular bundle) for identifying the brachial plexus on the axial images of a treatment planning computed tomography scan.

Cochlea_R/L: The cochlea should be defined using bone window (window width 3000 to 4500 and window level of 400 to 800). It is well visualized near the most lateral extent of the internal auditory canal. The spiral canals of the cochlea appear as small curved or round lucencies within the temporal bone. The cochlea should be defined in its entirety limited by vestibular apparatus posteriorly and middle ear laterally. See Figure 5.2.5.2 and https://pdfs.semanticscholar.org/2e9b/73b254b27d7f8724348057291b5a776c7b37.pdf for more details.

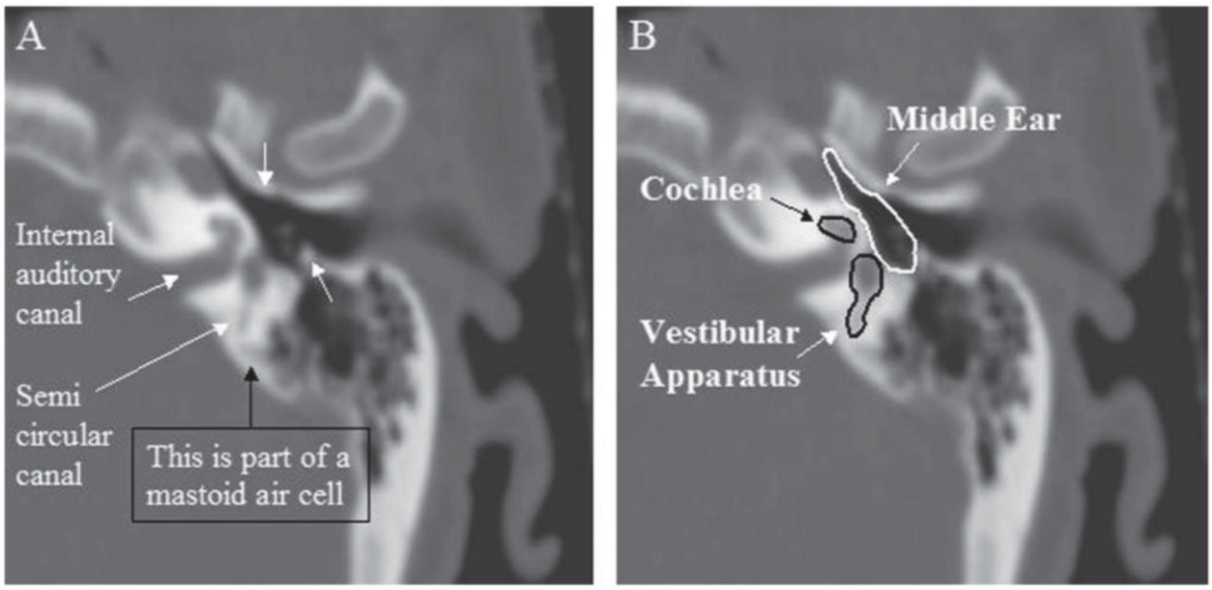


Figure 5.2.5.3 From Pacholke et al (2005): Major anatomic landmarks for identifying the cochlea on the axial images of a treatment planning computed tomography scan. The best way to locate the cochlea is to first identify the internal auditory canal. The image on the left (A) shows the anatomy of the temporal bone at the level of the inner ear without outlines of auditory structures. Important landmarks on this image are the internal auditory canal, the semicircular canals of the vestibular apparatus, and the bony prominences that mark the attachment of the tympanic membrane (un-marked arrows). The spiral canals of the cochlea appear as small curved or round lucencies within the temporal bone (B). Note that portions of a mastoid air cell may look similar to a semicircular canal.

Thyroid: The thyroid gland should be contoured in its entirety based on treatment planning CT scan. The thyroid gland has two connected lobes and is located inferior to the thyroid cartilage. The thyroid gland will have considerable contrast on contrast-enhanced CT compared to the surrounding tissues.

E-PTV: This will be defined as tissue located within external contour of the patient outside of all PTVs.

5.2.6 Dose Prescription

Note: The information provided in this section can be used for adjusting the dose constraints for treatment planning purposes. This table together with the planning priority table should be used during dose optimization. It is important to remember that ideal plans might not be achievable in all cases. Thus, the Compliance Criteria table could be different than the information given here. Cases will be scored using the Compliance Criteria table.

Table 5.2.6A: Dose Prescription and Plan Normalization

Arm	Target Standard Name	Dose (Gy)	Fraction Size (Gy)	# of fractions	Frequency	Dose specification technique
Arm 1	PTV_7000	70	2.0	35	6 fractions per week	Covering 95% of PTV
Arm 2 (Arm 2 closed to accrual 03-FEB-2023)	PTV_6000	60	2.0	30	5 fractions per week	Covering 95% of PTV
Arm 3	PTV_6000	60	2.0	30	6 fractions per week	Covering 95% of PTV

For Arm 1, radiotherapy will be delivered in an accelerated schedule over 6 weeks, which requires delivery of 6 fractions per week. The sixth fraction can be delivered either on a Saturday or as a second daily fraction (BID) on a weekday, with at least a 6 hour interfraction interval if 2 fractions are given on one of the weekdays.

For Arm 2, radiotherapy will be delivered once daily, 5 fractions per week for 6 weeks (Arm 2 closed to accrual 03-FEB-2023).

For Arm 3, radiotherapy will be delivered in an accelerated schedule over 5 weeks, which requires delivery of 6 fractions per week. The sixth fraction can be delivered either on a Saturday or as a second daily fraction (BID) on a weekday, with at least a 6 hour interfraction interval if 2 fractions are given on one of the weekdays.

Plan should be normalized such that 95% of the volume of PTV_7000 or PTV_6000 receives the prescribed dose with a minimum dose (defined as dose to 99% of PTVs) greater than 95% of the prescription dose and a maximum dose (defined as dose encompassing 0.03 cc of the PTV) less than 110-115% of the prescription dose.

It is recognized that portions of PTV close to the skin or critical PRVs (spinal cord and brainstem) may receive significantly less than the prescription doses. PTV_Eval_7000, PTV_Eval_6650, PTV_Eval_6020, or PTV_Eval_6000 should be created in this situation to evaluate target coverage. When under-dosing PTV_7000, PTV_6650, PTV_6020, or PTV_6000, care should be taken to ensure that the cold spots within these PTVs do not exist within the GTV. In cases of high-dose PTVs close to skin, tissue equivalent bolus must be utilized to ensure adequate dose coverage.
It is also recognized that PTVs abutting or enclosing higher dose PTVs will have regions of maximum dose that may exceed their prescribed dose in order to achieve acceptable minimal doses to the higher dose PTVs which are considered a higher priority target.

5.2.7 Compliance criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

VxGy [cc], VxGy [%], Vx%[cc], Vx%[%]: Volume [cc or %] receiving Dose [Gy, or %]
CVxGy[cc],CVxGy[%],CVx%[cc],CVx%[%]:Complement Volume [cc or %] receiving Dose [Gy, or %]
Dxcc[Gy], Dxcc[%], Dx%[Gy], Dx%[%]: Dose [Gy or %] to Volume [cc or % of total volume]
DCxcc[Gy], DCxcc[%], DCx%[Gy], DCx%[%]: Dose [Gy or %] to Complement Volume [cc or % of total volume]
Minimum dose is defined to D99%[Gy] or D99%[%]
Maximum dose is defined as D0.03cc[Gy] or D0.03cc[%]
Mean[Gy] or Mean[%]: Mean dose in Gy or %

Normalization of Dose: The plan is normalized such that 95% of the PTV_7000 or PTV_6000 volume receives prescription dose.

Note: Deviation Unacceptable occurs when dose limits for Variation Acceptable are not met.

Target Volume and OAR Constraints and Compliance Criteria
Arm 1

Table 5.2.7A: Target Volume and OAR Constraints and Compliance Criteria for Arm 1

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PTV_7000 or PTV_Eval_7000	D95%[Gy]	70	> 68.6 and < = 71.4
	D99%[Gy]	> = 66.5	> = 63
	D0.03cc[Gy]	< = 77	< = 80.5
PTV_5600	D95%[Gy]	> = 56	> = 53.2
PTV_5250	D95%[Gy]	> = 52.5	> = 49.9
SpinalCord_PRV05	D0.03cc[Gy]	< = 50	< = 52
SpinalCord	D0.03cc[Gy]	< = 45	< = 48
BrainStem_PRV03	D0.03cc[Gy]	< = 52	< = 54

Per Protocol range is excluded from Variation Acceptable range.

PTV_6650* or PTV_Eval_6650*	D95%[Gy]	> = 66.5	> = 65.2
	D99%[Gy]	> = 63.2	> = 59.9
PTV_6020* or PTV_Eval_6020*	D95%[Gy]	> = 60.2	> = 59
	D99%[Gy]	> = 57.2	> = 54.2

*** Note for Arm 1 only:** In a rare case of an excised primary tumor or pathologically involved lymph node with microscopically/focally positive margins, PTV_6650 should receive 66.5 Gy at 1.9 Gy/fraction over 35 fractions. For a case with an excision and clearly negative margins, PTV_6020 should receive 60.2 Gy at 1.72 Gy/fraction over 35 fractions.

Arm 3 (Arm 2 closed to accrual 03-FEB-2023)

Table 5.2.7B: Target Volume and OAR Constraints and Compliance Criteria for Arm 3
(Arm 2 closed to accrual 03-FEB-2023)

Name of Structure	Dosimetric parameter	Per Protocol	Variation Acceptable
PTV_6000 or PTV_Eval_6000	D95%[Gy]	60	> 58.8 and < = 61.2
	D99%[Gy]	> = 57	> = 54
	D0.03cc[Gy]	< = 66	< = 69
PTV_5400	D95%[Gy]	> = 54	> = 51.3
PTV_4800	D95%[Gy]	> = 48	> = 45.6
SpinalCord_PRV05	D0.03cc[Gy]	< = 48	< = 50
SpinalCord	D0.03cc[Gy]	< = 45	< = 48
BrainStem_PRV03	D0.03cc[Gy]	< = 50	< = 52

Per Protocol range is excluded from Variation Acceptable range.

Dose limitations to normal structures are described below. For the critical structures listed in Table 5.27B (SpinalCord, SpinalCord_PRV05, and BrainStem_PRV03), these are mandatory. For other structures recommended limits are provided, but the doses delivered should always be as low as reasonably achievable without compromising coverage to PTVs.

Table 5.2.7C: Recommended dose acceptance criteria for other normal tissue, but not to be used for plan score.

Structure	Recommended dose acceptance criteria*
BrachialPlexus_R/L	D0.03cc[Gy] < = 66
Parotid_R/L (at least one gland)	Mean[Gy] < = 26
Larynx_SG	Mean[Gy] < = 40
Pharynx (uninvolved)	Mean[Gy] < = 45
Cavity_Oral (uninvolved)	Mean[Gy] < = 35
Lips	Mean[Gy] < = 20
Esophagus_S	Mean[Gy] < = 30

Glnd_Submand_R/L (contralateral)	Mean[Gy] < = 39
Cochlea_R/L	Mean[Gy] < = 35
Bone_Mandible	D0.03cc[Gy] < = 73.5
Thyroid	Mean[Gy] < = 50
E-PTV	D1cc[Gy] < = 73.5

***** Please keep OAR doses as low as reasonably achievable without compromising coverage to PTVs.

Delivery Compliance criteria

Protocol treatment must begin within 14 days after randomization. Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, should not exceed 3 treatment days at a time and 5 treatment 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. Any treatment break(s) exceeding 4 treatment days for reasons other than toxicity/illness will be considered a protocol deviation.

Given the importance of timeliness of treatment delivery in this study, it is strongly recommended that patients receive twice-daily treatments with a minimum 6-hour interfraction interval to compensate for missed days including holidays and those for toxicity or illness once sufficiently recovered with the goal of keeping the overall treatment time within the limits defined in Table 5.2.7D.

Table 5.2.7D: Delivery Compliance Criteria

	Per Protocol	**Variation Acceptable**	**Deviation Unacceptable**
RT Start date Arm 1 (Arm 2 closed to accrual 03-FEB-2023)	≤ 14 days after randomization	15-18 days	≥ 19 days
Arm 3	≤ 21 days after randomization	22-25 days	≥ 26 days
Overall Treatment time Arm 1 (Arm 2 closed to accrual 03-FEB-2023)	≤ 45 days	46-51 days	≥ 52 days without medically appropriate indication for delay
Overall Treatment time Arm 3	< 38 days	39-43 days	≥ 44 days without a medically appropriate indication for delay
Interruptions (without medical indication)	≤ 2 days	3-4 days	≥ 5 days

5.2.8 Treatment Planning Priorities and Instructions

Critical Structure and Target priorities must be listed in order of decreasing importance.
Prioritization for IMRT Planning:
1. SpinalCord and SpinalCord_PRV05
2. BrainStem and BrainStem_PRV03
3. PTV_7000, PTV_6650, PTV_6020, or PTV_6000
4. PTV_5600 or PTV_5400
5. PTV_5250 or PTV_4800
6. BrachialPlexus_R/L
7. Contralateral Parotid_R/L

8. a. Larynx_SG
   b. Pharynx
9. a. Cavity_Oral
   b. Lips
10. Esophagus_S
11. Contralateral Glnd_Submand_R/L
12. Ipsilateral Parotid_R/L
13. Cochlea_R/L
14. Bone_Mandible
15. Thyroid
16. E-PTV

Required algorithms
Acceptable choices of algorithm are listed at: http://rpc.mdanderson.org/RPC/home.htm

For Convolution/Superposition type algorithms, dose should be reported as computed inherently by the given algorithm. For Monte Carlo or Grid Based Boltzmann Solver algorithms, conversion of Dm (dose-to-medium) to Dw (dose-to-water) should be avoided. Dm, computed inherently by these algorithms, should be reported. These principles hold for Pencil Beam type algorithms and for homogeneous dose calculations when allowed for a clinical trial (e.g., conical collimators in stereotactic radiosurgery).

Primary dataset for dose calculation
If treatment planning CT is acquired with IV contrast, whether the density of the contrast should be overridden to a representative background electron density should be tested to demonstrate such density overridden is negligible to dose calculation. In addition, image artifacts such as streaks near metal, dental implants, fillings, clips or other high-density objects should be overridden with appropriate HUs.

Dose matrix resolution
Dose grid size should be ≤ 3 mm in all directions.

Adaptive planning (Re-planning)
In cases of weight loss > 10% or substantial shrinkage of lymphadenopathy during therapy, it is recommended that the immobilization mask be adjusted or re-made in order to preserve adequate immobilization, and that a repeated simulation CT be performed to assess the dose distributions in the current anatomy. There may be other extenuating circumstances requiring a re-CT and re-planning process. Whether or not a new IMRT plan will be generated is at the discretion of the treating physician. If a new plan is made, the target and OAR nomenclature should be the same as those used for the initial plan and the target volumes should not be adjusted in cases of disease regression, except to respect clear anatomic barriers such as skin or fascial or muscle planes initially uninvolved by disease. Re-planning DICOM data and final plan sum dose statistics should be submitted at the end of treatment.

5.2.9 Patient specific QA

Any patient-specific QA that needs to be acquired should follow institutional guidelines and AAPM task group report recommendations.

For IMRT/VMAT plans, patient specific QA is highly recommended. The recommended patient specific QA criteria is for 90% of the comparison points to pass a ± 3%/3 mm Gamma Index analysis.

5.2.10 Treatment Localization/IGRT

Image-guided radiation therapy (IGRT) is radiation therapy using imaging to facilitate treatment accuracy and precision throughout its entire process. In this section we use the terminology IGRT to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment, with computer assisted process, i.e. image handling together with calculation of shift and rotations (if available) must be determined with computer assistance.

Daily image guidance of IMRT may be achieved using any one or more of the following techniques:

- Orthogonal kilovoltage (kV) images (e.g. ExacTrac)
- Linear-accelerator mounted kV and MV conebeam CT images
- Linear-accelerator mounted MV helical CT images (e.g. Tomotherapy)
- In room CT or CBCT
- MRI scouts or MRI 2D/3D images
- Other Mechanism, after discussion with the Radiation Oncology Co-chair

The institution's procedure to register treatment day imaging dataset with the 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 fusion software allows the user to create an irregular ROI (e.g., ExacTrac), treatment room objects seen on in-room X-rays should be excluded from the registration;
- Both manual (e.g., based on bony anatomy) 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 less than 2.5 mm, 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 2.5-5 mm, adjustment is necessary prior to treatment; however, re-imaging is not mandatory. If one or more of the corrections are larger than 5 mm, the imaging must be repeated in addition to performing table/positioning adjustments. However, the use of numerous repeated IGRT should be avoided.

Management of Radiation Dose to the Patient from IGRT

NRG Oncology is concerned about the estimated doses given from IGRT and is committed to limiting the imaging dose when IGRT is used in any of its protocols. This can be accomplished by avoiding re-imaging to make shifts in patient positioning that are already less than the stated PTV margins. The imaging dose to the patient may become significant if repeated studies are done for patients with severe set up problems (e.g. requiring frequent corrections that are larger than the PTV margins). It is recommended that patients demonstrating severe set up problems during the first week of treatment be moved to a treatment with larger margins.

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.

- Anticonvulsants
- Antiemetics
- Anticoagulants
- Antidiarrheals
- Analgesics
- Herbal products
- Nutritional supplementation
- Highly active antiretroviral therapy (HAART)
- Inhaled or topical steroids and adrenal replacement doses < 10 mg daily prednisone equivalents are permitted

5.3.2 Prohibited Therapies

- Hematopoietic Growth Factors
- Corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications (unless to treat immune-related adverse event). Corticosteroid use for chemotherapy premedication is allowed.

5.3.3 Participation in Other Trials

Patients are not to participate in other therapeutic trials. However, trials that do not include drug are allowed (e.g. imaging trials, quality of life, etc).

5.4 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), as described in Section 6 (see also specific nivolumab algorithms in the Investigator's Brochure),
- For patients receiving nivolumab: Any dosing interruption lasting > 6 weeks, with the following exceptions: Dosing interruptions > 6 weeks that occur for non-drug-related reasons may be allowed if approved by the Investigator. Prior to re-initiating treatment in a subject with a dosing interruption lasting > 6 weeks, the Principal Investigator must be consulted.
  Note: Tumor assessments should continue as per protocol even if dosing is interrupted,
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6. TREATMENT MODIFICATIONS/MANAGEMENT

NOTE: PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

6.1 Dose Modifications and Toxicity Management for Nivolumab (19-APR-2023)

Please refer to the Nivolumab Investigator Brochure or Appendix VI for nivolumab toxicity management algorithms which include specific treatment guidelines. These algorithms should be followed unless there are specific clinical circumstances for which the treating physician decides an alternative treatment approach is clinically appropriate. Consultation with the study PI or drug monitor is recommended. When there are differences in recommendations between the aforementioned sources and the toxicity management tables provided below, the protocol tables determine when experimental treatment is to be held or stopped.

Generally we strongly encourage early evaluation while withholding drug, and appropriate treatment as indicated in the management tables and event specific guidelines.

ALL OTHER EVENTS	Management/Next Dose for Nivolumab
≤ Grade 1	No change in dose.
Grade 2	Hold until ≤ Grade 1 OR baseline (exceptions as noted below).
Grade 3	Hold until ≤ Grade 1 OR baseline and patient no longer on steroid treatment if initiated (exceptions as noted below). Permanently discontinue for events with a high likelihood of morbidity or mortality with recurrent events.
Grade 4	Off protocol therapy.
Recommended management: As clinically indicated	

- 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 should go off protocol treatment.

- Any Grade 2, 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, that can be managed independently from underlying organ pathology with electrolyte replacement, hormone replacement, insulin or that does not require treatment **does not** require discontinuation.

- Any AE, laboratory abnormality, or intercurrent illness which, in the judgment of the investigator, presents a substantial clinical risk to the subject with continued study drug dosing should go off protocol treatment.

Skin Rash and Oral Lesions	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose*.
Grade 2	Hold* until 1 ≤ Grade resolved. Resume at same dose level.
Grade 3	Hold* until ≤ Grade 1. Resume at same level at investigator discretion
Grade 4	Off protocol therapy.
*Patients with purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, toxic epidermal necrolysis (TEN), and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid. Pruritus may occur with or without skin rash and should be treated symptomatically if there is no associated liver or GI toxicity. Note skin rash typically occurs early and may be followed by additional events particularly during steroids tapering.	
Recommended management: AE management guidelines	

Liver Function AST, ALT, Bilirubin	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold at investigator discretion until ULN or baseline. Resume at same dose level.
Grade 2	Grade 2 (3X UNL to 5X UNL): Hold until grade 1 (UNL-3X UNL) or baseline. Resume at same dose level at investigator discretion.
Grade 3	Grade 3 (5X UNL to 20X UNL) Hold until grade 1 or baseline. Resume at same dose level at investigator discretion with return to grade 1 or baseline within 7 days without steroids. If persistent or steroids are required, off protocol therapy.
Grade 4	Off protocol therapy.
Continued treatment of active immune mediated hepatitis may exacerbate ongoing inflammation.	

Holding drug to evaluate liver function test (LFT) changes and early treatment are recommended. LFT changes may occur during steroid tapers from other events and may occur together with other GI events including cholecystitis/pancreatitis. Please note: Grades for liver function follow UNL rather than multiples of baseline.
Recommended management: see Hepatic AE management algorithm

Diarrhea/Colitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold until baseline. No change in dose.
Grade 2	Hold until baseline. No change in dose.
Grade 3	Resume at same dose level at investigator discretion if resolved to grade 1 within 7 days without steroids and no evidence of colitis. If persistent or steroids are required off protocol therapy.
Grade 4	Off protocol therapy.
See GI AE Algorithm for management of symptomatic colitis. Patients with Grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients who require systemic steroids should be taken off study treatment. Please evaluate pituitary function prior to starting steroids if possible without compromising acute care. Evaluation for all patients for additional causes includes *C. diff*, acute and self-limited infectious and foodborne illness, ischemic bowel, diverticulitis, and IBD.	
Recommended management: see GI AE management Algorithm	

Pancreatitis Amylase/Lipase	**Management/Next Dose for Nivolumab**
≤ Grade 1	Continue at same dose level if asymptomatic at investigator discretion.
Grade 2	Continue at same dose level if asymptomatic at investigator discretion. If symptomatic, resume at same dose level when resolved
Grade 3	Continue at same dose level if asymptomatic at investigator discretion. Patients should have imaging study when clinically indicated (grade 3 symptomatic pancreatitis) before resuming treatment. Patients who develop diabetes mellitus should be taken off treatment.
Grade 4	Hold until grade 2. Resume at same dose level if asymptomatic. Patients who are symptomatic should have imaging study prior to resuming treatment and when clinically indicated. Patients who develop grade 4 symptomatic pancreatitis or diabetes mellitus should be taken off treatment.
Patients may develop symptomatic and radiologic evidence of pancreatitis as well as diabetes mellitus and diabetic ketoacidosis (DKA). Lipase elevation may occur during the	

period of steroid withdrawal and with other immune-mediated events or associated with colitis, hepatitis, and patients who have asymptomatic lipase elevation typically have self-limited course and may be retreated. For treatment management of symptomatic pancreatitis, please follow the Hepatic AE Management Algorithm.

Pneumonitis	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold dose pending evaluation and resolution to baseline including baseline pO_2. Resume no change in dose after pulmonary and/or infectious disease (ID) consultation excludes lymphocytic pneumonitis.
Grade 2	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off study if steroids are required.
Grade 3	Hold dose pending evaluation. Resume no change in dose after pulmonary and/or ID consultation excludes ipilimumab and associated lymphocytic pneumonitis as the cause of the pneumonitis. Off protocol treatment.
Grade 4	Off protocol therapy.
Distinguishing inflammatory pneumonitis is often a diagnosis of exclusion for patients who do not respond to antibiotics and have no causal organism identified, including influenza. Most patients with respiratory failure or hypoxia will be treated with steroids. Bronchoscopy may be required and analysis of lavage fluid for lymphocytic predominance may be helpful. Patients with new lung nodules should be evaluated for sarcoid like granuloma. Please consider recommending seasonal influenza killed vaccine for all patients.	
Recommended management: See Pulmonary AE Management Algorithm	

Other GI Nausea, Vomiting	**Management/Next Dose for Nivolumab**
≤ Grade 1	No change in dose.
Grade 2	Hold pending evaluation for gastritis, duodenitis, and other immune AEs or other causes. Resume at same dose level after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation until ≤ Grade 1. Resume at same dose level. If symptoms do not resolve within 7 days with symptomatic treatment, patients should go off protocol therapy.
Grade 4	Off protocol therapy.
Patients with Grade 2 or 3 N-V should be evaluated for upper GI inflammation and other immune related events.	

Fatigue	**Management/Next Dose for Nivolumab**
Grade 2	No change in dose.

Grade 3	Hold until ≤ Grade 2. Resume at same dose level.
Grade 4	Off protocol therapy.
Fatigue is the most common AE associated with immune checkpoint therapy. Grade 2 or greater fatigue should be evaluated for associated or underlying organ involvement including pituitary, thyroid, and hepatic, or muscle (CPK) inflammation.	

Neurologic Events	**Management/Next Dose for Nivolumab**
≤ Grade 1	Hold dose pending evaluation and observation. Resume with no change in dose when resolved to baseline.
Grade 2	Hold dose pending evaluation and observation. Hold until ≤ Grade 1. Off protocol therapy if treatment with steroids is required. Resume at same dose level for peripheral isolated n. VII (Bell's palsy).
Grade 3	Off protocol therapy.
Grade 4	Off protocol therapy.
Patients with any CNS events including aseptic meningitis, encephalitis, symptomatic hypophysitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, and myasthenia gravis should be off study.	
Recommended management: See Neurologic AE Management Algorithm	

Endocrine **Hypophysitis** **Adrenal Insufficiency**	**Management/Next Dose for Nivolumab**
≤ Grade 1	*Hold pending evaluation for evidence of adrenal insufficiency or hypophysitis. Asymptomatic thyroid stimulating hormone (TSH) elevation may continue treatment while evaluating the need for thyroid replacement.
Grade 2	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.
Grade 3	Hold until patients are on a stable replacement hormone regimen. If treated with steroids, patients must be stable off steroids for 2 weeks. Resume at same dose level.
Grade 4	Off protocol therapy.
Note all patients with symptomatic pituitary enlargement, exclusive of hormone deficiency, but including severe headache or enlarged pituitary on MRI should be considered Grade 3 events. Isolated thyroid or testosterone deficiency may be treated as Grade 2 if there are no other associated deficiencies and adrenal function is monitored. Please evaluate pituitary function before beginning steroid therapy or replacement therapy of any kind. *Note patients with thyroiditis may be retreated on replacement therapy. Patients must be evaluated to rule out pituitary disease prior to initiating thyroid	

replacement.
Recommended management: See Endocrine Management Algorithm

Renal	**Management/Next Dose for Nivolumab**
≤ Grade 1	Monitor closely and continue therapy.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

Infusion Reaction	**Management/Next Dose for Nivolumab**
≤ Grade 1	Monitor closely and continue therapy.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Off treatment.
Grade 4	Off treatment.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	

Fever	**Management/Next Dose for Nivolumab**
≤ Grade 1	Evaluate and continue at same dose level.
Grade 2	Hold until ≤ Grade 1. Resume at same dose level.
Grade 3	Hold until ≤ Grade 1. Resume at same dose level.
Grade 4	Off treatment.
Patients with fever should be evaluated as clinically appropriate. Patients may experience isolated fever during infusion reactions or up to several days after infusion. Evaluation over the course of 1-2 weeks should be done for other autoimmune events that may present as fever.	
See section 6.1.1 – Treatment of Nivolumab-Related Infusion Reactions.	

Any patients who require additional immune suppressive treatment beyond steroids should go off study treatment.

Prior to starting corticosteroids or hormone replacement for any reason, appropriate endocrine testing including cortisol, Cortrosyn® adrenocorticotrophic hormone (ACTH), thyroid stimulating hormone (TSH), and thyroxine (T4) must be obtained

to document baseline.

Please note that in some cases the treatment algorithms recommend steroids if symptoms do not resolve in 7 days. However, this recommendation is not meant to delay steroid treatment at any time it is clinically indicated.
Any patient started on corticosteroids initially, who is determined to not require steroid treatment for an autoimmune AE, may resume therapy after a 2-week observation period without further symptoms at the discretion of the PI or investigator.

Cardiac Dysfunction

- **Drug will be held for any indication suggestion of cardiac dysfunction of any grade pending evaluation**
- **Drug will be permanently discontinued for treatment related grade 3 or 4 cardiac dysfunction and grade 2 events that do not recover to baseline or that reoccur**
- **Treatment as clinically indicated for cardiomyopathy**

Cardiac *	**Management/Next Dose for BMS-936558 (Nivolumab) Cardiac Toxicities**
Less than grade 2	Hold dose pending evaluation and observation.** Evaluate for signs and symptoms of CHF, ischemia, arrhythmia or myositis. Obtain history EKG, CK (for concomitant myositis), CK-MB. Repeat troponin, CK and EKG 2-3 days. If troponin and labs normalize without evidence of myocarditis may resume therapy. If labs worsen or symptoms develop then treat as below.
Grade ≥2 with suspected myocarditis	Hold dose.** Admit to hospital. Cardiology consult. Rule out MI and other causes of cardiac disease. Cardiac Monitoring. Cardiac Echo. Consider cardiac MRI and cardiac biopsy. Initiate high dose methylprednisolone and immune suppression as clinically indicated. . If no improvement within 24 hours consider adding either infliximab, ATG or tacrolimus.. May resume therapy if there is a return to baseline and myocarditis is excluded or considered unlikely.
Grade ≥2 with confirmed myocarditis	Off protocol therapy. Admit to CCU (consider transfer to nearest Cardiac Transplant Unit). Treat as above. Consider high dose methylprednisolone Add ATG or tacrolimus if no improvement. Off protocol treatment.

Cardiac *	Management/Next Dose for BMS-936558 (Nivolumab) Cardiac Toxicities
**Including CHF, LV systolic dysfunction, Myocarditis, CPK, and troponin* ***Patients with evidence of myositis without myocarditis may be treated according as "other event"* Note: The optimal treatment regimen for immune mediated myocarditis has not been established. Since this toxicity has caused patient deaths, an aggressive approach is recommended.	

6.1.1 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, urticaria, angioedema, pruritis, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms.

Infusion reactions should be graded according to NCI CTCAE version 5.0 guidelines.

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

Remain at bedside and monitor subject until recovery from symptoms.

For Grade 1 symptoms:
(Mild reaction; infusion interruption not indicated; intervention not indicated)

Infusion rate may be slowed or interrupted and restarted 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.

The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen) at least 30 minutes before additional nivolumab administrations, slowing infusion rate as above.

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]; close observation for recurrence and treatment medications may need to be continued for 24-48 hours).

Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or paracetamol 325 to 1000 mg (acetaminophen); remain at bedside and monitor 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, re 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 (acetaminophen) (or paracetamol) 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 symptoms: prolonged [*i.e.*, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [*e.g.*, renal impairment, pulmonary infiltrates]).

Grade 4 symptoms: (life threatening; pressor or ventilatory support indicated).

Nivolumab will be permanently discontinued.

Immediately discontinue infusion of nivolumab. Begin an IV infusion of normal saline, and 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.

Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor patient until recovery from symptoms.

In the case of late-occurring hypersensitivity symptoms (*e.g.*, appearance of a localized or generalized pruritus within 1 week after treatment), symptomatic treatment may be given (*e.g.*, oral antihistamine, or corticosteroids). Additional treatment prior to next dose as per guidelines above.

Please note that late occurring events including isolated fever and fatigue may represent the presentation of systemic inflammation. Please evaluate accordingly.

6.2 Recommended Dose Modifications and Toxicity Management for Cisplatin (14-MAR-2023)

The following cisplatin dose modification and toxicity management guidelines are recommendations; sites may follow their institutional standards for cisplatin administration as well as the FDA labeling.

Note: If adverse events prevent the administration of cisplatin, the patient may continue to receive 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, v5.0 while receiving concurrent cisplatin with radiotherapy.

Radiation treatment interruptions are only allowed if there are significant toxicities or comorbidities, in the judgment of the clinician, necessitate 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).

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 5.1.1 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 prior to cisplatin and interim non-hematologic toxicities during the week prior to a particular cisplatin dose.

6.2.1 Cisplatin Dose Modifications for Hematologic Adverse Events during Concurrent Radiation

Neutropenia and thrombocytopenia: Chemotherapy must not be administered until the ANC is ≥ 1200 mm^3 and platelets are ≥ 75,000 mm^3. If not, delay 7 days. Cisplatin should be held every week (but RT continued) until the above ANC and platelet parameters are met, then treat at 100 mg/m^2 dose. Any thrombocytopenia resulting in bleeding will require a dose reduction to 75 mg/m^2 of the second cisplatin dose.

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

Neutropenic Fever: Grade 3 (CTCAE, v5.0) 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 will require a dose reduction to 75 mg/m^2 of the second cisplatin dose.

6.2.2 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. 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
≤ 1.5	Or	> 50	100 mg/m^2
> 1.5	And	40-50	50 mg/m^2
> 1.5	And	< 40	Hold drug*

*Cisplatin should be held (but RT continued) and the creatinine measured weekly until it is < 1.5 mg/dl or the creatinine clearance is > 50 ml/min, and then the second dose of cisplatin should be given at the reduced dose of 50 mg/m^2.

Neurologic (neuropathy) Adverse Events:

Grade (CTCAE, v. 5)	**Dose Reduction**
0-1	None
2	Hold until toxicity improves to Grade 1 then reduce dose to 75 mg/m^2
3-4	Discontinue 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, v5.0, 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 (> grade 2) hearing loss. However, for clinical grade 3 or higher hearing loss, cisplatin should be held and for grade 2 clinical hearing loss, reduce to cisplatin 50 mg/m^2. For hearing loss requiring a hearing aid, discontinue cisplatin. For grade 2-3 tinnitus, at the time of retreatment, hold cisplatin until improvement to grade 1 or less and then reduce the 2nd dose to 50 mg/m^2. If tinnitus does not improve to grade 1 or less by the last day of radiation therapy, discontinue cisplatin. An audiogram is strongly recommended when there is any report of significant change in hearing and/or an increase in tinnitus.

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 v5.0), 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 at 75 mg/m^2. 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.

7. ADVERSE EVENTS REPORTING REQUIREMENTS

7.1 Protocol Agents

Investigational Agent

The investigational agent administered in NRG-HN005, nivolumab, is being made available under an IND sponsored by CTEP.

Commercial Agent

The commercial agent in NRG-HN005 is cisplatin.

7.2 Adverse Events and Serious Adverse Events

7.2.1 NCI Common Terminology Criteria for Adverse Events (CTCAE)

This study will utilize the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for CTEP-AERS (CTEP Adverse Event Reporting System) CAERs reporting of adverse events (AEs), located on the CTEP web site, http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

For determination of whether an adverse event meets expedited reporting criteria, see the reporting tables in section 7.5 of the protocol.
PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting.

7.2.2 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 unrelated, unlikely, possible, probable, or definite). (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.

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

Clinician graded CTCAE is the AE (adverse event) safety standard. PRO-CTCAE items are to complement CTCAE reporting. Patients will respond to PRO-CTCAE items but no protocol directed action will be taken. The specific PRO-CTCAE items for this protocol can be found on the forms section of the CTSU protocol webpage and is titled “NRG-HN005 NCI PRO-CTCAE Item Library. PRO-CTCAE is not intended for expedited reporting, real time review or safety

reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

NOTE: PRO-CTCAE data should not be used for determining dose delays or dose modifications or any other protocol directed action.

7.3 Comprehensive Adverse Events and Potential Risks list (CAEPR) for Nivolumab (NSC 78726) (21-AUG-2023)

The Comprehensive Adverse Events and Potential Risks list (CAEPR) provides a single list of reported and/or potential adverse events (AE) associated with an agent using a uniform presentation of events by body system. In addition to the comprehensive list, a subset, the Specific Protocol Exceptions to Expedited Reporting (SPEER), appears in a separate column and is identified with bold and italicized text. This subset of AEs (SPEER) is a list of events that are protocol specific exceptions to expedited reporting to NCI (except as noted below). Refer to the 'CTEP, NCI Guidelines: Adverse Event Reporting Requirements' http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/aeguidelines.pdf for further clarification. *Frequency is provided based on 2069 patients.* Below is the CAEPR for Nivolumab.

NOTE: Report AEs on the SPEER **ONLY IF** they exceed the grade noted in parentheses next to the AE in the SPEER. If this CAEPR is part of a combination protocol using multiple investigational agents and has an AE listed on different SPEERs, use the lower of the grades to determine if expedited reporting is required.

Version 2.5, June 10, 2023[1]

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
BLOOD AND LYMPHATIC SYSTEM DISORDERS			
	Anemia		***Anemia (Gr 3)***
		Blood and lymphatic system disorders - Other (lymphatic dysfunction)	
CARDIAC DISORDERS			
		Cardiac disorders - Other (cardiomyopathy)	
		Myocarditis	
		Pericardial tamponade[2]	
		Pericarditis	
ENDOCRINE DISORDERS			
	Adrenal insufficiency[3]		
	Hyperthyroidism[3]		
	Hypophysitis[3]		
	Hypothyroidism[3]		
EYE DISORDERS			
		Blurred vision	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
		Dry eye	
		Eye disorders - Other (diplopia)[3]	
		Eye disorders - Other (Graves opthalmopathy)[3]	
		Eye disorders - Other (optic neuritis retrobulbar)[3]	
		Eye disorders - Other (Vogt-Koyanagi-Harada)[3]	
	Uveitis		
GASTROINTESTINAL DISORDERS			
	Abdominal pain		***Abdominal pain (Gr 2)***
	Colitis[3]		
		Colonic perforation[3]	
	Diarrhea		***Diarrhea (Gr 3)***
	Dry mouth		***Dry mouth (Gr 2)***
		Enterocolitis	
		Gastritis	
		Mucositis oral	
	Nausea		***Nausea (Gr 2)***
	Pancreatitis[4]		
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS			
Fatigue			***Fatigue (Gr 3)***
	Fever		***Fever (Gr 2)***
	Injection site reaction		***Injection site reaction (Gr 2)***
HEPATOBILIARY DISORDERS			
		Hepatobiliary disorders - Other (Immune-related hepatitis)	
IMMUNE SYSTEM DISORDERS			
		Allergic reaction[3]	
		Autoimmune disorder[3]	
		Cytokine release syndrome[5]	
		Immune system disorders - Other (GVHD in the setting of allotransplant)[3,6]	
		Immune system disorders - Other (sarcoid granuloma, sarcoidosis)[3]	
INJURY, POISONING AND PROCEDURAL COMPLICATIONS			
	Infusion related reaction[7]		
INVESTIGATIONS			
	Alanine aminotransferase increased[3]		***Alanine aminotransferase increased[3] (Gr 3)***
	Aspartate aminotransferase increased[3]		***Aspartate aminotransferase increased[3] (Gr 3)***
	Blood bilirubin increased[3]		***Blood bilirubin increased[3] (Gr 2)***
	CD4 lymphocytes decreased		***CD4 lymphocytes decreased (Gr 4)***
	Creatinine increased		

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
	Lipase increased		
	Lymphocyte count decreased		***Lymphocyte count decreased (Gr 4)***
	Neutrophil count decreased		
	Platelet count decreased		
	Serum amylase increased		
METABOLISM AND NUTRITION DISORDERS			
	Anorexia		
		Hyperglycemia	***Hyperglycemia (Gr 2)***
		Metabolism and nutrition disorders - Other (diabetes mellitus with ketoacidosis)	
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS			
	Arthralgia		
		Musculoskeletal and connective tissue disorder - Other (polymyositis)	
		Myositis	
		Rhabdomyolysis	
NERVOUS SYSTEM DISORDERS			
		Encephalopathy[3]	
		Facial nerve disorder[3]	
		Guillain-Barre syndrome[3]	
		Myasthenia gravis[3]	
		Nervous system disorders - Other (demyelination myasthenic syndrome)	
		Nervous system disorders - Other (encephalitis)[3]	
		Nervous system disorders - Other (meningoencephalitis)	
		Nervous system disorders - Other (meningoradiculitis)[3]	
		Nervous system disorders - Other (myasthenic syndrome)	
		Peripheral motor neuropathy	
		Peripheral sensory neuropathy	
		Reversible posterior leukoencephalopathy syndrome[3]	
RENAL AND URINARY DISORDERS			
		Acute kidney injury[3]	
		Renal and urinary disorders - Other (Immune-related nephritis)	
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS			
	Pleural effusion[3]		
	Pneumonitis[3]		
		Respiratory, thoracic and mediastinal disorders - Other (bronchiolitis obliterans with organizing pneumonia (BOOP))[3]	

Adverse Events with Possible Relationship to Nivolumab (CTCAE 5.0 Term) [n= 2069]			Specific Protocol Exceptions to Expedited Reporting (SPEER)
Likely (>20%)	**Less Likely (<=20%)**	**Rare but Serious (<3%)**	
SKIN AND SUBCUTANEOUS TISSUE DISORDERS			
		Erythema multiforme[3]	
	Pruritus[3]		***Pruritus[3] (Gr 2)***
	Rash maculo-papular[3]		***Rash maculo-papular[3] (Gr 2)***
		Skin and subcutaneous tissue disorders - Other (bullous pemphigoid)	
	Skin and subcutaneous tissue disorders - Other (Sweet's Syndrome)[3]		
	Skin hypopigmentation[3]		
		Stevens-Johnson syndrome	
		Toxic epidermal necrolysis	

[1]This table will be updated as the toxicity profile of the agent is revised. Updates will be distributed to all Principal Investigators at the time of revision. The current version can be obtained by contacting PIO@CTEP.NCI.NIH.GOV. Your name, the name of the investigator, the protocol and the agent should be included in the e-mail.

[2]Pericardial tamponade may be related to possible inflammatory reaction at tumor site.

[3]Nivolumab being a member of class of agents involved in the inhibition of "immune checkpoints", may result in severe and possibly fatal immune-mediated adverse events probably due to T-cell activation and proliferation. This may result in autoimmune disorders that can include (but are not limited to) autoimmune hemolytic anemia, acquired anti-factor VIII immune response, autoimmune aseptic meningitis, autoimmune hepatitis, autoimmune nephritis, autoimmune neuropathy, autoimmune thyroiditis, bullous pemphigoid, exacerbation of Churg-Strauss Syndrome, drug rash with eosinophilia systemic symptoms [DRESS] syndrome, facial nerve disorder (facial nerve paralysis), limbic encephalitis, hepatic failure, pure red cell aplasia, pancreatitis, ulcerative and hemorrhagic colitis, endocrine disorders (e.g., autoimmune thyroiditis, hyperthyroidism, hypothyroidism, autoimmune hypophysitis/hypopituitarism, thyrotoxicosis, and adrenal insufficiency), sarcoid granuloma, myasthenia gravis, polymyositis, and Guillain-Barre syndrome.

[4]Pancreatitis may result in increased serum amylase and/or more frequently lipase.

[5]Cytokine release syndrome may manifest as hemophagocytic lymphohistiocytosis with accompanying fever and pancytopenia.

[6]Complications including hyperacute graft-versus-host disease (GVHD), some fatal, have occurred in patients receiving allo stem cell transplant (SCT) after receiving Nivolumab. These complications may occur despite intervening therapy between receiving Nivolumab and allo-SCT.

[7]Infusion reactions, including high-grade hypersensitivity reactions which have been observed following administration of nivolumab, may manifest as fever, chills, shakes, itching, rash, hypertension or hypotension, or difficulty breathing during and immediately after administration of nivolumab.

Adverse events reported on Nivolumab trials, but for which there is insufficient evidence to suggest that there was a reasonable possibility that Nivolumab caused the adverse event:

BLOOD AND LYMPHATIC SYSTEM DISORDERS - Leukocytosis
CARDIAC DISORDERS - Atrial fibrillation; Atrioventricular block complete; Heart failure; Ventricular arrhythmia
EAR AND LABYRINTH DISORDERS - Vestibular disorder
EYE DISORDERS - Eye disorders - Other (iridocyclitis); Optic nerve disorder; Periorbital edema
GASTROINTESTINAL DISORDERS - Constipation; Duodenal ulcer; Flatulence; Gastrointestinal disorders - Other (mouth sores); Vomiting
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS - Chills; Edema limbs; Malaise; Pain
HEPATOBILIARY DISORDERS - Bile duct stenosis
IMMUNE SYSTEM DISORDERS - Anaphylaxis; Immune system disorders - Other (autoimmune thrombotic microangiopathy); Immune system disorders - Other (limbic encephalitis)
INFECTIONS AND INFESTATIONS - Bronchial infection; Lung infection; Sepsis; Upper respiratory infection
INVESTIGATIONS - Blood lactate dehydrogenase increased; GGT increased; Investigations - Other (protein total decreased); Lymphocyte count increased; Weight loss
METABOLISM AND NUTRITION DISORDERS - Dehydration; Hyperuricemia; Hypoalbuminemia; Hypocalcemia; Hyponatremia; Hypophosphatemia
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS - Back pain; Musculoskeletal and connective tissue disorder - Other (musculoskeletal pain); Musculoskeletal and connective tissue disorder - Other (polymyalgia rheumatica); Myalgia; Pain in extremity
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS) - Neoplasms benign, malignant and unspecified (incl cysts and polyps) - Other (Histiocytic necrotizing lymphadenitis)
NERVOUS SYSTEM DISORDERS - Dizziness; Headache; Intracranial hemorrhage
PSYCHIATRIC DISORDERS - Insomnia
RENAL AND URINARY DISORDERS - Hematuria; Renal and urinary disorders - Other (tubulointerstitial nephritis)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS - Bronchospasm; Cough; Dyspnea; Hypoxia

SKIN AND SUBCUTANEOUS TISSUE DISORDERS - Alopecia; Dry skin; Hyperhidrosis; Pain of skin; Photosensitivity; Rash acneiform; Skin and subcutaneous tissue disorders - Other (rosacea)
VASCULAR DISORDERS - Flushing; Hypertension; Hypotension; Vasculitis

Note: Nivolumab in combination with other agents could cause an exacerbation of any adverse event currently known to be caused by the other agent, or the combination may result in events never previously associated with either agent.

7.4 Adverse Events for Commercial Study Agent: Cisplatin

Refer to the package insert for detailed pharmacologic and safety information.

7.4.1 Adverse Events and PRO-CTCAE

PRO-CTCAE

The PRO-CTCAE instrument will be used to assess patient reported toxicity outcomes.

PRO-CTCAE is a validated instrument developed by the National Cancer Institute to assess clinical trial toxicity outcomes by patient report; it complements information collected by physician-reported CTCAE. PRO-CTCAE is available in English, Spanish, and French for this study. Patients participating on the electronic patient-reported outcome (Medidata Patient Cloud ePRO) will only have the option to complete the English and Spanish language PRO-CTCAE. French language PRO-CTCAE is not currently available on the Medidata Patient Cloud ePRO. French speaking patients will only have the option to complete the PRO-CTCAE on paper. Collection time points are listed in Section 4.

Assessments will be collected before and at the end of radiation treatment and in follow-up as specified in the Section 4 assessment tables.

The patient-reported AEs that will be assessed using PRO-CTCAE are listed in the table below. These adverse events are considered expected and, if reported, should also be clinician graded using the CTCAE v5.0.

	CTCAE v5.0	**PRO-CTCAE Items With Attributes**
1	Dry mouth	Dry mouth (Severity)
2	Esophagitis Dysphagia	Difficulty swallowing (Severity)
3	Mucositis oral Pharyngeal mucositis	Mouth or throat sores (Severity)
4	Voice alteration	Voice quality changes (Presence)
5	Dysgeusia	Taste changes (Severity)
6	Rash acneiform Rash maculo-papular	Rash (Presence)
7	Pruritus	Itching (Severity)
8	Dermatitis radiation	Radiation skin reaction (Severity)

9	Peripheral sensory neuropathy	Numbness & tingling (Severity)
10	Tinnitus	Ringing in ears (Severity)
11	Concentration impairment	Concentration (Severity)
12	Memory Impairment	Memory (Severity)
13	Depression	Sad (Severity)
14	Blurred vision	Blurred vision (Severity)
15	Abdominal pain	Abdominal pain (Severity)

7.5 Expedited Reporting of Adverse Events (19-APR-2023)

All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the CTEP Adverse Event Reporting System, CTEP-AERS, accessed via the CTEP web site, https://ctepcore.nci.nih.gov/ctepaers/security/login.

Submitting a report via CTEP-AERS serves as notification to the NRG Biostatistical/Data Management Center and satisfies NRG requirements for expedited adverse event reporting.

In the rare event when Internet connectivity is disrupted, a 24-hour notification must be made to CTEP by telephone at 301-897-7497 and the NRG Oncology by phone at 1-215-574-3191. An electronic report must be submitted immediately upon re-establishment of the Internet connection.

7.5.1 Expedited Reporting Methods

- Per CTEP NCI Guidelines for Adverse Events Reporting, a CTEP-AERS 24-hour notification must be submitted within 24 hours of learning of the adverse event. Each CTEP-AERS 24-hour notification must be followed by a complete report within 5 days.
- Supporting source documentation is requested by NRG as needed to complete adverse event review. Supporting source documentation should include the protocol number, patient ID number, and CTEP-AERS ticket number on each page; fax supporting documentation to CTEP at 301-897-7404 and contact NRG Oncology at 1-215-574-3191 for source documentation assistance.
- A serious adverse event that meets expedited reporting criteria outlined in the AE Reporting Tables but is assessed by the CTEP-AERS as "an action *not* recommended" must still be reported to fulfill NRG safety reporting obligations. Sites must bypass the "NOT recommended" assessment; the CTEP-AERS allows submission of all reports regardless of the results of the assessment.

7.5.2 Expedited Reporting Requirements for Adverse Events

Arms 1 and 2 (Arm 2 closed to accrual 03-FEB-2023): Any Phase Study Utilizing a Commercial Agent[1]

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

NOTE: Investigators **MUST** immediately report to the sponsor **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 the NCI via CTEP-AERS within the timeframes detailed in the table below.

Attribution	Grade 4		Grade 5	
	Unexpected	Expected	Unexpected	Expected
Unrelated Unlikely			10 day	10 day
Possible Probable Definite	24-h/5 day		24-h/5 day	24-h/5 day

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS 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 30 days after the last administration of investigational agent/intervention and have an attribution of **possible, probable, or definite** require reporting as follows:

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

- Unexpected Grade 4 and all Grade 5 AEs

Arm 3: Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of Nivolumab[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 the NCI via CTEP-AERS within the timeframes detailed in the table below.

Hospitalization	Grade 1 Timeframes	Grade 2 Timeframes	Grade 3 Timeframes	Grade 4 & 5 Timeframes
Resulting in Hospitalization ≥ 24 hrs	10 Calendar Days			24-Hour 5 Calendar Days
Not resulting in Hospitalization ≥ 24 hrs	Not required		10 Calendar Days	

NOTE: Protocol specific exceptions to expedited reporting of serious adverse events are found in the Specific Protocol Exceptions to Expedited Reporting (SPEER) portion of the CAEPR

Expedited AE reporting timelines are defined as:

- "24-Hour; 5 Calendar Days" - The AE must initially be reported via CTEP-AERS 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 30 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 4, and Grade 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 adverse events resulting in hospitalization or prolongation of hospitalization
- Grade 3 adverse events

[2]For studies using PET 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.

Effective Date: May 5, 2011

7.5.3 Reporting to the Site IRB/REB

Investigators will report serious adverse events to the local Institutional Review Board (IRB) or Research Ethics Board (REB) responsible for oversight of the patient according to institutional policy.

7.5.4 Secondary Malignancy

A secondary malignancy is a cancer caused by treatment for a previous malignancy (e.g., treatment with investigational agent/intervention, radiation or chemotherapy). A secondary malignancy is not considered a metastasis of the initial neoplasm.

CTEP requires all secondary malignancies that occur during or subsequent to treatment with an agent under an NCI IND/IDE be reported via CTEP-AERS. In addition, secondary malignancies following radiation therapy must be reported via CTEP-AERS. Three options are available to describe the event:

- Leukemia secondary to oncology chemotherapy (e.g., acute myelocytic leukemia [AML])
- Myelodysplastic syndrome (MDS)
- Treatment-related secondary malignancy

Any malignancy possibly related to cancer treatment (including AML/MDS) should also be reported via the routine reporting mechanisms outlined in each protocol.

Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is NOT a metastasis from the initial malignancy). Second malignancies require ONLY routine reporting via CDUS unless otherwise specified.

7.6 Routine Reporting Requirements for Adverse Events

All Adverse Events **must** be reported in routine study data submissions. **AEs reported expeditiously through CTEP-AERS must also be reported in routine study data submissions.**

7.6.1 Reporting PRO-CTCAE

Symptomatic Adverse Events reported by patients through PRO-CTCAE are not safety reporting and should also be clinician graded using the CTCAE v5.0 and reported as routine AE data.

7.7 Pregnancy

Although not an adverse event in and of itself, pregnancy as well as its outcome must be documented via **CTEP-AERS**. In addition, the ***Pregnancy Information Form*** included within the NCI Guidelines for Adverse Event Reporting Requirements must be completed and submitted to CTEP. Any pregnancy occurring in a patient or patient's partner from the time of consent to 5 months or 7 months, respectively, after the last dose of nivolumab or 6 months after the last dose of cisplatin must be reported and then followed for outcome. Newborn infants should be followed until 30 days old. Please see the "NCI Guidelines for Investigators: Adverse Event Reporting Requirements for DCTD (CTEP and CIP) and DCP INDs and IDEs" (at http://ctep.cancer.gov/protocolDevelopment/adverse_effects.htm) for more details on how to report pregnancy and its outcome to CTEP.

8. REGISTRATION AND STUDY ENTRY PROCEDURES (21-AUG-2023)

CTEP Registration Procedures and Access requirements for OPEN, Medidata Rave, and TRIAD

Food and Drug Administration (FDA) regulations require sponsors to select qualified investigators. National Cancer Institute (NCI) policy require all individuals contributing to NCI-sponsored trials to register with their qualifications and credentials and torenew their registration annually. To register, all individuals must obtain a Cancer Therapy Evaluation Program (CTEP) Identity and Access Management (IAM) account at https://ctepcore.nci.nih.gov/iam. Investigators and clinical site staff who are significant contributors to research must register in the Registration and Credential Repository (RCR). The RCR is a self-service online person

registration application with electronic signature and document submission capability.
RCR utilizes five person registration types.

- Investigator (IVR) — MD, DO, or international equivalent;
- Non Physician Investigator (NPIVR) — advanced practice providers (e.g., NP or PA) or graduate level researchers (e.g., PhD);
- Associate Plus (AP) — clinical site staff (e.g., RN or CRA) with data entry access to CTSU applications such as the Roster Update Management System [RUMS], OPEN, Rave, acting as a primary site contact, or with consenting privileges;
- Associate (A) — other clinical site staff involved in the conduct of NCI-sponsored trials; and
- Associate Basic (AB) — individuals (e.g., pharmaceutical company employees) with limited access to NCI-supported systems.

RCR requires the following registration documents:

Documentation Required	IVR	NPIVR	AP	A	AB
FDA Form 1572	✓	✓			
Financial Disclosure Form	✓	✓	✓		
NCI Biosketch (education, training, employment, license, and certification)	✓	✓	✓		
GCP training	✓	✓	✓		
Agent Shipment Form (if applicable)	✓				
CV (optional)	✓	✓	✓		

IVRs and NPIVRs must list all clinical practice sites and Institutional Review Boards (IRBs) covering their practice sites on the FDA Form 1572 in RCR to allow the following:

- Added to a site roster
- Selection as the treating, credit, or drug shipment investigator or consenting person in OPEN
- Ability to be named as the site-protocol Principal Investigator (PI) on the IRB approval

In addition, all investigators acting as the Site-Protocol PI (investigator listed on the IRB approval), consenting/treating/drug shipment investigator in OPEN, must be rostered at the enrolling site with a participating organization.

Refer to the NCI RCR page on the CTEP website for additional information. For questions,

please contact the RCR ***Help Desk*** by email at RCRHelpDesk@nih.gov.

8.1 Cancer Trials Support Unit Registration Procedures (21-AUG-2023)

Permission to view and download this protocol and its supporting documents is restricted and is based on the person and site roster assignment housed in the Roster Maintenance application and in most cases viewable and manageable via the Roster Update Management System (RUMS) on the Cancer Trials Support System Unit (CTSU) members' website.

This study is supported by the NCI Cancer Trials Support Unit (CTSU).

IRB Approval

As of March 1, 2019, all U.S.-based sites must be members of the NCI Central Institutional Review Board (NCI CIRB) in order to participate in Cancer Therapy Evaluation Program (CTEP) and Division of Cancer Prevention (DCP) studies open to the National Clinical Trials Network (NCTN) and NCI Community Oncology Research Program (NCORP) Research Bases. In addition, U.S.-based sites must accept the NCI CIRB review to activate new studies at the site after March 1, 2019. Local IRB review will continue to be accepted for studies that are not reviewed by the CIRB, or if the study was previously open at the site under the local IRB. International sites should continue to submit Research Ethics Board (REB) approval to the CTSU Regulatory Office following country-specific regulations.

Sites participating with the NCI CIRB must submit the Study Specific Worksheet (SSW) for Local Context to the CIRB using IRBManager to indicate their intent to open the study locally. The NCI CIRB's approval of the SSW is automatically communicated to the CTSU Regulatory Office, but sites are required to contact the CTSU Regulatory Office at CTSURegPref@ctsu.coccg.org to establish site preferences for applying NCI CIRB approvals across their Signatory Network. Site preferences can be set at the network or protocol level. Questions about establishing site preferences can be addressed to the CTSU Regulatory Office by email or calling 1-888-651-CTSU (2878).

Sites using their local IRB or REB, must submit their approval to the CTSU Regulatory Office using the Regulatory Submission Portal located in the Regulatory section of the CTSU website. Acceptable documentation of local IRB/REB approval includes:

- Local IRB documentation;
- IRB-signed CTSU IRB Certification Form; and/or
- Protocol of Human Subjects Assurance Identification/IRB Certification/Declaration of Exemption Form.

In addition, the Site-Protocol Principal Investigator (PI) (i.e. the investigator on the IRB/REB approval) must meet the following criteria for the site to be able to have an Approved status following processing of the IRB/REB approval record:

- Have an active CTEP status;
- Have an active status at the site on the IRB/REB approval and on at least one participating roster;

- If using NCI CIRB, be active on the NCI CIRB roster under the applicable CIRB Signatory Institution(s) record;
- Includes the IRB number of the IRB providing approval in the Form FDA 1572 in the RCR profile;
- List all sites on the IRB/REB approval as Practice Sites in the Form FDA 1572 in the RCR profile; and
- Have the appropriate CTEP registration type for the protocol

Additional Requirements for Protocol NRG-HN005 Site Registration:
Additional requirements to obtain an approved site registration status include:

- An active Federal Wide Assurance (FWA) number
- An active roster affiliation with the Lead Protocol Organization (LPO) or a Participating Organization (PO);
- An active roster affiliation with the NCI CIRB roster under at least one CIRB Signatory Institution (US sites only);
- Compliance with all protocol-specific requirements (PSRs);
- This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider (see further information below).
- IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process

RTI Provider

This is a study with a radiation and/or imaging (RTI) component and the enrolling site must be aligned to an RTI provider. To manage provider associations or to add or remove associated providers, access the Provider Association page from the Regulatory section on the CTSU members' website at https://www.ctsu.org/RSS/RTFProviderAssociation. Sites must be linked to at least one Imaging and Radiation Oncology Core (IROC) provider to participate on trials with an RTI component. Enrolling sites are responsible for ensuring that the appropriate agreements and IRB approvals are in place with their RTI provider. An individual with a primary role on any roster is required to update provider associations, though all individuals at a site may view provider associations. To find who holds primary roles at your site, view the Person Roster Browser under the RUMS section on the CTSU members' website.

IROC Credentialing Status Inquiry (CSI) Form – this form is submitted to IROC Houston to verify credentialing status or to begin a new modality credentialing process.

To complete protocol-specific credentialing the RTI provider or enrolling site should follow instructions in the protocol to submit documentation or other materials to the designated IROC Quality Assurance (QA) center. Upon the IROC QA center approving the RTI provider for the study modality, IROC will send the approval to the provider and/or enrolling site. The provider and/or enrolling site will need to upload the approval letter to the Regulatory Support System (RSS) to comply with the protocol-specific requirement.

Upon site registration approval in RSS, the enrolling site may access OPEN to complete enrollments. The enrolling site will select their credentialed provider treating the subject in the

OPEN credentialing screen and may need to answer additional questions related to treatment in the eligibility checklist.

Additional Requirements for sites in Canada

All institutions in Canada must conduct this trial in accordance with International Conference on Harmonization-Good Clinical Practice (ICH-GCP) Guidelines [per section 6.2.5 of ICH E6(R2)]. This trial is being conducted under a Clinical Trial Application (CTA) with Health Canada. As a result essential documents must be retained for 15 years following the completion of the trial at the participating site (15years post final analysis, last data collected, or closure notification to REB, whichever is later), or until notified by the sponsor, NRG Oncology, that documents no longer need to be retained [per C.05.012 (4) of the FDR]. In addition, upon request by the auditor, REB or regulatory authority, the investigator/institution must make all required trial-related records available for direct access [per section 4.9.7 of ICH]. Prior to clinical trial commencement, sites in Canada must also complete and submit to NRG Regulatory (CanadianRegulatory@NRGOncology.org):

- Clinical Trial Site Information Form,
- Qualified Investigator Undertaking Form
- Research Ethics Board Attestation Form
- Protocol Signature Page
- Investigator Brochure (IB) Signature Page
- Delegation of Tasks (DTL) Log
- List of Laboratories
- SIV/Training Confirmation of Completion Form – Research Associate (please refer to the activation memo for details)
- SIV/Training Confirmation of Completion Form – Qualified Investigator (please refer to the activation memo for details)
- IRB/REB approved consent (English and native language versions*). Must submit English version of consent form to NRG Regulatory for review prior to submission to local IRB/REB.

The following items are collected by NRG Oncology Regulatory on a yearly or biyearly basis:

- IRB/REB Membership Roster
- Laboratory Certificates and Normal Values
- CVs for Qualified Investigator and Sub-Investigators noted on the DTL log

Record Retention: The sponsor, NRG Oncology, shall maintain records identified in *Health Canada guidelines Part C, Division 5, section C.05.012* for a period of at least 15 years.

*Note: Certification/verification of IRB/REB consent translation must be provided with submission to CTSU (described below).
Translation of documents is critical. The institution is responsible for all translation costs. All regulatory documents, including the IRB/REB approved consent, must be provided in English and in the native language. Certification of the translation is optimal but due to

the prohibitive costs involved NRG will accept, at a minimum, a verified translation. A verified translation consists of the actual REB approved consent document in English and in the native language, along with a cover letter on organizational letterhead/stationery that includes the professional title, credentials, and signature of the translator as well as signed documentation of the review and verification of the translation by a neutral third party. The professional title and credentials of the neutral third party translator must be specified as well.

Downloading Site Registration Documents:

Download the site registration forms from the protocol-specific page located on the CTSU members' website. Permission to view and download this protocol and its supporting documents is restricted to institutions and their associated investigators and staff on a participating roster. To view/download site registration forms:

- Log on to the CTSU members' website (https://www.ctsu.org)
- Click on *Protocols* in the upper left of the screen
    - Enter the protocol number in the search field at the top of the protocol tree; or
    - Click on the By Lead Organization folder to expand, then select *NRG* and protocol number *NRG-HN005*.
- Click on *Documents*, select *Site Registration*, and download and complete the forms provided. (Note: For sites under the CIRB, IRB data will load automatically to the CTSU.)

Submitting Regulatory Documents:

Submit required forms and documents to the CTSU Regulatory Office using the Regulatory Submission Portal on the CTSU website.

To access the Regulatory Submission Portal log in to the CTSU members' website, go to the Regulatory section and select Regulatory Submission.

Institutions with patients waiting that are unable to use the Regulatory Submission Portal should alert the CTSU Regulatory Office immediately by phone or email: 1-866-651-CTSU (2878), or CTSURegHelp@coccg.org to receive further instruction and support.

Checking Site's Registration Status:

Site registration status may be verified on the CTSU members' website.

- Click on *Regulatory* at the top of the screen;
- Click on *Site Registration*; and
- Enter the site's 5-character CTEP Institution Code and click on Go
    - Additional filters are available to sort by Protocol, Registration Status, Protocol Status, and/or IRB Type.

Note: The status shown only reflects institutional compliance with site registration requirements as within the protocol. It does not reflect compliance with protocol requirements for individuals participating on the protocol or the enrolling investigator's status with NCI or their affiliated networks.

8.2 RT-Specific Pre-Registration Requirements (21-AUG-2023)

For detailed information on the specific technology requirement required for this study, please refer to the table below and utilize the web link provided for detailed instructions. The check marks under the treatment modality columns indicate whether that specific credentialing requirement is required for this study. Specific credentialing components may require you to work with various QA centers; however, IROC Houston will notify your institution when all credentialing requirements have been met and the institution is RT credentialed to enter patients onto this study. This document must be uploaded by the site to the CTSU Regulatory Submission Portal for RSS to be updated.

RT Credentialing Requirements	Web Link for Credentialing Procedures and Instructions **http://irochouston.mdanderson.org**	
	Treatment Modality	
	Photon	**Key Information**

Credentialing Status Inquiry Form	**x**	To determine if your institution has completed the requirements above, please complete a "Credentialing Status Inquiry Form" found under Credentialing on the IROC Houston QA Center website (**http://irochouston.mdanderson.org**).
Facility Questionnaire	**x**	The IROC Houston electronic facility questionnaire (FQ) should be completed or updated with the most recent information about your institution. To access this FQ, email **irochouston@mdanderson.org** to receive your FQ link.
Phantom Irradiation	**x**	An IMRT Head & Neck phantom study provided by the IROC Houston QA Center must be successfully completed. Instructions for requesting and irradiating the phantom are found on the IROC Houston web site (**http://irochouston.mdanderson.org**).
IGRT	**x**	Instructions for IGRT credentialing may be found on the IROC Houston website (**http://irochouston.mdanderson.org**).
Credentialing Notification Issued to:		
Institution		Institution will be credentialed for the treatment modality that they intend to use on all patients. IROC Houston QA Center will notify the institution and NRG Headquarters that all desired credentialing requirements have been met.

8.2.1 Digital Radiation Therapy Data Submission Using Transfer of Images and Data

Transfer of Images and Data (TRIAD) is the American College of Radiology's (ACR) image exchange application. TRIAD provides sites participating in clinical trials a secure method to transmit images. TRIAD anonymizes and validates the images as they are transferred.

TRIAD Access Requirements:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems;
- Registration type of: Associate (A), Associate Plus (AP), Non-Physician Investigator (NPIVR), or Investigator (IVR) registration type. Refer to the CTEP Registration Procedures section for instructions on how to request a CTEP-IAM account and complete registration in RCR.
- TRIAD Site User role on an NCTN ETCTN, or other relevant roster.

All individuals on the Imaging and Radiation Oncology Core provider roster have access

to TRIAD and may submit images for credentialing purposes, or for enrollments to which the provider is linked in OPEN.

TRIAD Installation:
To submit images, the individual holding the TRIAD Site User role will need to install the TRIAD application on their workstation. TRIAD installation documentation is available at https://triadinstall.acr.org/triadclient/.

This process can be done in parallel to obtaining your CTEP-IAM account and RCR registration.

For questions, contact TRIAD Technical Support staff via email TRIAD-Support@acr.org or 1-703-390-9858.

8.3 Patient Enrollment (21-AUG-2023)

Patient registration can occur only after evaluation for eligibility is complete, eligibility criteria have been met, and the study site is listed as 'approved' in the CTSU RSS. Patients must have signed and dated all applicable consents and authorization forms.

Informed Consent: Patients must be aware of the neoplastic nature of their disease and informed of the procedure(s) to be followed, the experimental nature of the therapy, alternatives, potential benefits, side-effects, risks, and discomforts prior to signing the informed consent in accordance with institutional and federal guidelines. Current IRB/REB/REC approval of this protocol and a consent form is required prior to patient consent and registration. The model consent form created for this study adheres to the NCI informed consent template requirements.

8.3.1 Oncology Patient Enrollment Network (OPEN)

The Oncology Patient Enrollment Network (OPEN) is a web-based registration system available on a 24/7 basis. OPEN is integrated with CTSU regulatory and roster data and with the LPOs registration/randomization systems or the Theradex Interactive Web Response System (IWRS) for retrieval of patient registration/randomization assignment. OPEN will populate the patient enrollment data in NCI's clinical data management system, Medidata Rave.

Requirements for OPEN access:

- Active CTEP registration with the credentials necessary to access secure NCI/CTSU IT systems
- To perform enrollments or request slot reservations: Must be on an LPO roster, ETCTN corresponding roster, or participating organization roster with the role of Registrar. Registrars must hold a minimum of an Associate Plus (AP) registration type;
- Have an approved site registration for the protocol prior to patient enrollment.

To assign an Investigator (IVR) or Non-Physician Investigator (NPIVR) as the treating, crediting, consenting, drug shipment (IVR only), or receiving investigator for a patient transfer in OPEN, the IVR or NPIVR must list the IRB number used on the site's IRB approval on their

Form FDA 1572 in RCR.

Prior to accessing OPEN, site staff should verify the following:

- Patient has met all eligibility criteria within the protocol stated timeframes; and
- All patients have signed an appropriate consent form and Health Insurance Portability and Accountability Act (HIPAA) authorization form (if applicable).

Note: The OPEN system will provide the site with a printable confirmation of registration and treatment information. You may print this confirmation for your records.

Access OPEN at https://open.ctsu.org or from the OPEN link on the CTSU members' website. Further instructional information is in the OPEN section of the CTSU website at https://www.ctsu.org or https://open.ctsu.org. For any additional questions, contact the CTSU Help Desk at 1-888-823-5923 or ctsucontact@westat.com.

9.0 DRUG INFORMATION

9.1 Agent Ordering and Agent Accountability (21-AUG-2023)

NCI-supplied agents may be requested by eligible participating Investigators (or their authorized designee) at each participating institution. The CTEP-assigned protocol number must be used for ordering all CTEP-supplied investigational agents. The eligible participating investigators at each participating institution must be registered with CTEP, DCTD through an annual submission of FDA Form 1572 (Statement of Investigator), NCI Biosketch, Agent Shipment Form, and Financial Disclosure Form (FDF). If there are several participating investigators at one institution, CTEP-supplied investigational agents for the study should be ordered under the name of one lead investigator at that institution. Submit agent requests through the PMB Online Agent Inventory Management System (AURORA) application. Access to (AURORA) requires the establishment of a CTEP Identity and Access Management (IAM) account and the maintenance of an "active" account status, a "current" password, and active person registration status. For questions about drug orders, transfers, returns, or accountability, call or email PMB any time. Refer to the PMB's website for specific policies and guidelines related to agent management.

Sites can order study agents in AURORA when a patient is enrolled to treatment. Agent orders can be expedited overnight Monday-Thursday when sites provided expedited courier information.

9.1.1 Starter supplies are not being provided. Patients must be registered prior to sites ordering study agents.

Refer to the Policy and Guidelines for Investigational Agent Ordering and the contact information below for order processing time and conditions. Normal order processing time is two business days. An express courier account number must be provided for next-day delivery.

CTEP Forms, Templates, Documents: http://ctep.cancer.gov/forms/
NCI CTEP Investigator Registration: RCRHelpDesk@nih.gov
PMB policies and guidelines:
http://ctep.cancer.gov/branches/pmb/agent_management.htm

PMB Online Agent Order Processing (OAOP) application:
https://ctepcore.nci.nih.gov/OAOP/
CTEP Identity and Access Management (IAM) account:
https://ctepcore.nci.nih.gov/iam/
CTEP IAM account help: ctepreghelp@ctep.nci.nih.gov
PMB email: PMBAfterHours@mail.nih.gov
PMB phone and hours of service: (240) 276-6575 Monday through Friday between 8:30 am and 4:30 pm (ET)
IB Coordinator: IBCoordinator@mail.nih.gov

The investigator, or a responsible party designated by the investigator, must maintain a careful record of the receipt, dispensing and final disposition of all agents received from the PMB using the appropriate NCI Investigational Agent (Drug) Accountability Record (DARF) available on the CTEP forms page. Store and maintain separate NCI Investigational Agent Accountability Records for each agent, strength, formulation and ordering investigator on this protocol.

9.1.2 Investigator Brochure

To supplement the toxicity information contained in this document, investigators must obtain the current version of the investigator brochure (IB), if available, for comprehensive pharmacologic and safety information. The current version of the Investigator Brochure (IB) will be accessible to site investigators and research staff through the PMB AURORA application. Access to AURORA requires the establishment of a CTEP IAM account and the maintenance of an "active" account status, a "current" password, and active person registration status. Questions about IB access may be directed to the PMB IB Coordinator via email.

9.2 Investigational Study Agent: Nivolumab (IND, NSC 748726) (21-AUG-2023)

Sites must refer to the investigator brochure for detailed pharmacologic and safety information. The Investigator Brochure will be provided by the Pharmaceutical Management Branch (PMB). See Section 9.1.

Amino Acid Sequence: 4 polypeptide chains, which include 2 identical heavy chains with 440 amino acids and 2 identical light chains.

Other Names: BMS-936558, MDX1106

Classification: Anti-PD-1MAb

M.W.: 146,221 Daltons

Mode of Action: Nivolumab targets the programmed death–1 (PD-1, cluster of differentiation 279 [CD279]) cell surface membrane receptor. PD-1 is a negative regulatory receptor expressed by activated T and B lymphocytes. Binding of PD-1 to its ligands, programmed death–ligand 1 (PD-L1) and 2 (PD-L2), results in the down-regulation of lymphocyte activation. Nivolumab inhibits the binding of PD-1 to PD-L1 and PD-L2. Inhibition of the interaction between PD-1 and its ligands promotes immune responses and antigen-specific T-cell responses to both foreign antigens as well as self-antigens.

Description: Nivolumab Injection is a clear to opalescent, colorless to pale yellow liquid; light

(few) particulates may be present. The drug product is a sterile, nonpyrogenic, single-use, isotonic aqueous solution formulated in sodium citrate, sodium chloride, mannitol, diethylenetriaminepentacetic acid (pentetic acid) and polysorbate 80 (Tween® 80), and water for injection. Dilute solutions of hydrochloric acid and/or sodium hydroxide may be used for pH adjustment (pH 5.5-6.5).

How Supplied: Nivolumab is supplied by Bristol-Myers Squibb and distributed by the Pharmaceutical Management Branch, CTEP/DCTD/NCI as 100 mg vials (10 mg/mL) with a 0.7mL overfill. It is supplied in 10 mL type I flint glass vials, with fluoropolymer film-laminated rubber stoppers and aluminum seals.

Preparation: Nivolumab injection can be infused undiluted (10 mg/mL) or diluted with 0.9% Sodium Chloride Injection, USP or 5% Dextrose. When the dose is based on patient weight (i.e., mg/kg), nivolumab injection can be infused undiluted or diluted to protein concentrations as low as 0.35 mg/mL. When the dose is fixed (eg, 240 mg), nivolumab injection can be infused undiluted or diluted so as not to exceed a total infusion volume of 160 mL. For patients weighing less than 40 kilograms (kg), the total volume of infusion must not exceed 4 mL per kg of patient weight. During drug product preparation and handling, vigorous mixing or shaking is to be avoided.

Nivolumab infusions are compatible with polyvinyl chloride (PVC) or polyolefin containers and infusion sets, and glass bottles.

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

If a storage temperature excursion is identified, promptly return Nivolumab to 2°C-8°C and quarantine the supplies. Provide a detailed report of the excursion (including documentation of temperature monitoring and duration of the excursion) to PMBAfterHours@mail.nih.gov for determination of suitability.

Stability: Shelf-life surveillance of the intact vials is ongoing.

Following the preparation of nivolumab injection, it is preferred to administer the drug product immediately. If not used immediately, the infusion solution may be stored under refrigeration conditions (2°-8°C (36°-46°F)) and protected from light for up to 7 days, including the product administration period or as described in the instructions provided to the clinical site. The infusion solution may be stored at room temperature (up to 25°C, 77°F) and room light for a maximum of 8 hours, including the product administration period.

*Caution: The single-use dosage form contains no antibacterial preservative or bacteriostatic agent. Therefore, it is advised that the product be discarded 8 hours after initial entry.

Route of Administration: Intravenous infusion over 30 minutes. Do not administer as an IV push or bolus injection.

Method of Administration: Administer through a 0.2 micron to 1.2 micron pore size, low-protein binding (polyethersulfone membrane) in-line filter.

Potential Drug Interactions: The indirect drug-drug interaction potential of nivolumab was assessed using systemic cytokine modulation data for cytokines known to modulate CYP enzymes. There were no meaningful changes in cytokines known to have indirect effects on CYP enzymes across all dose levels of nivolumab. This lack of cytokine modulation suggests that nivolumab has no or low potential for modulating CYP enzymes, thereby indicating a low risk of therapeutic protein-drug interaction.

Patient Care Implications: Women of childbearing potential (WOCBP) receiving nivolumab must continue contraception for a period of 5 months after the last dose of nivolumab. Men receiving nivolumab and who are sexually active with WOCBP must continue contraception for a period of 7 months after the last dose of nivolumab. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she (or the participating partner) should inform the treating physician immediately.

9.3 Commercial Agent: Cisplatin (NSC# 119875)

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

9.3.1 Availability/Supply

Drug will be supplied commercially. Please see Section 5.1 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.

9.3.2 Patient Care Implications

Females of childbearing potential must use adequate contraception during treatment and for 6 months after the last dose of cisplatin chemotherapy. Male patients must use highly effective contraception for a total of 6 months after last dose of cisplatin chemotherapy.

10. PATHOLOGY/BIOSPECIMEN

10.1 Optional Biospecimen Submission Tables for Future Research (19-APR-2023)

See detailed specimen collection/processing/shipping instructions on the protocol-specific website.
(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 per protocol. Sites are not permitted to delete the specimen component from the protocol or from the sample consent.)

See detailed specimen collection/processing/shipping instructions on the protocol-specific website, www.ctsu.org.

This study will include collection of biospecimens for future analyses. An amendment for any correlative science studies to be performed on biological samples will be submitted to CTEP,

NCI for review and approval according to NCTN guidelines or via the Navigator portal after the trial has been reported. Amendments to the protocol and/or proposals for use of banked tissue or blood samples will include the appropriate background, experimental plans with assay details, and a detailed statistical section. Samples for testing will not be released for testing until the appropriate NCI approvals have been obtained.

FFPE Specimen Collection for Biobanking for Potential Future Research (to be offered to all patients)

- H&E stained slides and block (or punch biopsy of paraffin block) to the Biospecimen Bank at UCSF
- Required Forms: ST form and pathology reports with study and case # on each page, date of procedure, pathology accession number; any other personal health information (PHI) should be redacted by sites before sending. Pathology reports must include the p16-positive staining result for each patient.
- FFPE Punch Kits can be requested from the Biospecimen Bank when requesting the frozen specimen kits.
- Shipping costs: Submitting site pays cost of shipping FFPE samples and returns.
- FFPE specimens will be retained at the Biospecimen Bank unless needed for immediate patient continuing care. One to two 3-mm punches will be taken from the blocks before shipping to sites that have requested the return of their blocks.

Ship all biospecimens to:
NRG Oncology Biospecimen Bank – San Francisco
University of California San Francisco
2340 Sutter Street, Room S341
San Francisco, CA 94115
415-476-7864; FAX 415-476-5271
NRGBB@ucsf.edu

Specimen Type	Collection Time Points	Collection Information and Requirements	Shipping
One H&E slide from primary tumor; H&E slides can be duplicate cut slides, they do not have to be the diagnostic slide	Pre-Treatment Baseline tumor specimen	H&E stained slide.	Slides shipped ambient to NRG Biospecimen Bank San Francisco
FFPE Block or one to two 3-mm punches taken from the tumor block (embedded*)	Pre-Treatment Baseline tumor specimen	Corresponding FFPE Block or one to two 3-mm punches from the same block as the H&E slide that is being	Shipped ambient or with cold pack to the NRG Biospecimen Bank San Francisco

		submitted. An H&E from the punch block must be included. (embedded*)	

*For sites with the capability to do so, the one to two punch biopsies should be embedded into one new paraffin block from which an H&E slide should be obtained. The constructed block containing the punch and the H&E slide must then be submitted to the NRG Oncology Biospecimen Bank in San Francisco. An H&E from the original block must still be submitted. Alternatively, sites can either 1) send the block to the Biospecimen Bank, and the bank will punch and embed the blocks for the sites before returning them, or 2) send the one to two 3-mm punches to the bank to be embedded by the Biospecimen Bank.

Plasma, Serum, and Whole Blood Collection for Biobanking for Potential Future Research (to be offered to all patients)

Forms: ST Form – filled out completely with study, case, date of procedure, institution name, NCI ID and time points.

Kits: Can be requested from the NRGBB-SF at NRGBB@ucsf.edu. Allow 5-10 business days for kits. Sites must have IRB approval before requesting kits.

Shipping: One prepaid return label provided for each case for batch shipping frozen biospecimens only.
Batch ship frozen samples Monday-Wednesday (US sites) and Monday-Tuesday (Canadian Sites).

Processing Instructions: Located on the CTSU website protocol specific documents.

Ship all frozen specimens on dry ice in batches by overnight courier to:
NRG Oncology Biospecimen Bank – San Francisco
UCSF – Dept of Radiation Oncology
2340 Sutter Street- Room S341
San Francisco, CA 94115

For questions, please contact the San Francisco Bank at:
Email: NRGBB@ucsf.edu
415-476-7864/Fax 415-476-5271

Specimen Type	Collection Time Points	Collection Information and Requirements/Instructions for Site	Shipping
Plasma: Two Purple Top EDTA	● Baseline Pre-treatment	Process plasma and aliquot a minimum of 1.5 mL plasma	Batch ship frozen samples

tubes (10 mL each, centrifuged and processed for plasma collection)	● During RT treatment, obtained after 20 Gy RT but before 28 Gy ● After completion - within 4 weeks from end of all treatment*	into five 2 mL cryovials. Place into biohazard bag and immediately freeze tubes upright at -70 to -90ºC. Samples should be frozen and stored at -80^{0}C until ready to batch ship.	on Dry Ice by Overnight Courier to NRGBB-San Francisco
Serum: One 10 mL red top (clot) tube	● Baseline Pre-treatment ● During RT treatment, obtained after 20 Gy RT but before 28 Gy ● After completion - within 4 weeks from end of all treatment*	Serum centrifuged and aliquotted. Frozen serum samples containing a minimum of 0.5 mL per aliquot in 1 mL cryovials (up to 5 per tube drawn). Place into biohazard bag and immediately freeze tubes upright at -70 to -90ºC. Samples should be frozen and stored at -80^{0}C until ready to batch ship.	Batch ship frozen samples on Dry Ice by Overnight Courier to NRGBB-San Francisco
Whole Blood: One 5-10 mL EDTA tube	Baseline Pre-treatment *Note: If site missed this collection, they may collect at any other time but must note this on the ST form when submitting*	Collect blood, mix and aliquot 1-1.5 mL of whole blood per vial into three 2 mL cryovials. Place into biohazard bag and immediately freeze tubes upright at -70 to -90ºC. Samples should be frozen and stored at -80^{0}C until ready to batch ship.	Batch ship frozen samples on Dry Ice by Overnight Courier to NRGBB-San Francisco

*Arm 1 (Arm 2 closed to accrual 03-FEB-2023): Specimen will be collected at the end of RT.
Arm 3: Specimen will be collected after the last dose of Nivolumab. Note: If Nivolumab is discontinued prior to end of RT then the specimen will be collected at the end of RT.

11. SPECIAL STUDIES (NON-TISSUE)

11.1 Association of FDG-PET/CT Imaging with Locoregional Control and PFS

All patients are highly recommended to have a baseline FDG-PET/CT scan (see section 3.1.4). A post-therapy FDG-PET/CT scan is highly recommended at 12-14 weeks post-therapy for assessment of response to therapy. Scans that are obtained will be submitted per Section 11.1.5.

11.1.1 Rationale for FDG-PET/CT and Association with Clinical Outcomes

The purpose of studying FDG-PET/CT in the context of NRG-HN005 is to determine the association of baseline and12-14 week post therapy FDG-PET/CT for locoregional control and PFS.

At pre-therapy baseline PET/CT imaging, the intensity of FDG uptake is highly associated with patients' survival outcomes. Intense FDG uptake is significantly associated with worse survival outcomes in HNSCC. Zhang et al (2010) analyzed eight clinical trials dedicated to HNSCC and determined the values of SUVmax and mean SUV as related to outcomes. They concluded that increased SUV of the primary tumor is a poor prognostic factor and has a potential value in its association to local control, disease-free survival and OS. Another similar meta-analysis by Xie et al (2011) confirmed that low primary tumor SUVs were associated with better survival outcomes. Other PET-derived parameters for the primary tumor such as MTV and TLG have also been studied in a meta-analysis by Pak et al (2014). Authors reviewed 13 studies including 1180 patients and found these volumetric measurements to be valuable for their association to future recurrence, progression, or both.

The sensitivity and specificity of post-treatment FDG-PET/CT depend on the time interval between the completion of therapy and FDG-PET/CT. In a study of 26 patients, Goerres et al. (2004) observed a sensitivity and specificity of 91% and 93%, respectively, for PET/CT scans performed as early as 6 weeks after chemoradiotherapy. However, other studies have not been able to reproduce these data (Porceddu 2005, Yao 2005) and instead suggest that PET/CT after chemoradiotherapy should not be performed before 10-12 weeks after the end of radiation treatment. By that time, most of the post-treatment inflammatory changes will have subsided, reducing the number of potentially false-positive interpretations. In general, the rate of false-positive cases declines with the interval between the end of therapy and PET/CT imaging (Lonneux 2000). The optimal timing of the first response assessment FDG-PET/CT after definitive (chemo) radiation is not precisely known, but an interval of at least 12 weeks has generally been recommended to balance the drawbacks of imaging too early versus too late. In rare cases, early detection of residual/recurrent disease is central to successful surgical salvage if appropriate, while a demonstration of a clinical and radiographic complete response obviates the need for further unnecessary and potentially morbid interventions. A recent meta-analysis involving 51 studies and 2335 patients (Gupta 2011) estimated the sensitivity and specificity of post-treatment FDG-PET/CT at 91.9% and 86.9% for primary tumor and 90.4% and 94.3% for neck nodes, respectively, when the PET/CT was performed > 12 weeks after completion of

concurrent chemoradiation therapy.

PET-NECK was a standard-setting, multicenter randomized Phase III non-inferiority trial comparing an FDG-PET/CT-guidance versus planned neck dissection for head and neck cancer patients receiving chemoradiation for N2/N3 nodal metastases. This study showed that surveillance based on 10-12 week post-treatment FDG-PET/CT resulted in noninferior survival to neck dissection but was more cost-effective and resulted in fewer complications. At 36 months of follow-up, the true-negative rate of FDG-PET/CT in the neck was 86.4% and the true-negative rate in the primary was 84.9% (Mehanna 2017). Another small retrospective study indicated that a post-treatment FDG-PET/CT-directed policy could specifically ensure low rates of 3-year locoregional failure even for patients presenting with very bulky neck adenopathy (> 6 cm) (Adams 2014). It should be noted that all of these research findings have been in head and neck cancer patients receiving traditional chemoradiation and standard radiation doses.

Currently, FDG-PET/CT is commonly used for staging and assessment of treatment response in head and neck cancer. The Centers for Medicare and Medicaid services and most third party payers in USA provide reimbursement for a pre-treatment and a post-treatment FDG-PET/CT in head and neck cancer patients scheduled to receive definitive-intent radiotherapy.

Because of the frequent use of PET/CT in local centers, it is of interest to the study investigators to document the performance of PET/CT under "real-world" conditions. This approach may increase the future generalizability of any findings. Therefore, we will collect clinical accreditation of PET/CT scanners of the participating institutions as well as minimum standard for parameters for performing a PET/CT for head and neck cancers. Because the PET/CT images will be scored on a standardized basis, the impact of variations in the imaging technique should be substantially lessened. Regarding PET/CT technique, the study investigators recommend that the standard-of-care guidelines from the National Cancer Institute and ACRIN Imaging Standards for PET should be followed as closely as possible (Shankar 2006).

11.1.2 Post-acquisition scoring methodology for FDG-PET/CT scans

To provide a platform for standardizing research interpretations of the PET/CT scans, the study investigators have developed a reader-based scoring system to minimize the effect of varying acquisition techniques. This ordinal scoring system (see below) was utilized in NRG-HN002 and identifies those patients who have complete metabolic response and those who did not have complete metabolic response, retrospectively. Submitted baseline and post-treatment PET/CT images will be reviewed at the end of the recruitment period and correlated with the clinical treatment outcomes.

The scoring system ("Hopkins criteria") was modified from the well-validated and clinically most useful five-point scoring system for mid-therapy and post-therapy assessment for lymphoma (Deauville criteria). This scoring system has been previously validated as a collapsed three-point categorization (negative for tumor, indeterminate, positive for tumor) for head and neck FDG-PET/CT scans performed between 4 and 24 months after therapy completion (Paidpally 2013). The scoring system successfully predicted outcome in these patients and added

value to the clinical assessment at the time of the scans. In addition, the five-point scoring system has been recently validated in head and neck FDG-PET/CT scans performed between five weeks and 6 months after therapy completion in 214 head and neck squamous cell carcinoma patients. There was 90%, 97.2%, 94.9% and 91.3% agreement between the readers for overall, left neck, right neck and primary tumor site response scores, respectively. The corresponding Kappa coefficients for inter-reader agreement were k=0.70 ($p<0.0001$), k=0.81 ($p<0.0001$), k= 0.69 ($p<0.0001$), and k=0.67 ($p<0.0001$), respectively. The accuracy of the scoring system against a 6 month clinical follow up as the reference standard is excellent with ROC area under the curve 0.98 (95% CI 0.97-0.99; $P < 0.001$). Cox regression analysis showed a significant difference in overall survival between the patients who had a score between 1-3 (negative for tumor) and those who had a score 4 or 5 (positive for tumor) (log-rank, $P<0.0001$ with a hazard ratio of 0.056 [95% CI 0.022-0.138] (Marcus 2014). This system of standardization is now well validated in multicenter clinical trial (Van den Wyngaert 2017).

Harmonization of FDG-PET/CT Ordinal Scoring and Classification of Results

The baseline diagnosis and post treatment tumor response evaluation will be carried out using a 5-point ordinal scale.

(a) At baseline neck lymph node standardized interpretation:

Score 1: Definitely benign lymph node: The FDG uptake in the nodal sites is less than the background blood pool FDG uptake.
Score 2: Likely benign lymph node: The FDG uptake in the nodal sites is greater than the background blood pool uptake but it is equal to or less than the liver FDG uptake.
Score 3: Likely inflammatory uptake: There is diffuse FDG uptake at nodal sites. This diffuse FDG uptake is greater than the liver FDG uptake and likely related to inflammation and unlikely tumor.
Score 4: Likely nodal metastasis: There is focal FDG uptake in the nodal sites. The focal FDG uptake is greater than the liver FDG uptake.
Score 5: Definite nodal metastasis: There is intense focal FDG uptake in the nodal sites. This focal FDG uptake is 3 – 4 times greater than the liver FDG uptake.

(b) Post therapy primary site and neck lymph node standardized interpretation:

Score 1: Definite complete metabolic response: The FDG uptake in the primary tumor or nodal sites is less than the background blood pool FDG uptake.
Score 2: Likely complete metabolic response: The FDG uptake in the primary tumor or nodal sites is greater than the background blood pool uptake but it is equal to or less than the liver FDG uptake.
Score 3: Likely inflammatory: There is diffuse FDG uptake in the primary tumor or nodal sites. This diffuse FDG uptake is greater than the liver FDG uptake and likely related to post-radiation inflammation.
Score 4: Likely residual metabolic disease: There is focal FDG uptake in the primary or nodal sites. The focal FDG uptake is greater than the liver FDG uptake.
Score 5: Definite residual metabolic disease: There is intense focal FDG uptake in the primary

tumor or nodal sites. This focal FDG uptake is 3 – 4 times greater than the liver FDG uptake.

Definitions of 'Positive,' 'Negative' and 'Indeterminate' FDG Uptake and PET/CT Results
A score of 1 or 2 will be interpreted as 'Negative,' a score of 3 as 'Indeterminate,' and a score of 4 or 5 as 'Positive.' A 'Negative' result at the primary or nodal sites is defined as equal or less FDG uptake than the blood pool and liver FDG uptake. Uptake for the local blood pool reference value will be measured from the carotid or the aortic arch. The 'Indeterminate' result is defined as diffuse FDG uptake in the treatment field with intensity of the uptake greater than the liver FDG uptake. A 'Positive' result is defined as focal uptake visually greater than the background and at a higher level than the activity seen in the liver.

It is important to note that local sites will decide the post-therapy management and may incorporate the information from FDG-PET/CT into decision making according to these guidelines. However, determination of PFS events should be confirmed with clinical follow-up and/or pathologic confirmation from biopsy or surgery directed by the local site according to its institutional practices; and an indeterminate or positive reading on FDG-PET/CT in itself will not be considered to affect the primary endpoint unless the local site reports and/or confirms disease recurrence.

11.1.3 Recommended FDG-PET/CT Imaging Sequence and Details
See section 5.2.3.

11.1.4 FDG-PET/CT Image Reconstruction
See section 5.2.3.

11.1.5 Submission of FDG-PET/CT Image and Site Read

- Following the completion of PET/CT imaging at the site, the institution will submit images in DICOM format via TRIAD to IROC Imaging; See section 8.2 for details regarding TRIAD.
- Institutions must submit a case report form (CRF) for each PET/CT image in which a site reader characterizes the baseline disease state (baseline scan) and patient's therapy response (post treatment scan) using the 5-point scale outlined in Section 11.1.2 (i.e. the local site read).

11.1.6 FDG-PET/CT Research-Directed Image Evaluation
For study purposes, PET/CT images will be retroactively interpreted by an NRG Oncology Imaging Core Panel (NRGICP) of expert PET/CT readers who will have no involvement or knowledge of the participant's clinical care and who will be blinded to the participant's diagnosis, local PET/CT scan results, and clinical history.

11.2 Swallowing Substudy (04-NOV-2020)
Submitted data from institutions that routinely administer a Modified Barium Swallow (MBS)

study to patients at baseline and at 12 and 24 months post radiation therapy will be part of an exploratory analysis (See Sections 1.3.4; Section 4/Pre-Treatment and Follow-Up Assessment tables; and Appendix IV).

The MBS is an objective dynamic, radiographic imaging study, where the patient is administered a series of increasing volumes of radiopaque labeled standardized liquid and solid food consistencies to examine oropharyngeal swallow physiology, aspiration and/or pharyngeal residue. Many institutions will have standard guidelines for acquisition of MBS. For purposes of this protocol, individual investigators may use their local guidelines to acquire the MBS. One possible approach is outlined in Appendix IV which is suggested to optimize MBS scan acquisition. Please refer to Appendix IV to see specifics.

The submitted digital DICOM images from the MBS will be collected and stored via TRIAD. They will be retroactively scored, pending funding, by an NRG Oncology Swallowing Core Panel (NRGSCP) of expert speech-language pathologists who will have no involvement or knowledge of the participant's clinical care and who will be blinded to the participant's diagnosis, local PET/CT scan results, and clinical history. The evaluation will be carried out using the following 4 measures:

Modified Barium Swallow Impairment Profile (MBSImP™©)
The MBSImP™© profiles 17 components of the oropharyngeal swallow physiology along a 3- to 5-point ordinal scale from normal to severe impairment. The component ratings for each patient generate two continuous overall summary scores: the oral total (OT) and pharyngeal total (PT) for each patient. The OT is derived from adding scores of components 1# to #6 and ranges from 0-22, where a score of 22 is worse. The PT is derived from adding scores of components #7 to #16 and ranges from 0-29, where a score of 29 is worse. The rating of esophageal motility, item #17, will be excluded as it is beyond the focus of this study.

Pharyngeal Constriction Ratio (PCR)
The PCR is a pixel-based measure computing area of the pharynx at maximum constriction at peak swallow over the resting area of the pharynx from the mid-sagittal radiograph. PCR provides a reliable radiographic surrogate measure of pharyngeal strength (measured against gold standard pharyngeal manometry), and discriminates aspiration status in dysphagia populations.

Penetration-Aspiration Scale (PAS)
The PAS is an 8-point ordinal scale of swallow airway safety capturing bolus penetration and aspiration, where a score ≤ 2 indicates a safe swallow, 2-5 indicates penetration, and 6-8 indicates aspiration. PAS ratings are highly reliable (ICC for inter- and intra-rater reliability: 0.96 and 0.95-0.97, respectively) and predictive of aspiration pneumonia after chemoradiation ($p<0.001$, AUC=0.72).

DIGEST grade
The DIGEST was developed and validated as a CTCAE compatible MBS-derived severity grade

of pharyngeal dysphagia. The DIGEST is highly reliable (intra- and inter-rater weighted *k* 0.82-0.84 and 0.67-0.81, respectively) and discriminates pharyngeal pathophysiology ($r = 0.77$, $p<0.001$), perceived dysphagia ($r = -0.41$, $p<0.001$), and diet ($r = -0.49$, $p<0.001$) in HNC survivors.

11.3 Patient-Reported Outcomes (PROs) and Quality of Life (QOL) (19-APR-2023)

All participating centers will be required to participate in the patient-reported outcome and quality of life assessments.

11.3.1 Rationale for QOL/PRO

Dysphagia-related QOL is one of two primary endpoints in this Phase II/III trial. In this trial, the hypothesis is that dysphagia-related QOL in a reduced-dose arm with cisplatin or nivolumab would not be worse than in a standard-of-care arm, while desirable PFS would be maintained in one of these experimental arms. This major endpoint of dysphagia-related QOL will be measured with the MDADI, the MD Anderson Dysphagia Inventory. This is a well-validated, reliable, self-reported questionnaire that has been designed to evaluate the impact of dysphagia on the QOL of patients with head and neck cancer (Chen 2001).

To measure the generic aspects of QOL, we will use the EORTC-QLQ-C30, a well-developed questionnaire that has been used in multiple NRG Oncology Group trials. This questionnaire has also been used in a recent Phase III trial that used nivolumab for patients with recurrent or metastatic squamous-cell carcinoma of the head and neck (Harrington 2017). In this trial, patients treated with nivolumab were stable across functional and symptom domains as measured by the EORTC QLQ-C30, while patients in a standard therapy group had clinically meaningful worsening in 8 of those 15 domains. Further, the differences between the two treatment arms were statistically and clinically significant (Harrington 2017). However, the effect of nivolumab on QOL remains unclear for patients newly diagnosed with HPV-associated oropharyngeal cancer and in the aforementioned study, because the reported difference between the two arms was only measured during 15 weeks of treatment, the long-term effect of nivolumab on QOL for patients with head and neck cancer is still unclear. For these reasons, it is meaningful and novel to study the generic aspects of QOL in our trial.

As a National Cancer Institute (NCI)-funded initiative to improve the accuracy and precision of clinician-reported CTCAE, the PRO-CTCAE will be used to measure symptomatic adverse events associated with oropharyngeal cancer and the proposed cancer treatments. The goal of the PRO-CTCAE project is to standardize use in all clinical trials on cancer (Basch 2014). Validation studies, which have been conducted at NCI-designated, comprehensive cancer centers and by the NRG/RTOG, have shown favorable validity, reliability, and responsiveness in patients undergoing cancer treatment (Dueck 2015). Using this reporting system for symptomatic adverse events is particularly important for patients receiving immunotherapy because it captures novel immunotherapy-related side effects while other questionnaires, which were developed prior to advent of immunotherapy, do not. Additionally, core physical symptoms and side effects associated with radiotherapy and chemotherapy for head and neck cancer patients are also included in the PRO-CTCAE.
Hearing loss has a significant, negative impact on patients' QOL by hampering speech, communication, and social life (Cioba 2012). Cisplatin, a platinum-based chemotherapy drug,

will be used in this trial. However, cisplatin can damage the cochlea, leaving 40-80% of adults with significant, permanent hearing loss. Regrettably, no cures or preventive treatments have yet become part of the standard of care for cisplatin-induced ototoxicity (Rybak 2009). Cisplatin-induced hearing loss is particularly serious in patients with head and neck cancer because radiation of the base of the skull adds to the risk of damage (Chen 2006). Moreover, patients with HPV-positive oropharyngeal cancer might be at high risk of hearing changes after treatment because they are usually younger and have better hearing than HPV-negative patients (Ang 2010). Thus, we will study auditory damage from chemoradiation in this population and examine whether reducing radiation or substituting cisplatin with immunotherapy would measurably improve this aspect of QOL.

In the light of growing concerns about the increasing cost of cancer and health care, clinicians must carefully consider the economic consequences of introducing new agents, especially those that are exorbitantly expensive. The goal of such considerations should be to reach a balance between best cost and effectiveness and to inform clinical decision making. Immunotherapies such as nivolumab have been associated with better disease outcomes and QOL (Ferris 2016; Harrington 2017), but the current cost is high (Couzin-Frankel 2013; Tringale 2018). In this trial, we will use a cost-utility analysis, including utilities like QOL, to compare different treatment choices. Specifically, the ratio of the incremental cost to gain an extra, quality-adjusted life-year (QALY) will be used to compare different treatment arms. The EQ-5D-5L, a well-validated instrument for calculating QALY and cost-utility analysis, will be used in this trial.

All QOL/PRO instruments will be administrated at baseline, end of RT, at 12 weeks from end of RT, at 6 months, 12 months, and 24 months post-RT. These time points were selected to best capture the changes in QOL/PRO throughout the various phases of treatment across the arms and follow-ups. Evidence from published studies and other NRG Oncology trials have also indicated that those time points reflect the acute and late effects of treatment on patients QOL/PRO status (Xiao 2017; Truong 2017; Ringash 2017).

11.3.2 Description of QOL/PRO Instruments

MD Anderson Dysphagia Inventory (MDADI)

Swallowing will be evaluated using the validated PRO swallowing instrument, the MD Anderson Dysphagia Inventory (MDADI). The MDADI is a 20-item self-administered patient reported dysphagia-specific instrument consisting of global, emotional, functional, and physical subscales (Chen 2001), and is currently being used on several prospective multicenter randomized NRG oncology clinical trials. Two summary scores: global and composite, can be obtained from the MDADI. The global score is from a single item to assess the overall impact of swallowing abilities on QOL. The composite score summarizes the remaining 19 items, as a weighted average of the physical, emotional, and functional subscales. The scores range from 0 (extremely low functioning) to 100 (high functioning). Hutcheson et al. (2016) evaluated the MDADI questionnaire (scored out of 100) for swallowing-related QOL in 1,136 patients with HNC. Using anchor-based methods, a ten-point difference between groups in composite MDADI scores was identified as clinically meaningful (Hutcheson 2016). This recommendation is from a cross-sectional study, but there are no published recommendations with a longitudinal design. A range of 5%-10% differences in instrument range has also been recommended for clinical meaningful changes (Ringash 2007). To be consistent with prior use of the survey in NRG-

HN002, a 5% difference in the MDADI global change scores from baseline to one year after radiation between arms will be considered as being clinically meaningful in this proposed trial. The time for administration is about 7-10 minutes.

NRG Oncology has obtained permission to use the MDADI for this study in English, Spanish, and French.

Hearing Handicap Inventory for Adults-Screening (HHIA-S) Instrument
The Hearing Handicap Inventory for Adults (HHIA) was developed to target hearing impaired adults and a screening version of the HHIA (HHIA-S) was subsequently developed as a screening tool (Newman CW, 1990). The HHIA-S includes 10 items with a high test-retest reliability of 0.97. The overall score is the sum of the 10 items, and ranges from 0 to 40. A score from 0-8 indicates no self-perceived handicap; a score from 10-24 indicates mild to moderate handicap; and a score from 24-40 indicates severe handicap (Ventry & Weinstein 1982). HHIA-S was used in RTOG 1016 successfully to assess the hearing loss. The time for administration is about 3-5 minutes. Since a recommended clinical meaningful change has not been published for HHIA-S, we will use a similar approach as MDADI: a range of 5% to 10% differences in instrument range will be considered as clinical meaningful changes (Ringash 2007).

NRG Oncology has obtained permission to use the HHIA-S for this study in English and Spanish. The HHIA-S has not been validated in French.

EORTC QLQ-C30
The European Organization for Research and Treatment of Cancer Core Questionnaire (EORTC QLQ-C30 Version 3.0) (Aaronson NK, 2012, Sherman AC, 2000) is a well-established, 30-item self-reporting questionnaire developed to assess overall QOL of patients with cancer. The EORTC QLQ-C30 is grouped into five functional subscales (role, physical, cognitive, emotional and social functioning), three multi-item symptom scales (fatigue, pain, and nausea and vomiting), individual questions concerning common symptoms in cancer patients, and two questions assessing overall QOL. The subscales and symptom measures range in score from 0 to 100; a high scale score represents better functioning or higher symptom burden (symptom scales will be reversed to facilitate presentation). The EORTC QLQ-C30 has been used in clinical trials using nivolumab for patients with recurrent or metastatic head and neck cancer (Ferris 2016, Harrington 2017) and using the EORTC QLQ-C30 in this trial will provide a reliable comparison among trials. The time for administration is about 7-10 minutes. Clinical meaningful changes in the EORTC QLQ-C30 will be defined as a 10-point difference (Osoba 1998, Mazieres 2019).

NRG Oncology has obtained permission to use the EORTC QLQ-C30 for this study in English, Spanish, and French.

EQ-5D-5L
The EQ-5D™, a trademark of the EuroQol Group, is a standard measure of health status. The

EQ-5D-5L provides a simple descriptive profile and a single index value for health status that can be used for clinical and economic evaluation of health care (EuroQol Group 1990). The EQ-5D-5L is a 2-part questionnaire and has been translated into multiple languages. The first part is the descriptive system and consists of 5 items covering 5 dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension is graded on 5 levels: 1-no problems, 2-slight problems, 3-moderate problems, 4-severe problems, and 5-unable to perform/extreme problems. The score from the descriptive system will be converted into a single index value to compare the health status and facilitate the calculation of QALYs that will inform economic evaluation of this intervention. The second part is a visual analogue scale (VAS) valuing current health state, measured on a 20 cm, 10 point-interval scale. The score of VAS ranges from 100 to 0, with 100 indicating the best health the patient can imagine and 0 indicating the worst health the patient can imagine. Patients can complete in a few minutes.

NRG Oncology has obtained permission to use the EQ-5D-5L for this study in English, Spanish, and French.

11.3.3 Administration of NRG-HN005 Patient-Completed Questionnaires
Time points for administration are located in Section 4.

11.3.4 Administration Instructions
Questionnaires are to be administered per section 4. For patient opting out of ePRO, the PRO Forms should be administered during an office visit if at all possible, preferably while the patient is waiting to be seen. Once the questionnaires are completed by the patient, the staff member should review it to ensure that no items were unintentionally left blank. When absolutely necessary, it may also be administered by mail or phone. The completed forms will be data entered in Medidata Rave.

Patients who never initiate NRG-HN005 study therapy or who experience disease progression should continue participating in the PRO study. If a patient does not come in to clinic, the questionnaires will either be mailed to the patient or the research assistant will call the patient to complete the forms. If the patient does not return the forms within two weeks the patient will be called and either another set will be sent or the patient will complete the questionnaires over the phone with the research assistant.

If a patient declines to complete a scheduled PRO forms or if the questionnaire is not completed for any other reason (and cannot be completed by phone or mail), the QOL coversheet must be completed in Rave. For patients who agree to use ePRO for PRO collection please refer to Appendix II.

12. MODALITY REVIEWS

12.1 Radiation Therapy Quality Assurance Reviews

The Principal Investigator and Radiation Oncology Co-Chairs or NRG Oncology Headquarters approved designee(s) will perform an RT Quality Assurance Review after NRG Headquarters has received complete data for each case. These reviews will be ongoing and will be facilitated by IROC Philadelphia RT. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of radiotherapy treatment data.

The scoring mechanism is: **1) Per Protocol, 2) Variation Acceptable, 3) Deviation Unacceptable, and 4) Not Evaluable**.

12.2 Medical Oncology Modality Quality Assurance Reviews

The Medical Oncology Co-Chair or NRG Oncology Headquarters approved designee(s) will perform a Chemotherapy Assurance Review of all patients who receive or are to receive chemotherapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data. The scoring mechanism is: **1) Per Protocol, 2) Variation Acceptable, 3) Deviation Unacceptable, and 4) Not Evaluable**.

The Medical Oncology Co-Chair or designee will perform a Quality Assurance Review after NRG Headquarters has received complete data for each case enrolled. The reviews will be ongoing.

13. DATA AND RECORDS

13.1 Data Management/Collection (19-APR-2023)

Medidata Rave is a clinical data management system being used for data collection for this trial/study. Access to the trial in Rave is controlled through the CTEP-IAM system and role assignments.

Requirements to access Rave via iMedidata:

- A valid CTEP-IAM account and linked ID.me account (ID.me accounts are required for all newly created CTEP-IAM accounts and by July 1, 2023 for all users); and
- Assigned a Rave role on the LPO or PO roster at the enrolling site of: Rave CRA, Rave Read Only, Rave CRA (LabAdmin), Rave SLA, or Rave Investigator.

Rave role requirements:

- Rave CRA or Rave CRA (Lab Admin) role must have a minimum of an Associate Plus (AP) registration type;
- Rave Investigator role must be registered as an Non-Physician Investigator (NPIVR) or Investigator (IVR); and
- Rave Read Only role must have at a minimum an Associates (A) registration type.

Refer to https://ctep.cancer.gov/investigatorResources/default.htm for registration types and documentation required.

Upon initial site registration approval for the study in Regulatory application, all persons with

Rave roles assigned on the appropriate roster will be sent a study invitation e-mail from iMedidata. To accept the invitation, site staff must log in to the Select Login (https://login.imedidata.com/selectlogin) using their CTEP-IAM username and password and click on the *accept* link in the upper right-corner of the iMedidata page. Site staff will not be able to access the study in Rave until all required Medidata and study specific trainings are completed. Trainings will be in the form of electronic learnings (eLearnings) and can be accessed by clicking on the link in the upper right pane of the iMedidata screen. If an eLearning is required and has not yet been taken, the link to the eLearning will appear under the study name in iMedidata instead of the *Rave EDC* link; once the successful completion of the eLearning has been recorded, access to the study in Rave will be granted, and a *Rave EDC* link will display under the study name.

Site staff that have not previously activated their iMedidata/Rave account at the time of initial site registration approval for the study in the Regulatory application will receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website in the Data Management section under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Additional information on iMedidata/Rave is available on the CTSU members' website in the Data Management > Rave section or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

13.2 Summary of Data Submission (04-NOV-2020)

Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of patients enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during the trial using Medidata Rave®. Additionally, certain adverse events must be reported in an expedited manner for more timely monitoring of patient safety and care. See Section 7 for information about expedited and routine reporting. PRO-CTCAE is not intended for expedited reporting, real time review, or safety reporting. PRO-CTCAE data are exploratory and not currently intended for use in data safety monitoring or adverse event stopping rules.

Summary of Data Submission: Refer to the CTSU website.

Digital Data Submission Requirements
Summary of Dosimetry Digital Data Submission
Submit Digital RT Data via TRIAD; see Section 8.2.1 for TRIAD account access and installation instructions.

<table>
<tr><td rowspan="5">DICOM DIGITAL DATA</td><td>DICOM CT IMAGE SET</td><td rowspan="9">TRIAD submission time point =

RT DIGITAL PLAN

Due within 1 week of the start of RT</td></tr>
<tr><td>DICOM RT STRUCTURE</td></tr>
<tr><td>DICOM RT DOSE</td></tr>
<tr><td>DICOM RT PLAN</td></tr>
<tr><td>*DICOM PET (Required when applicable)
*DICOM PET/CT (Required when applicable)
*DICOM MRI (Required when applicable)</td></tr>
<tr><td colspan="2">*All image data sets used for structure delineation must be submitted with RT data (Section 5.2.2).</td></tr>
<tr><td colspan="2">All required structures MUST be labeled per the tables in Sections 5.2.4 and 5.2.5.</td></tr>
<tr><td colspan="2">Upon submission of the Digital Data via TRIAD, complete an online Digital Data Submission Information Form (DDSI)

https://www.irocqa.org/Resources/TRIAD-for-RT-QA</td></tr>
<tr><td colspan="3">NOTE: ALL SIMULATION AND PORTAL FILMS AND OR DIGITAL FILM IMAGES WILL BE KEPT BY THE INSTITUTION AND ONLY SUBMITTED IF REQUESTED.</td></tr>
</table>

13.3 Data Quality Portal (21-AUG-2023)

The Data Quality Portal (DQP) provides a central location for site staff to manage unanswered queries and form delinquencies, monitor data quality and timeliness, generate reports, and review metrics.

The DQP is located on the CTSU members' website under Data Management. The Rave Home section displays a table providing summary counts of Total Delinquencies and Total Queries. DQP Queries, DQP Delinquent Forms and the DQP Reports modules are available to access details and reports of unanswered queries, delinquent forms, forms with current status, and timeliness reports. Site staff should review the DQP modules on a regular basis to manage specified queries and delinquent forms.

The DQP is accessible by site staff who are rostered to a site and have access to the CTSU website. Staff who have Rave study access can access the Rave study data via direct links available in the DQP modules.

CTSU Delinquency Notification emails are sent to primary contacts at sites twice a month. These notifications serve as alerts that queries and/or delinquent forms require site review, providing a summary count of queries and delinquent forms for each Rave study that a site is participating in. Additional site staff can subscribe and unsubscribe to these notifications using the CTSU Report and Information Subscription Portal on the CTSU members' website.

To learn more about DQP use and access, click on the Help icon displayed on the Rave Home, DQP Queries, and DQP Delinquent Forms modules.

13.4 Global Reporting/Monitoring (04-NOV-2020)

Data for this study will be submitted via the Data Mapping Utility (DMU). Cumulative protocol- and patient-specific data will be submitted weekly to CTEP electronically via the DMU. DMU Light reporting consists of Patient Demographics, On/Off Treatment Status, Abbreviated Treatment and Course information, and Adverse Events as applicable. Instructions for setting up and submitting data via DMU are available on the CTEP Website: https://ctep.cancer.gov/protocolDevelopment/dmu.htm.

Note: All adverse events (both routine and serious) that meet the protocol mandatory reporting requirements must be reported via DMU in addition to expedited reporting of serious adverse events via CTEP-AERS.

14. STATISTICAL CONSIDERATIONS

14.1 Study Design (19-APR-2023)

This is a prospective randomized phase II/III trial comparing the standard of care (70 Gy over 6 weeks plus concurrent high-dose cisplatin) to two experimental arms: reduced-dose RT (60 Gy over 6 weeks) plus concurrent high-dose cisplatin (Arm 2) and reduced-dose RT (60 Gy over 5 weeks) plus concurrent nivolumab (Arm 3). Patients will be stratified by Zubrod performance status (0 vs. 1) and then randomized to one of the arms in a 1:1:1 ratio. **Arm 2 was dropped after an interim futility analysis in phase II. The randomization ratio for Arms 1 and 3 is 1:1.** The experimental arm(s) found to be non-inferior in terms of PFS in phase II will continue in a phase III comparison against the control, with co-primary hierarchical endpoints of non-inferiority for PFS and superiority for QOL. A QOL interim futility analysis will be conducted at the time of phase II primary endpoint to determine whether to proceed to phase III. Patients enrolled in phase II will contribute to the phase III target accrual.

14.2 Study Endpoints (04-NOV-2020)

14.2.1 Primary endpoints:

- Phase II:
  - Progression-free survival
- Phase III:
  - Progression-free survival
  - Quality of life, as measured by the MDADI global QOL score

14.2.2 Secondary endpoints:

- Locoregional failure
- Distant failure
- Overall survival
- Toxicity, as measured by the CTCAE and PRO-CTCAE
- Hearing, as measured by the HHIA-S
- Quality of life, as measured by the EORTC QLQ-C30
- Association of baseline FDG-PET/CT locoregional control and PFS
- Negative predictive value of post-RT FDG-PET/CT for locoregional control and PFS at 1 and 2 years

14.2.3 Exploratory endpoints:

- Quality of life, as measured by EQ-5D-5L
- Swallowing physiology, as measured by a Modified Barium Swallow (MBS) test

14.3 Primary Objectives Study Design (19-APR-2023)

14.3.1 Primary Hypothesis and Endpoints

For patients with early-stage, p16-positive oropharyngeal cancer with a smoking history of ≤ 10 pack-years, reduced-dose radiation therapy given with either concurrent cisplatin or concurrent nivolumab is non-inferior to the current standard of care in terms of progression-free survival (PFS) in Phase II. In phase III, experimental arm(s) shown to have non-inferior PFS as compared to the standard arm is hypothesized to have superior QOL, as measured by the MDADI global QOL score.

REVISED: For patients with early-stage, p16-positive oropharyngeal cancer with a smoking history of ≤ 10 pack-years, reduced-dose radiation therapy given with nivolumab is non-inferior to the current standard of care in terms of progression-free survival (PFS) in Phase II. In phase III, reduced-dose radiation therapy given with nivolumab shown to have non-inferior PFS as compared to the standard arm is hypothesized to have superior QOL, as measured by the MDADI global QOL score.

14.3.2 How Primary Endpoints Will Be Analyzed

Like in its predecessor NRG-HN002 trial, progression-free survival (PFS) is defined as from time of randomization to local- regional failure, distant metastasis, or deaths due to any causes. The following are considered a PFS failure: local-regional progression or recurrence, distant metastasis, death due to study cancer or unknown causes, death due to any other reason, salvage surgery of primary with tumor present/unknown, salvage neck dissection with tumor present/unknown, > 20 weeks from end of RT (PFS failures are listed in table in Section 14.6.1). Patients without a PFS failure at the time of the analysis will be censored at the last follow-up.

PFS rates will be estimated for all treatment arms using the Kaplan-Meier method (1958). The primary phase IIR and co-primary phase III endpoint will be tested using a confidence interval (CI) approach. The null hypothesis for each comparison in phase II will be rejected if the 90% upper confidence limit excludes the HR=2.4. Similarly, the null hypothesis for each comparison in phase III will be rejected if the 95% upper confidence limit excludes the HR=1.75. Multivariate analysis will be performed using the Cox proportional hazards model.

Quality of life scores for the phase III co-primary endpoint, will be compared between arms using a two-sample independent t-test at a one-sided significance level of 0.05 for each experimental arm comparison. MDADI global score and change from baseline will be summarized using mean and standard deviation at each time point for each arm. Missing data will be assessed and appropriate analysis techniques will be used according to the missing data mechanism as further described in Section 14.6.2.

The table below outlines the decision algorithm.

Phase II PFS result	**Phase II QOL futility analysis result**	**Phase III trial**
Both experimental arms are non-inferior to the control arm	Did not cross futility boundary	3 arm trial with 2 experimental arms
Both experimental arms are non-inferior to the control arm	One experimental arm did not cross the futility boundary and one experimental arm did cross the futility boundary	2 arm trial with 1 experimental arm that did not cross the futility boundary
Both experimental arms are non-inferior to the control arm	Both experimental arms crossed the futility boundary	No phase III trial
Only one	This experimental arm did not cross	2 arm trial with 1

experimental arm is non-inferior to the control arm	the futility boundary	experimental arm
Only one experimental arm is non-inferior to the control arm	This experimental arm crossed the futility boundary	No phase III trial
Both experimental arms are inferior to the control arm	N/A	No phase III trial

A decision regarding both experimental arms in phase II must be made prior to opening to phase III.

In phase III, the experimental arms will first be compared to the standard arm in terms of PFS. If the experimental arm(s) is found to be non-inferior, then the MDADI global QOL score change from baseline to 1 year will be compared between the experimental arm(s) and the standard arm. If only 1 experimental arm is shown to have non-inferior PFS and superior QOL, then that arm is the winner. If both experimental arms meet these thresholds, then the experimental arms will be compared first with respect to PFS and then with respect to MDADI global QOL score in order to determine which is superior. If no difference exists between the experimental arms, then experimental arms will be compared with respect to toxicity and other QOL measures.

14.3.3 Sample Size and Power Calculations:

Phase II
The estimated 9 month PFS for this population is 96.5% based on the eligible population of patients on the RT + cisplatin arm of RTOG 1016 (n=179 patients). A lower threshold of the 9 month PFS rate that is considered acceptable is 91.8% which is based on the eligible population of patients on both arms in RTOG 0129 (n=61) which results in a non-inferiority margin of 4.7%. Under the null hypothesis, the hazard ratio is 2.4 while under the alternative hypothesis the hazard ratio is 1.0. With one-sided type I error rate of 10% (20% after Bonferroni adjustment for each experimental arm comparison), 80% power, 24 months of accrual (rate of 10 patients/month per comparison) with 1 year of additional follow-up, and 1% increasing yearly rate of drop-out up to 3%, a log rank test requires 22 events from 266 patients per comparison resulting in 133 patients per arm (399 patients in total).

Arm 2 was dropped after an interim futility analysis in phase II. The original phase II sample size calculations remain unchanged due to the Bonferroni adjustment for each comparison versus the control arm. For clarity, the phase II accrual target for Arms 1 and 3 is 266 randomized patients.

Phase III
The study will be on hold to analyze the phase II PFS endpoint and be reopened once PFS non-inferiority is established in at least 1 experimental arm. The co-primary endpoints of PFS and QOL will be assessed in a hierarchical manner with PFS being assessed first. If PFS is found to be non-inferior for the experimental arm(s), the QOL of the experimental arm(s) will be

compared to that of the control arm. The estimated 2 year PFS for this population is 92.3% based on the eligible population of patients on the RT + cisplatin arm of RTOG 1016. A lower threshold of the 2-year PFS rate that is considered acceptable is 86.9% which is based on the eligible population of patients on both arms in RTOG 0129 which results in a non-inferiority margin of 5.4%. Under the null hypothesis, the hazard ratio is 1.75 while under the alternative hypothesis the hazard ratio is 1.0. A smaller hazard ratio, as compared to the phase IIR, is desired due to the definitive nature of this phase III trial. With one-sided type I error rate of 5%, 80% power, and 1% increasing yearly rate of drop-out up to 5%, a log rank test requires 79 events from 237 patients/arm.

Effective with Amendment 3: Given that the actual accrual rate in the trial prior to Amendment 3 is about 10 patients/month (same accrual rate for a comparison vs the control arm with the original design), if Arm 3 moves forward, 474 patients will be randomized in about 21 months from activation of phase III portion. After accrual completion, patients will be followed for additional 2.7 years for phase III primary endpoint completion (Arms 1 vs 3). Patients enrolled on phase II will contribute to the phase III target accrual resulting in 104 patients/arm to be enrolled when phase III opens to accrual.

Additional phase III design details prior to Amendment 3: If only 1 experimental arm moves forward, 474 patients will be enrolled at a rate of 15 patients/month (10 patients/month during phase II accrual) with 3.25 years of additional follow-up. If both experimental arms move to the phase III, the overall type I error rate will be 10% after a Bonferroni correction and 711 patients will be enrolled at a rate of 10 patients/comparison (5 patients/month in the standard arm and 5 patients/month in each experimental arm) with 2.7 years of additional follow-up. Patients enrolled on phase II will contribute to the phase III target accrual resulting in 104 patients/arm to be enrolled when phase III opens to accrual.

The change from baseline to 1 year in global MDADI score will be assessed once PFS non-inferiority is established. Change in global MDADI score will be assessed only if the experimental Arm 3 is shown to be non-inferior. Using data from NRG-HN002, a change score of -5 with a standard deviation of 22 will be assumed for the experimental arm(s). Since some non-compliance is expected, the projected number of evaluable patients per comparison is 378, which assumes a 20% rate of non-compliance. As reported by Ringash et al (2017), a change score of -11 will be used for the control arm which results in an effect size of 0.27. A two-sample t-test with a one-sided type I error of 5% and 1 interim look will provide 82.7% statistical power to detect a difference from -11 to -5 in 378 patients (for a two-arm comparison).

Note: Arm 2 was dropped after interim futility analysis in phase II. Please see the sample sizes for phases II and III with arms 1 and 3 after Amendment 3 in Table 3; 116 patients were already randomized to Arm 2 in phase II.

Tables 1 and 2 below provide the number of randomized patients if one or both experimental arms move to phase III.

Table 1. Number of randomized patients if **both experimental arms** move to phase III

	Phase II	Phase III	Phase II/III
Arm 1 (Control)	133	104	237
Arm 2	133	104	237
Arm 3	133	104	237
Total	*399*	*312*	*711*

Table 2. Number of randomized patients if **one experimental arm** move to phase III

	Phase II	Phase III	Phase II/III
Arm 1 (Control)	133	104	237
Arm 2	133	104*	237*
Arm 3	133		
Total	*399*	*208*	*607*

*If one experimental arm (2 or 3) moves to phase III

Table 3. Accrual target (number of randomized patients) for phases II and III with Arms 1 and 3 effective with Amendment 3

	Phase II	Phase III	Phase II/III
Arm 1 (Control)	133	104	237
Arm 3	133	104	237
Total	*266*	*208*	*474*

14.4 Study Monitoring of Primary Objectives

Interim reports will be prepared twice each year until the final analysis has been accepted for presentation or publication. These reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates, pretreatment characteristics of patients accrued, and the frequency and severity of adverse events.

Monitoring of MDADI Compliance

Completion rates of the MDADI will be monitored monthly. Since not all patients will have 1 year MDADI data by the time the study closes to accrual, the end of RT, 6 months and 1 year time points will be used to monitor compliance (noting that the 2 year time point will also be monitored). If the MDADI non-compliance rate is ≥ 20% at any of these time points, the study PI and QOL co-chair will work in collaboration with the NRG Oncology Statistics and Data Management Center to contact sites and RAs with delinquent data, assessments completed too early or too late, and assessments not completed due to institution errors. If the MDADI non-compliance rate is > 30% at any of these time points, the study will be presented to the NRG Oncology Data Monitoring Committee (DMC) for reassessment of feasibility or change in study design.

Interim Analysis

The phase IIR will have an early interim analysis to assess futility once 50% of the events (11/22) have occurred. This is projected to occur approximately at the time of study closure.

There will be a futility interim analysis during the phase III trial as well. This will occur once 50% of the events (40/79) have occurred. If the observed HR at either of these looks is equal to or worse than the non-inferiority margin, the study statistician will recommend to the DMC that the trial should be terminated for futility (Korn 2018).

At the time of the projected phase II final analysis, an interim futility analysis for the phase III QOL primary endpoint will occur. It is projected that 51% of patients (approximately 96 patients per arm) will contribute to the analysis at this time. The phase II primary endpoint analysis is projected to occur approximately 1 year from study closure which is also the required length of follow-up required for the QOL interim analysis. The O'Brien & Fleming boundary will be used to assess futility for the MDADI global QOL 1 year change score. The table below specifies the boundary.

MDADI Global QOL Futility Bound				
Analysis	Sample size per arm	Cumulative β spent	Futility Boundary (|z scale|)	Futility Boundary (|δ|)
Interim	96	0.057	0.311	0.986
Final	189	0.173	1.645	3.722

Interim Analysis for the DMC
The NRG Oncology DMC will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

14.5 Accrual/Study Duration Considerations (19-APR-2023)

NRG/RTOG 1016 enrolled 15 patients/month and HN002 accrued 16.2 patients/month in the last 6 months of accrual. Therefore, a rate of 15 patients/month will be expected on this trial. After a ramp-up period of 6 months with no expected enrollment, it will take approximately 2.7 years for 382 patients to be enrolled in the randomized phase II. If granted, an additional 1.8 years of accrual will complete the randomized phase III (474 randomized patients with Arms 1 and 3) after a hold of approximately 1 year to analyze the phase II.

14.6 Secondary Endpoints (including correlative science aims) (19-APR-2023)

14.6.1 Secondary Hypotheses and Endpoints:

- Phase II/III:
  - Locoregional failure
    Hypothesis: The rate of locoregional failure will be similar between arms.
  - Distant failure
    Hypothesis: The rate of distant failure will be similar between arms.
  - Overall survival
    Hypothesis: The survival rate will be similar between arms.
  - Toxicity, as measured by the CTCAE and PRO-CTCAE
    Hypothesis: The experimental arms will experience less toxicity than the control arm.
  - Hearing, as measured by the HHIA-S
    Hypothesis: Hearing will be affected more on the control arm as compared to the

experimental arms.

- Quality of life, as measured by the EORTC QLQ-C30
  Hypothesis: Worsening in quality of life will be less in the experimental arms than the control arm.
- Association of baseline FDG-PET/CT for locoregional control and PFS
  Hypothesis: Baseline FDG-PET/CT will be associated with locoregional control and PFS.

14.6.2 Definitions of Secondary Endpoints and How These Will Be Analyzed

Time-to-Event Endpoints

Overall survival (OS) will be measured from the date of randomization to the date of death or last known follow-up date, with patients alive at the last known follow-up time treated as censored. OS will be estimated using the Kaplan-Meier method and treatment arms compared using the log-rank test (Kaplan 1958).

All other secondary time to event endpoints have precluding events that act as competing risks. Failure events and competing risks for local-regional and distant metastasis failure endpoints is outlined in the table below.

First event	**Progression-Free Survival**	**Local-regional failure**	**Distant metastasis**
None	Censored	Censored	Censored
Local-regional progression or recurrence	Failure	Failure	Competing risk
Distant metastasis	Failure	Competing risk	Failure
Death due to study cancer or unknown causes	Failure	Failure	Competing risk
Death due to any other reason	Failure	Competing risk	Competing risk
Salvage surgery of primary with tumor present/unknown	Failure	Failure	Competing risk
Salvage neck dissection with tumor present/unknown, > 20 weeks from end of RT	Failure	Failure	Competing risk

Time to locoregional failure will be measured from the time of randomization to the date of failure, date of precluding event, or last known follow-up date. Time to distant metastasis will similarly be measured from the time of randomization to the date of distant metastasis, date of precluding event, or last known follow-up date. Definitions of locoregional and distant failure are provided in Section 4. The cumulative incidence estimator will be used to estimate time to event distributions for locoregional failure and distant metastasis with between arm differences tested using cause-specific log-rank test.

For all efficacy endpoints, Cox proportional hazards models will be used to determine hazard ratios (cause-specific hazard ratios in the case of endpoints with competing risks) and to assess the effects of covariates of interest, such as age, race, ethnicity, T stage, and ECOG performance

status on outcomes (Cox 1972). The Fine-Gray subdistribution hazards model may be applied to further explore outcomes by treatment arm and other covariates for endpoints with competing risks (Fine and Gray 1999).

All efficacy endpoints will be reported at the time of the primary endpoint analysis. A two-sided significance level of 0.05 will be used to determine significance for these secondary endpoints. The long-term analysis will be performed after initial reporting, if warranted, for the PFS and OS endpoints.

Toxicity
Adverse events (AEs) will be graded using CTCAE v5.0. Counts of all AEs by grade will be provided by treatment arm. Counts and frequencies will be provided for the worst grade AE experienced by the patient by treatment arm. The number of patients with at least 1 grade 3 or higher AE will be compared between the treatment arms. A comparison between treatment arms of grade 3 and higher AEs related to treatment will also be tested. There is a list of pre-specified AEs in the table in Section 7.4.1. A comparison of grade 3 and higher events will be compared between treatment arms. All comparisons will be tested using a Chi-Square test, or Fisher's exact test if cell frequencies are < 5, with a significance level of 0.05.

Adverse events will also be assessed using PRO-CTCAE items. The specific symptoms to be evaluated for this study are listed in the table in Section 7.5. Assessments will be collected before the start of radiotherapy treatment and as specified in the Section 4 assessment tables. For each symptom, counts and frequencies will be provided for the worst score experienced by the patient by treatment arm. The proportion of patients with scores ≥ 1 and ≥ 3 will be compared between groups using a Chi-square test, or Fisher's exact test if cell frequencies are < 5, using a significance level of 0.05. Analysis of changes in patient reported outcomes over time will analyzed by fitting GEE models using a logit link (dichotomizing the symptom scores as 0 vs. > 1 and 0-2 vs. 3-4) with time of assessment, treatment arm, and treatment-by-time interaction terms in the model.

All toxicity analyses will be conducted at the time of the primary endpoint analysis. Additional toxicity analyses will be conducted during the time of the long-term analysis to assess late effects of RT.

Patient-Reported Outcomes (PROs)
The EORTC QLQ-C30, MDADI, and HHIA-S are collected at baseline, end of RT, 12 weeks from end of RT, 6, 12, and 24 months.

There are several scores that will be assessed from the EORTC QLQ-C30: global health status (higher score represents high QOL), functional scales (high score represents higher level of functioning), and symptom scales excluding dyspnea and financial difficulties (high score represents high level of symptoms). The MDADI has 4 scores, all with higher scores indicating better QOL/functioning: a global QOL question and function, emotional, and physical subscale scores. The overall score (higher scores indicates handicap) will be assessed from the HHIA-S.

For all scores, change from baseline will be summarized using mean and standard deviation at the end of RT, 12 weeks from the end of RT, 6, 12, and 24 months. A longitudinal analysis incorporating the baseline, end of RT, 12 weeks, 6, 12, and 24 month time points will be conducted separately for the HHIA-S overall score, EORTC QLQ-C30 global QOL, functional and symptom scale scores, and MDADI global QOL, emotional, functional and physical scale scores using mixed effects models with the effect of time, treatment and its interaction. Adjustment for additional covariates such as race, and other clinical variables will be done if it is deemed necessary based on missing data patterns. The treatment by time interaction will be of primary interest. Due to the multiple tests involving treatment by time interaction terms across tools and scales, a Hochberg's multiplicity adjustment will be made when testing these eight hypotheses (Hochberg 1988): HHIA-S (overall score), MDADI (global QOL, emotional, functional and physical scales), and the EORTC (global QOL, functional and symptom scales). If individual tests for change from baseline scores between arms for specific time points are further required, the adjusted alpha from the Hochberg's multiplicity procedure leading to the rejection of the interaction hypotheses will be used.

Prior to performing analyses, an evaluation of the amount, reasons and patterns of missing data will be performed, using the well-known categories of missing completely at random (MCAR), missing at random (MAR) and missing not at random (MNAR) (Fairclough 2010, Verbeke 2000). If $\geq$ 15% of the data is missing at any time point for the PROs, patient characteristics will be compared between patients with completed assessments and those with missing assessments. If any are found to differ significantly, they will be included in the mixed effects model, which assumes that the data is MAR. If the missingness is determined to be non-ignorable, other methods may be applied. Specifically, a joint model that allows a shared parameter between the repeated measurements and time to death or drop out can be used if considered MNAR due to the high number of patient deaths or dropouts (Rizopoulos 2012). Other options for MNAR data are pattern mixture and selection models (Fairclough 2010, Little 1995). Sensitivity analyses will be performed to compare the results of different analytic strategies (Fairclough 1998).

All QOL analyses will be conducted at the time of the primary endpoint analysis. For patients on an arm not moving to phase III, phase II patients will be analyzed.

Association of Baseline FDG-PET/CT Imaging with Locoregional Control and PFS

The association between baseline FDG-PET/CT and locoregional failure/PFS will be assessed using (cause-specific) Cox proportional hazards models (unadjusted and adjusted by key covariates including the stratification factor; 0.05 two-sided alpha). In phase III, it is projected that approximately 75% of patients (~355) will have a FDG-PET/CT at baseline (i.e., approximately 59 PFS events available for analysis). Based on NRG-HN002 data, about 75-80%, 11-12% , and 8-14% are expected to have a negative, positive, and indeterminate read, respectively (see definitions of a negative, indeterminate, and positive FDG-PET/CT read in Section 11.1.2). The table below shows the statistical power to detect an HR for the FDG-PET/CT of 2.5. For instance, if 20% of patients have a positive FDG-PET/CT, then a Cox model will have at least a 81% power to detect such an effect.

% of patients with positive PET/CT at baseline	Power
20%	81%
15%	71%
10%	56%

Indeterminate cases in both PET/CT analyses will be removed from this analysis, however if the rate of indeterminate scans > 10% then sensitivity analyses for both outcome variables will be conducted assuming all are positive and all are negative. This analysis will be conducted at the time of the PFS and locoregional failure analyses.

Negative Predictive Value (NPV) of 12-14 Weeks Post-RT FDG-PET/CT vs. Locoregional Control and PFS

Based on data from NRG-HN002, about 35% of the patients will have a 12-14 week post-RT FDG-PET/CT. The expected number of patients with 12-14 weeks post-RT FDG-PET/CT are listed in the table below. About 65% of the FDG-PET/CT's are expected to come from patients enrolled in the phase II.

	Number of enrolled patients	Expected number of patients with FDG-PET/CT at 12-14 weeks post-RT
Phase II	382	134
Phase III with 2 arms	208*	73
Phase II/III with 2 arms in phase III	590**	207

*Additional number of patients enrolled in phase III portion (Arms 1 and 3).

** It includes 382 patients randomized in phase II (Arms 1, 2, and 3) and 208 additional patients randomized in phase III (Arms 1 and 3).

At 12-14 weeks post-RT, it is projected that approximately 98% will be negative and, 2% positive for residual tumor based on NRG-HN002. The negative predictive value (NPV) of FDG-PET/CT for 1-yr and 2-yr locoregional control, and PFS will be estimated using binomial proportions and confidence intervals (CI) based on normal approximation. A negative result in the computation of the NPV refers to the absence of a PFS event or a locoregional failure at the specified time points. From the table above, about 202 patients are expected with negative FDG-PET/CT at 12-14 weeks post-RT in the phase III trial with two arms. The half-widths of the 90% CIs when the true NPV is equal to 80%, 85%, 90% and 95% are 4.6%, 4.1%, 3.4%, and 2.5%, respectively. These true NPV's cover potential values for locoregional control and PFS rates at 1 and 2 years.

14.7 Exploratory Endpoints (04-NOV-2020)

14.7.1 Definitions of Exploratory Endpoints and How These Will Be Analyzed

Cost effectiveness

The EQ-5D-5L is collected at baseline, end of RT, 12 weeks from end of RT, 6, 12, and 24 months. The VAS and index scores will be assessed with higher scores indicating better QOL. Missing data will be assessed as described in Section 14.6.2. The change from baseline will be calculated at the end of RT, 12 weeks from end of RT, 6, 12, and 24 months and compared between arms using a t-test. A longitudinal analysis incorporating the end of RT, 12 weeks from end of RT, 6,

12, and 24 month time points will be conducted for the EQ-5D index score using mixed effects models, adjusting for baseline score and treatment arm. A treatment by time interaction will also be assessed in each model.

The following analysis will only be conducted if the nivolumab arm is shown to be non-inferior to the control arm for PFS and has at least 1 significant difference in index change score. Quality-adjusted life years (QALYs) is defined by the weighted sum of different time episodes added up to a total quality-adjusted survival time. A Markov model will be used to model cost for this analysis. The Medicare reimbursement in dollars/QALY will be calculated as a function of the monetary cost per relative value of each health state and its duration. The EQ-5D-5L index score at end of RT, 12 weeks from end of RT, 6, 12, and 24 months will be used for the cost-utility analysis. The z-test will be used to test the hypothesis that the cost-utility in the two treatment arms is the same with significance level of 0.05. The cost-utility using the Medicare reimbursement in dollars/QALY will be compared between the two treatment arms after adjusting for baseline variables.

Swallowing

The determination of aspiration (yes vs. no) will be assessed by sites as a SOC exam. Therefore, the proportion of aspiration (yes) for each arm will be estimated assuming a binomial distribution and between arm comparison will be performed using a Fisher's exact test.

14.8 Gender/Ethnicity/Race Distribution (19-APR-2023)

The following distribution is based on the accrual target of 590 randomized patients, which includes 116 already randomized to Arm 2 (arm dropped in phase II) and 474 randomized patients in Arms 1 and 3 (266 in phase II + 208 in phase III portion).

Racial Categories	DOMESTIC PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	1	4	0	0	5
Asian	2	12	0	0	14
Native Hawaiian or Other Pacific Islander	1	4	0	0	5
Black or African American	2	12	0	1	15
White	83	322	5	18	428
More Than One Race	1	4	0	0	5
Total	90	358	5	19	472

Racial Categories	INTERNATIONAL (including Canadian participants) PLANNED ENROLLMENT REPORT				
	Ethnic Categories				
	Not Hispanic or Latino		Hispanic or Latino		Total
	Female	Male	Female	Male	
American Indian/Alaska Native	0	0	0	0	0
Asian	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0	0	0
Black or African American	1	2	0	0	3
White	22	90	0	1	113
More Than One Race	0	2	0	0	2
Total	23	94	0	1	118

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APPENDIX I: Medidata Patient Cloud ePRO Operational Instructions

1.1 Introduction

Electronic collection of patient-reported outcomes (ePRO) through Medidata Patient Cloud ePRO is preferred but not mandatory. Traditional paper submission is the other option. Patients who will be submitting PRO data via Patient Cloud ePRO must be registered to Patient Cloud ePRO by an authorized site user after the patient has been registered to the study. Patients may use their own device or one provisioned by the site.

Sites can use a site-specific tablet for multiple study participants. If a site-specific tablet is used, CRAs need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log in to Patient Cloud ePRO with their passwords or their PIN codes on the same device.

1.2 ePRO Application Download

Note that there are multiple versions of the Medidata Patient Cloud ePRO Application. Patients should be instructed to download the version chosen by the study team for the protocol. The patient will receive an error if the wrong version is downloaded.

Patient Cloud ePRO

Patient Cloud

1.3 CRA Site Users

Site users of Patient Cloud ePRO require the same access as Rave. Access to the trial in the Patient Cloud ePRO is granted through the iMedidata. Site users will receive an invitation to Patient Cloud application and the site user must accept the invitation to begin patient registration. Users who have not previously activated their iMedidata/Rave account at the time of initial approval of site registration will also receive a separate invitation from iMedidata to activate their account. Account activation instructions are located on the CTSU website, Rave tab under the Rave resource materials (Medidata Account Activation and Study Invitation Acceptance). Please note, site users will not be able to access the study in the Patient Cloud application until all required Rave and study specific trainings are completed.

Additional information on iMedidata/Rave is available on the CTSU members' website under the Rave tab at www.ctsu.org/RAVE/ or by contacting the CTSU Help Desk at 1-888-823-5923 or by e-mail at ctsucontact@westat.com.

1.4 CRA Instructions for Setting the Patient Cloud App to Multi-User Mode

Sites conducting studies entirely on-premise, where participants travel to the sites to fill out questionnaires, can use multi-user mode. Multi-user mode lets multiple study participants log in to Patient Cloud with their passwords or their PIN codes on the same device. If patients will be using devices supplied by the institution, site staff will need to help the patient to access the device if the device is locked.

The study provider will download the Patient Cloud app to the device and set the Patient Cloud ePRO App to multi-user mode if applicable. **Verify the correct version is downloaded per the study build requirements. Note only 1 version of the app is active per protocol.
To switch from personal mode (default setting) to multi-user mode:

1. Tap **About** at the bottom of the log in screen.
2. Scroll to the bottom and tap **Advanced User**.
3. Tap **Mode**, then select **Multi-User**.
4. Tap **Yes** to confirm.
5. Tap the back arrows to return to the log in screen.

Note: If enabling multi-user mode on a device, it is highly recommended that completion reminders are turned off on that device.

For a video demonstration, see Show Me How to Switch to Multi-User Mode.

1.5 Patient Users

To use the Patient Cloud application, patients will need to use their own device (IOS, Android phone or tablet). Short term data will only appear on the patient's device until responses are completed and submitted. The patient data will import directly into the database once the patient selects the "Submit" button and will no longer be visible on the patient's device.

Sites can provide a site-specific tablet for multiple study participant use on site. If a site-specific tablet is used, study staff need to setup the tablet for multiple users. Multi-user mode lets multiple study participants log into Patient Cloud ePRO with their passwords or their PIN codes on the same device. **Refer to Appendix E on Setting the Patient Cloud App to Multi-User Mode.**

1.6 Patient Instructions for Accessing the Patient Cloud Using Your Personal Device

Downloading the Patient Cloud ePRO App
If you are using your personal device, and you do not have the Patient Cloud app, use the following instructions. When downloading the app, you must use the Apple ID or Google account associated with the device. If the Patient Cloud app is already on the device, or if you are using a provider's device, you can skip this section. There are multiple versions of the app available. Ensure that the correct version of the ePRO app is downloaded by the patient.

You will need an email address that you agree to use for this purpose. The e-mail address is needed to identify you on the Patient Cloud Application and for you to receive notifications to let you know when forms are due. Your e-mail address will only be used for this survey study, and will not be used for mail or marketing purposes.

If you decide to use the electronic method to complete the questionnaires, and do not have an e-

mail address, you may sign up for one at no charge at many different websites. A few sites that are commonly used and will allow you to create an email address very easily are Yahoo, Gmail, and Outlook.

For iOS:

1. An Apple ID is required for downloading the Patient Cloud app.
2. Tap the *App Store* icon.
3. Search for the appropriate Medidata Patient Cloud ePRO application and follow the installation instructions.

Note: Patient Cloud is listed as an iPhone App in the App store. When using an iPad, please view the search results under iPhone apps.

For Android:

1. A Google account is required for downloading the Patient Cloud app
2. Tap the *Play Store* icon.
3. Search for the appropriate Medidata Patient Cloud ePRO application and follow the installation instructions.

Registering

You must register in order to complete and submit your study forms. When you register, you will create a username, which is your email address, and a password that allows you to log in to the Patient Cloud ePRO app.

Note**:** You must have an activation code to begin this process. If you do not have an activation code, please contact your provider.

There are two possible ways to register. Your provider may have sent you a link to a web address where you may register from any web browser, including the one on your device. The other way to register is on the Patient Cloud app.

1. If registering from the Patient Cloud app, tap Register on the bottom of the log in page. If registering on the web, open the URL shield.imedidata.com on a web browser.
2. Enter your activation code and tap Activate.
3. On the next page, read the instructions and tap Next.
4. Read the privacy notice and tap I agree. Then tap OK to confirm.
5. Enter and confirm your email address. Tap Next.
6. Enter and confirm your password. Tap Next.
7. Choose a security question by scrolling through the dropdown menu to display the question of your choice.
8. Enter your security question response.
9. Tap Create my account to complete your registration.

If you registered on the Patient Cloud app, it automatically logs you out. If you registered on the

web, you are presented with the option to download the Patient Cloud app. You can then proceed to log in with the credentials you created.

Logging in to the App

1. Enter your Email and Password that you created during the registration process. (If you previously set a PIN code, just enter your four-digit PIN.)
2. Tap Log in.

Note: If you do not remember your password, tap **Forgot Password**, and follow the instructions provided.

Setting a PIN Code

The first time you log in to the Patient Cloud app, you are given the option to create a PIN code. A PIN code allows you to bypass the step of entering your email and password every time you need to log in to the Patient Cloud app. Instead, you can enter a four-digit PIN.

1. If you wish to set a PIN code the first time you log in, tap Yes when prompted.
2. Note: You can also set your PIN at a later time by tapping the options menu on the top left of most pages and selecting Set PIN.
3. Enter a four-digit PIN.
4. Re-enter the four-digit PIN to confirm.

If you forget your PIN code, tap **Forgot PIN** and you can access the app using your email and password. You may reset your PIN by tapping the options menu on the top left of most pages and selecting Set PIN.

Resetting Your Password

You can reset your password by using the options menu at the top left of most pages.

1. Tap the options menu icon.
2. Tap Reset Password.
3. Follow the instructions to reset your password.

Completing and Submitting Forms

Once logged in, forms related to your study display on the Tasks page. If you are enrolled in multiple studies, select the appropriate study first, and then select a form. New forms can appear on the Tasks page at any time, depending on how the study is designed.

There are two types of forms displayed on the Task List page:

- *Scheduled Forms* (with a  icon): These forms have a "Due Date" indicator in them so you are aware of the last day by which you will need to complete the form. If the form is due in less than one day, you will see the due time in hours.

- *Anytime Forms* (with a + icon): These forms have "Last Completed Time" indicator on them which tells the most recent date or time when you completed the form. If you start a form, but do not complete it, you will see an 'Incomplete" status beneath the form name, along with a half-moon icon.

To complete and submit form(s):

1. Select the appropriate form.
2. Follow the on-screen instructions until you reach the end of the form where you are given the opportunity to review and change your responses prior to submitting.
3. Review your responses by scrolling down the list.
4. If you need to change an answer, tap the question to go back and change the answer.
5. When you are ready to submit, tap Submit Your Data.

Note: Once a form is submitted, you will be unable to edit any of your responses. In some cases, you may be asked to acknowledge your submission by entering your password.

1.7 Patient Compliance

The patient data imports directly from a device into the Rave database. There are no documents to audit. The patient-submitted electronic responses are the source documentation.

1.8 Security

All data is encrypted on the device (256 bit encryption and Hyper Text Transfer Protocol Secure [https]) and the app requires each user to have a unique username and password for access. If the user is idle for too long (5 minutes inactivity time), the app will time out and the user will need to log in again.

The data will only reside on the device for a short period of time. Once the user clicks “Submit,” the data is securely transferred over HTTPS between the device and internal relay to the Rave database. Except for the patient's email address, no identifying information is stored in iMedidata. The email address is stored for what purpose? The patient’s email links the device (used) and (ePRO) account to where the data is stored. The patient’s email is not visible to anyone in the system.

The Patient information (email/password) does not reside in Medidata Rave EDC and the patient accounts are hidden in iMedidata from sites and LPOs.

The Patient Cloud application is 21 CFR Part 11 compliant and acts as a gateway between the device and Medidata Clinical Cloud (MCC).

Messages and information communicated to and from the Patient Cloud are encrypted and therefore this information cannot be read if intercepted while in transit.

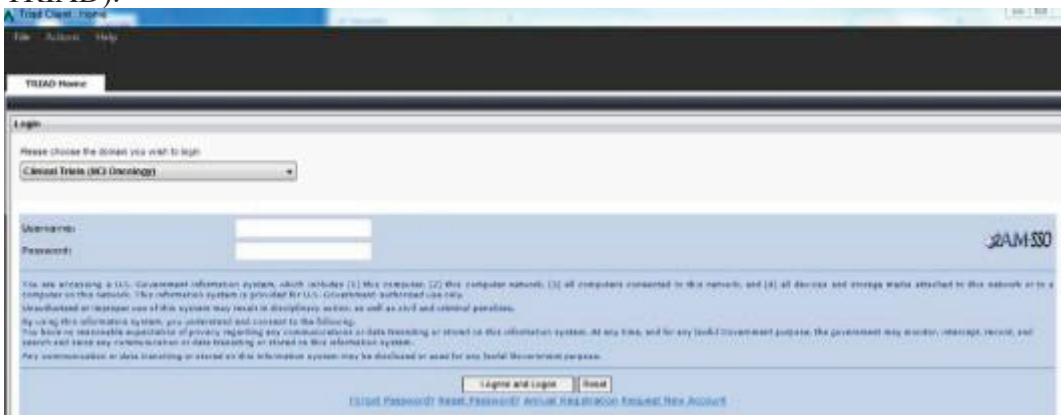
1.9 Site checklist for activities prior to consenting a patient

- ☐ Site staff must have already completed required eLearning for the Patient Cloud ePRO application. See last bullet with hyperlink to training video library. Contact the LPO to request appropriate Rave access to register patients in Patient Cloud ePRO
- ☐ Accept study invitation at iMedidata.com
    - Note: you must be rostered in RSS and have received an invitation to Patient Cloud ePRO
- ☐ Verify the IOS or Android operating system is using the most current version
        - ☐ Verify the correct Patient Cloud app is being used. Note only 1 version of the app is active per protocol.
        - ☐ Include an image of the app icon to document version used per the protocol in the appendix of the protocol.
- ☐ If using institutional shared devices, first patient only: Verify Patient Cloud application is in Multi-User mode
- ☐ Refer to Review Quick Reference Guides for videos and other procedural information

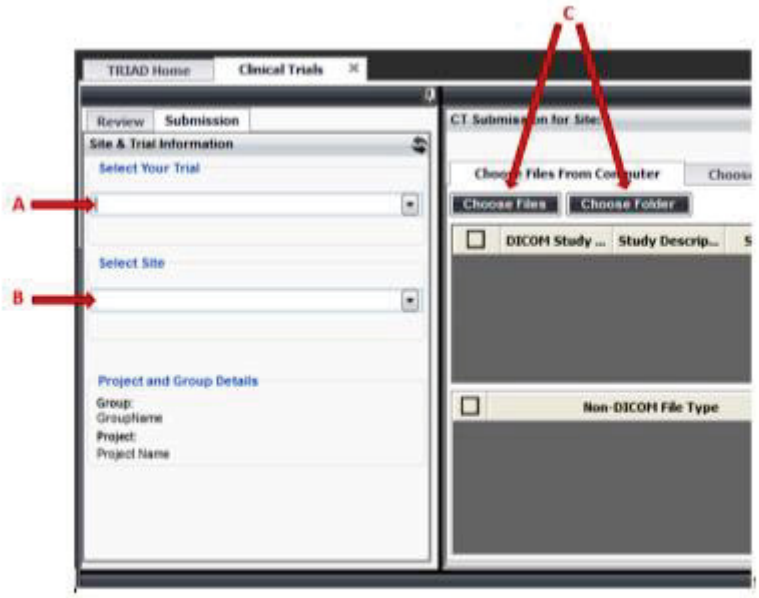
Patient withdraws study consent or withdraws consent from participating on ePRO
CRA must instruct the patients that are participating on ePRO who decide to withdraw consent to delete the App from their smart phones. This will prevent QOL reminders from being sent to the patient.

APPENDIX II: INSTRUCTIONS FOR SUBMISSION OF IMAGES TO TRIAD

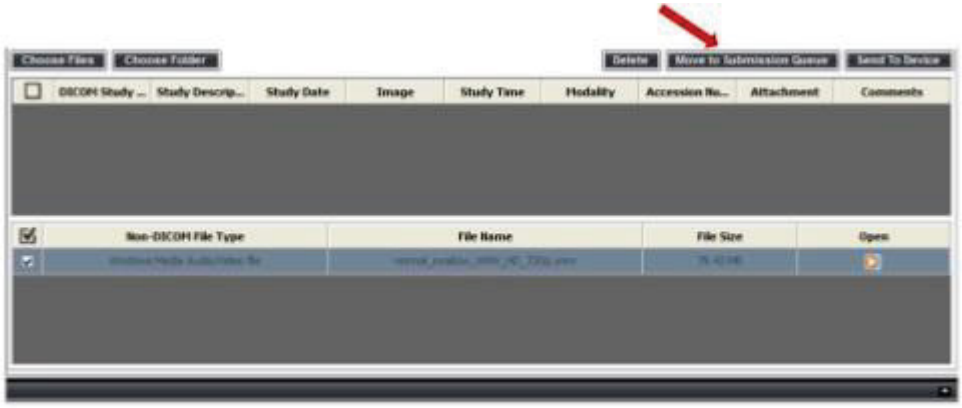
1. Download and install TRIAD 4.13 via https://triadinstall.acr.org/triadclient/
2. Launch TRIAD, click the dropdown to select Clinical Trials (NCI Oncology). Login using your CTEP ID and password (see Section 8 for access requirements for OPEN, Medidata Rave, and TRIAD).



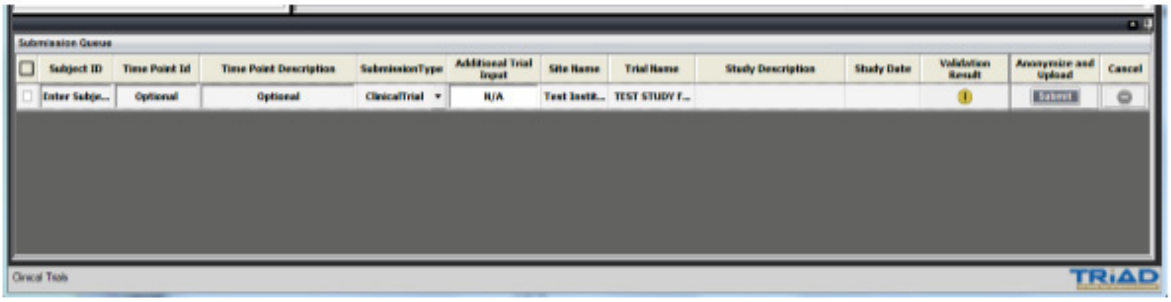
3. To begin file submission: A. Select the HN005 Trial from the Trial dropdown. B. Select your Hospital from the Site dropdown. C. Once these options are selected, select Import Folder (to select a group of video files), or Import Files (to import an individual video file).



4. Your selected file(s) will appear in the preview screen for review. Select Move to Submission Queue to move your files to the submission queue.



5. To complete, enter subject information (Subject ID, Time Point ID, Time Point Description, Submission Type, etc.), then select Submit.



APPENDIX III: Dental Assessment Tooth Count and Dental Management (04-NOV-2020)

Dental Tooth Count Diagram

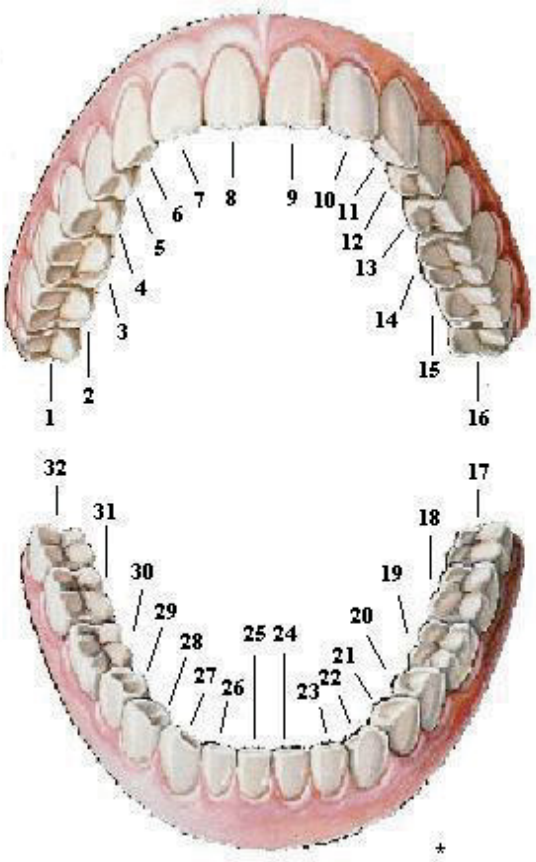
Use the diagram below as a guide to count the number of native teeth in place, not including full or partial dentures or bridges.

The exact location of teeth does not need to be recorded, only the total number of native teeth in place (attached to bone in mandible or maxilla) on the day of evaluation.

This exam should be completed by a physician or designee, such as a physician's assistant, nurse or nurse practitioner, or a dentist/hygienist.

Date of evaluation: Total number of native teeth in place (0-32):

Right



Left

APPENDIX III (Continued)

Dental Effects Health Scale

0 Normal: Edentulous, with no gingival disease; native teeth in place with gingiva in excellent condition.

1 Mild changes/good dental health: mild periodontal inflammation-routine cleaning indicated; < 5 restorations indicated; no extractions indicated.

2 Moderate/fair dental health: moderate periodontal inflammation; deep periodontal cleaning indicated; 6 or more restorations indicated; less than full mouth extractions indicated.

3 Severe changes in dental health: widespread periodontal disease with extensive procedure/surgery indicated; full mouth extractions indicated.

4 Life-threatening dental condition: extensive abscess, extensive soft issue or bone infection, sepsis; urgent intervention indicated.

APPENDIX III (Continued)

Management of Dental Problems in Irradiated Patients

Goals for a dental care program include:
1. To reduce incidence of bone necrosis.
2. To reduce incidence of irradiation caries.
3. To allow proper fitting of dentures following treatment.

Pre-irradiation Care and Procedures
The patients may be grouped into four groups in accordance with the problems they present prior to irradiation.

- Group 1: Includes edentulous patients. They may require surgical removal of any symptomatic cysts, infected retained root tips, or alveolar hyperplasia. These patients require hygiene instruction and precautionary instruction about trauma with premature use of a prosthesis.

- Group 2: Includes those with poor dental hygiene, including those patients whose teeth are beyond repair by ordinary dental procedure, those with generalized oral sepsis, those with generalized periodontal disease, and those with chronic periapical abscesses or granulomas.

  Procedures performed on this group include removal of all remaining teeth prior to irradiation with primary closure and surgical preparation of the alveolar ridges to laterally support a prosthesis. There should be antibiotic coverage during the healing stage and adequate time prior to the start of radiation therapy. These patients need complete hygiene instruction and precautionary instruction about premature use of a prosthesis.

- Group 3: Includes those in whom dental condition is fair, including those patients whose teeth are restored, ordinary dental procedures, periodontal pockets are less than 3 mm deep, carious lesions are not in proximity to the pulp, and no more than 20 restorable carious lesions are present. X-ray examinations show at least 1/2 of the bone still present around root surfaces. These patients require removal of any teeth that are non-salvageable in accordance with the above and restorations of the remaining teeth as required. The patients are instructed for dental prophylaxis and the patients utilize custom-made fluoride carriers.

- Group 4: Includes those in whom dental hygiene is good. This includes patients who do not have severe malocclusion in whom few carious lesions are present. Carious lesions are not in close proximity to the pulp and are correctable by conventional methods. These patients require periodontal evaluation and dental prophylaxis training, restorations as needed, no extractions prior to radiation therapy, and fitting for custom carriers.

Extraction of Teeth

If extraction of teeth is necessary prior to radiation therapy, the bone must be contoured so that closure at the extraction site is possible. All loose spicules and sharp projections must be removed. The approximation of the gingival tissue must be such that the closure is neither too loose nor too tight. At least 10 days are required for adequate healing prior to initiation of therapy.

Causative Factors

The major causative factors appear to be the reduction of the amount of saliva and secondarily, reduced pH in the mouth. This occurs following high dose radiation to the major salivary glands using parallel opposed fields. The decay process usually occurs in the first year following radiation therapy. It tends to occur more quickly in teeth which have a large amount of root cementum exposed to those teeth with large amounts of plaque formation present. Doses of radiation in excess of 20 Gy to salivary tissue place the teeth at risk.

Preventive Program

The rationale behind the use of fluoride treatments is to make the tooth surfaces less susceptible to the decay process. This is accomplished by a combination of increasing fluoride concentration on the tooth surface and by the effect of fluoride on the plaque and flora that are present in the oral cavity. Adequate results are obtained by: 1) cleansing the teeth thoroughly, followed by a good home care dental prophylaxis program, 2) construction of
fluoride carriers, custom-made mouth guards, which provide local application of fluoride solution to the gingiva and tooth surfaces. Fluoride carriers are made individually with the use of casts. Material used for making a mouth guard is "Sta-Guard" plastic used in conjunction with vacutrole unit produced by Jelrus Technical Products, Corp., both of which are available through local dental supply. This material is molded to the cast impression and allowed to harden. A fluoride solution prepared at the M.D. Anderson Hospital is now available from the Emerson Laboratories, Inc., Dallas, Texas 75221. It has been used to coat the plastic carrier for use in the mouth. The patients are instructed to cleanse their teeth prior to placement of the carrier. It is then worn in place for 5 minutes each day. The patients are instructed to rinse their mouths thoroughly following the use of the carrier. This will be continued for an indefinite period of time. Close follow-up is necessary.

Results

In the 5-1/2 year program at the M.D. Anderson Hospital beginning in 1966, a study of 304 patients shows that the incidence of necrosis of the jaw was reduced to approximately 21% compared to 37% prior to initiation of the study. Groups 3 and 4 patients randomized with and without fluoride treatment showed reduction in radiation carries from 67% to 34% among Group 3 patients, and from 65% to 22% among Group 4 patients.

Failure to Control Decay

Management of failure to control radiation decay includes silver fillings with continued use of fluoride treatments. If the decay process is sufficiently advanced that a filling will no longer stay in place, these teeth are merely smoothed so that there will be no sharp, irritating edges. The mere existence of such a decayed tooth is not necessarily reason for extraction, for it must be remembered that extraction could lead to complications such as bone necrosis.

Pulp exposure resulting from the decay process can usually be handled by use of antibiotics and/or root-canal therapy.

Hypersensitivity of Teeth

Occasionally, a patient will exhibit extreme sensitivity of the teeth secondary to diminished amounts of saliva. This has been shown to be reduced in incidence with the fluoride treatments. Should this problem become manifest, increasing the fluoride treatment to 10 to 15 minutes 3 times a day is recommended.

Infections

Infections occurring in patients under or after radiation therapy are best managed conservatively with good oral hygiene, irrigation and flushing procedures, and systemic antibiotics.

Bone Necrosis

The patients receiving radiation therapy to a high dose to the head and neck region have increased susceptibility to bone necrosis for several reasons including: impairment of normal metabolism, increased susceptibility to infection and severely limited repair process. Bone necrosis occurs most often after dental or oral surgery in patients who have been previously radiated. Conservative management should be tried first, though in more aggressive lesions a more radical approach may ultimately be necessary.

APPENDIX IV: SUGGESTED ACQUISITION GUIDELINES FOR THE MODIFIED BARIUM SWALLOW (MBS) ADMINISTRATION AT BASELINE AND POST RT YEAR ONE AND TWO

For questions, please contact Rosemary Martino, MA, MSc, PhD at rosemary.martino@utoronto.ca.

Many institutions will have standard guidelines for acquisition of MBS. For purposes of this protocol, individual investigators may use these local guidelines. One possible approach is outlined below which is suggested to optimize acquisition.

MBS Administration Parameter
Pulse rate on fluoroscopy unit set at continuous or no less than 30 fps
Capture of images set at uncompressed
Capture of images set at 30 fps
MBS test stimuli procedural conducted as per Table 1 below
Preparation of standardized barium liquids and foods as per Table 2 below (or Varibar)
Audio stamp for each video clip to label series (i.e., to record SLP audio cue of the amount/texture bolus trial, e.g., "5-mL thin")
Series descriptions for each video clip to label series (as per Table 3 below)
Have the capacity to remove all patient health information/or hospital identifying information typically embedded in the video
Capture each lateral image with full view the regions of Interest (ROI): C1 vertebrae (superiorly); posterior spine (posteriorly); cervical esophagus (inferiorly)
Capture each A/P image with full view the regions of Interest (ROI): hard palate (superiorly); cervical esophagus (inferiorly)

TABLE 1. RECOMMENDED MBS CONDUCT PROTOCOL

Many institutions will have standard guidelines for acquisition of modified barium swallow. For purposes of this protocol, individual investigators may use these local guidelines. One possible approach is outlined below which is suggested to optimize acquisition.

- *Before starting the MBS, place a **standardized coin** under patient's chin secured with surgical tape for lateral views. For A/P the quarter can only be along the lateral neck just below the ear lobe.*
- *Provide **audio label** of Amount-Texture during **each** bolus trial, as per table below.*
- *Protocol deviations (i.e. additional texture trials, compensatory strategies, etc.) are permitted at the SLP's discretion, but only AFTER the MBS protocol (sequence 1-13) is completed.*

Sequence	View	Amount – Texture	Instruction *
1	Lateral	1-ml Tsp– Thin liquid	*Hold this liquid in your mouth until I ask you to swallow*
2	Lateral	5-ml – Thin liquid	*Hold the liquid in your mouth, then swallow when ready.*
3	Lateral	5-ml – Thin liquid	
4	Lateral	10-ml cup sip – Thin liquid	*Hold the liquid in mouth, then try to drink the entire amount when ready.*
5	Lateral	10-ml cup sip – Thin liquid	
6	Lateral	Cup sip – Thin liquid	*Take a sip from the cup and hold it in your mouth, then swallow when ready.*
7	Lateral	Cup sip – Thin liquid	
8	Lateral	5-ml – Pudding thick barium	*Hold the pudding in your mouth, then swallow when ready.*
9	Lateral	5-ml – Pudding thick barium	
10	Lateral	Half of digestive cookie or cracker	*Take your usual bite, then chew and swallow when ready.*
11	Lateral	Half of digestive cookie or cracker	
12	A/P	Cup sip – Thin liquid	*Take a sip from the cup and hold it in your mouth, place the cup down on your lap, then swallow when ready.*
13	A/P	5-ml – Pudding thick barium	*Hold the pudding in your mouth, then swallow when ready.*

TABLE 2. BARIUM FOOD RECIPES

Texture	Recipe
Thin liquid	135 mL Water + 45 mL Polibar Plus Barium Sulfate Suspension 105% w/v
Pudding thick	99 g Pudding cup (99g package) + 40g EZ HD barium Sulfate powder
Solid	Coat Social Tea cookie with layer of pudding +barium (above recipe)
Nectar thick liquid *	120mL Sysco Nectar thickened liquid + 10mL water + 15g EZ HD barium Sulfate powder
*Honey thick liquid**	120mL Sysco Nectar thickened liquid + 48 g EZ HD barium Sulfate powder

*Thickened fluids are not part of the recommended standard MBS protocol. If deemed appropriate to add to MBS procedure by the Speech Language Pathologist (SLP), this should be given AFTER completion of the above-mentioned protocol, unless safety concerns arise to preclude completion of standard protocol.

TABLE 3. RECOMMENDED VIDEO LABEL LIST

Sequence	Label
1	q1: 1-ml – Thin liquid
2	q2: 5-ml – Thin liquid
3	q3: 5-ml – Thin liquid
4	q4: 10-ml – Thin liquid
5	q5: 10-ml – Thin liquid
6	q6: Cup sip – Thin liquid
7	q7: Cup sip – Thin liquid
8	q8: 5-ml – Pudding thick
9	q9: 5-ml – Pudding thick
10	q10: Bite size solid
11	q11: Bite size solid
12	q12: Cup sip – Thin liquid, A/P
13	q13: 5-ml – Pudding thick barium, A/P

APPENDIX V: NCI/DCTD Collaborative Agreement

The agent(s) supplied by CTEP, DCTD, NCI used in this protocol is/are provided to the NCI under a Collaborative Agreement (CRADA, CTA, CSA) between the Pharmaceutical Company(ies) (hereinafter referred to as "Collaborator(s)") and the NCI Division of Cancer Treatment and Diagnosis. Therefore, the following obligations/guidelines, in addition to the provisions in the "Intellectual Property Option to Collaborator" (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm) contained within the terms of award, apply to the use of the Agent(s) in this study:

1. Agent(s) may not be used for any purpose outside the scope of this protocol, nor can Agent(s) be transferred or licensed to any party not participating in the clinical study. Collaborator(s) data for Agent(s) are confidential and proprietary to Collaborator(s) and shall be maintained as such by the investigators. The protocol documents for studies utilizing Agents contain confidential information and should not be shared or distributed without the permission of the NCI. If a copy of this protocol is requested by a patient or patient's family member participating on the study, the individual should sign a confidentiality agreement. A suitable model agreement can be downloaded from: http://ctep.cancer.gov.

2. For a clinical protocol where there is an investigational Agent used in combination with (an)other Agent(s), each the subject of different Collaborative Agreements, the access to and use of data by each Collaborator shall be as follows (data pertaining to such combination use shall hereinafter be referred to as "Multi-Party Data"):

    a. NCI will provide all Collaborators with prior written notice regarding the existence and nature of any agreements governing their collaboration with NCI, the design of the proposed combination protocol, and the existence of any obligations that would tend to restrict NCI's participation in the proposed combination protocol.

    b. Each Collaborator shall agree to permit use of the Multi-Party Data from the clinical trial by any other Collaborator solely to the extent necessary to allow said other Collaborator to develop, obtain regulatory approval or commercialize its own Agent.

    c. Any Collaborator having the right to use the Multi-Party Data from these trials must agree in writing prior to the commencement of the trials that it will use the Multi-Party Data solely for development, regulatory approval, and commercialization of its own Agent.

3. Clinical Trial Data and Results and Raw Data developed under a Collaborative Agreement will be made available to Collaborator(s), the NCI, and the FDA, as appropriate and unless additional disclosure is required by law or court order as described in the IP Option to Collaborator (http://ctep.cancer.gov/industryCollaborations2/intellectual_property.htm). Additionally, all Clinical Data and Results and Raw Data will be collected, used and disclosed consistent with all applicable federal statutes and regulations for the protection of human subjects, including, if applicable, the *Standards for Privacy of Individually Identifiable Health Information* set forth in 45 C.F.R. Part 164.

4. When a Collaborator wishes to initiate a data request, the request should first be sent to the NCI, who will then notify the appropriate investigators (Group Chair for Cooperative Group studies, or PI for other studies) of Collaborator's wish to contact them.

5. Any data provided to Collaborator(s) for Phase 3 studies must be in accordance with the guidelines and policies of the responsible Data Monitoring Committee (DMC), if there is a DMC for this clinical trial.

6. Any manuscripts reporting the results of this clinical trial must be provided to CTEP by the Group office for Cooperative Group studies or by the principal investigator for non-Cooperative Group studies for immediate delivery to Collaborator(s) for advisory review and comment prior to submission for publication. Collaborator(s) will have 30 days from the date of receipt for review. Collaborator shall have the right to request that publication be delayed for up to an additional 30 days in order to ensure that Collaborator's confidential and proprietary data, in addition to Collaborator(s)'s intellectual property rights, are protected. Copies of abstracts must be provided to CTEP for forwarding to Collaborator(s) for courtesy review as soon as possible and preferably at least three (3) days prior to submission, but in any case, prior to presentation at the meeting or publication in the proceedings. Press releases and other media presentations must also be forwarded to CTEP prior to release. Copies of any manuscript, abstract and/or press release/ media presentation should be sent to:

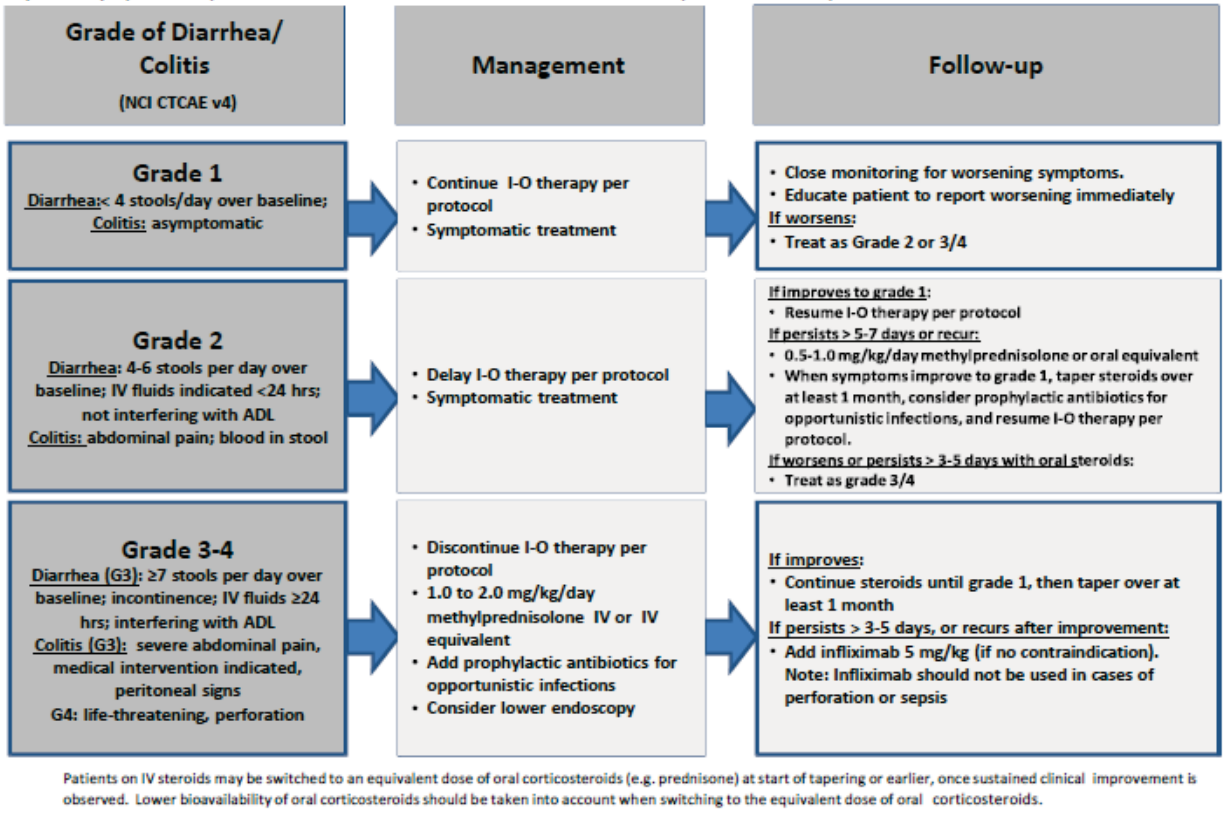
Email: ncicteppubs@mail.nih.gov

The Regulatory Affairs Branch will then distribute them to Collaborator(s). No publication, manuscript or other form of public disclosure shall contain any of Collaborator's confidential/ proprietary information.

APPENDIX VI: NIVOLUMAB TOXICITY MANAGEMENT ALGORITHMS

GI Adverse Event Management Algorithm

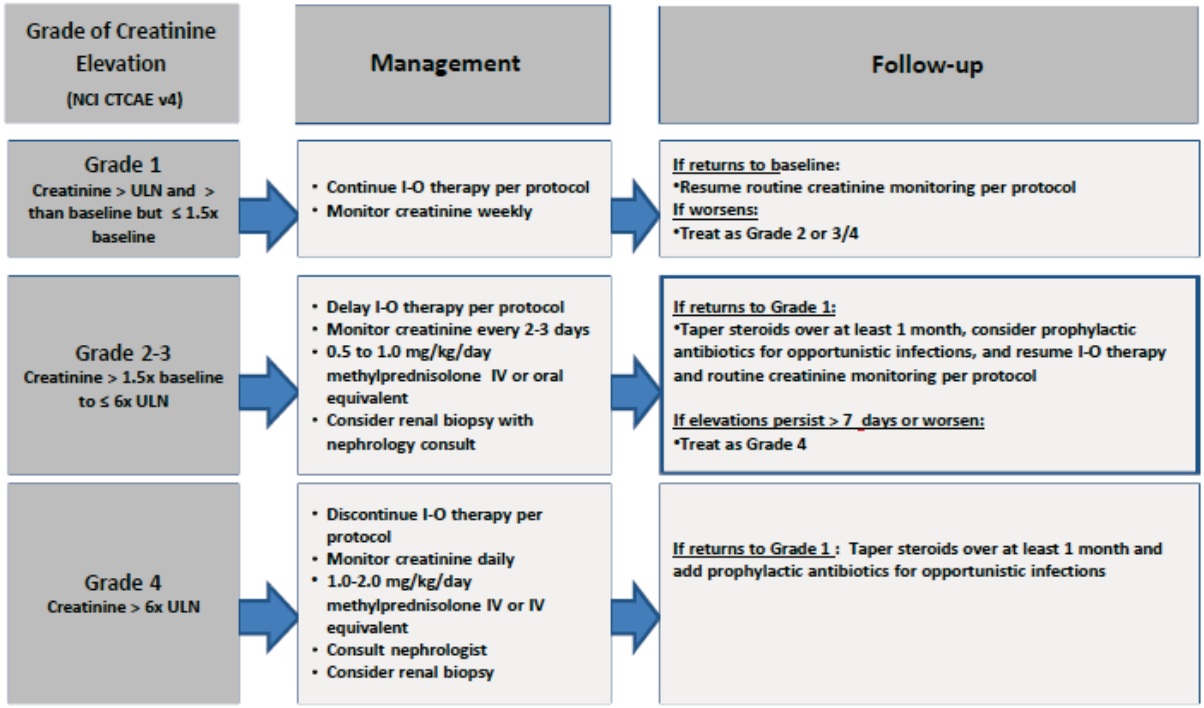
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

Renal Adverse Event Management Algorithm

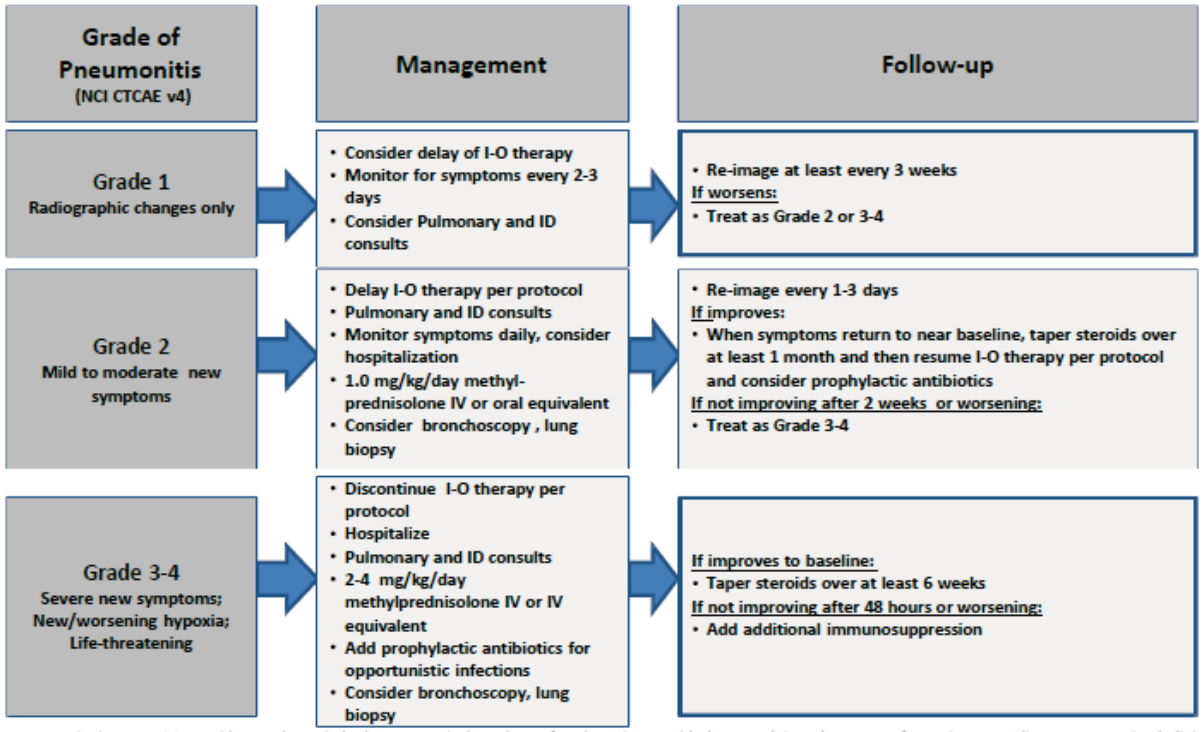
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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

Pulmonary Adverse Event Management Algorithm

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



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

Hepatic Adverse Event Management Algorithm

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

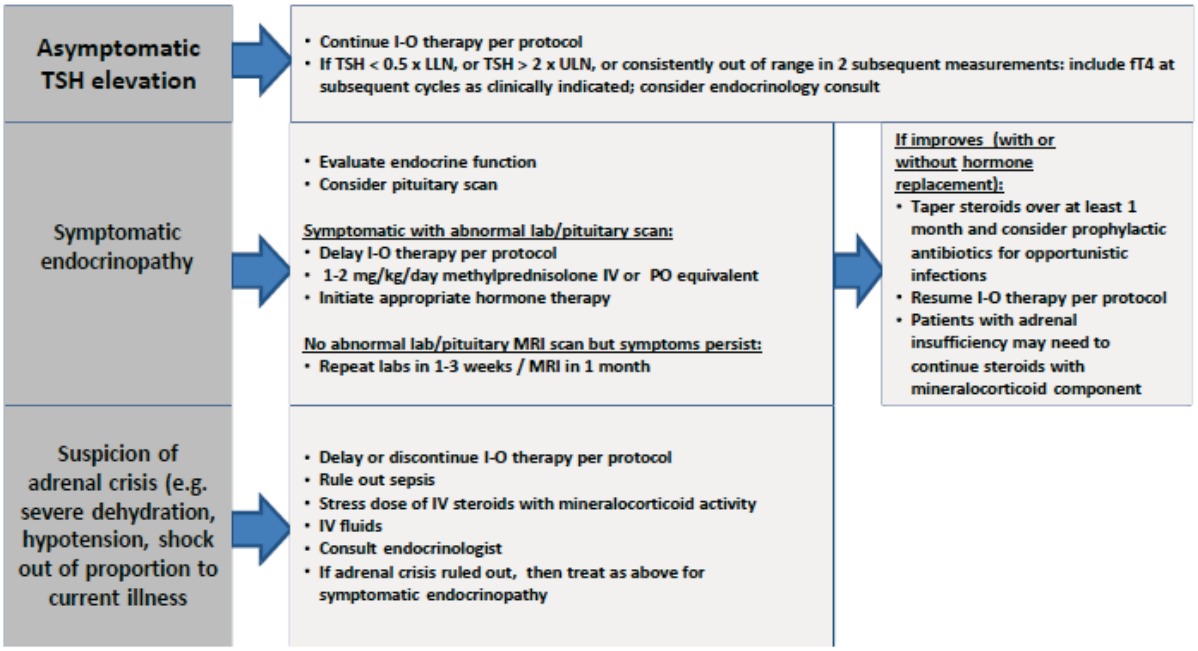
Grade of Liver Test Elevation (NCI CTCAE v4)	Management	Follow-up
Grade 1 AST or ALT > ULN to 3.0 x ULN and/or T. bili > ULN to 1.5 x ULN	• Continue I-O therapy per protocol	• Continue LFT monitoring per protocol If worsens: • Treat as Grade 2 or 3-4
Grade 2 AST or ALT > 3.0 to ≤ 5 x ULN and/or T. bili > 1.5 to ≤ 3 x ULN	• Delay I-O therapy per protocol • Increase frequency of monitoring to every 3 days	If returns to baseline: •Resume routine monitoring, resume I-O therapy per protocol If elevations persist > 5-7 days or worsen : • 0.5-1 mg/kg/day methylprednisolone or oral equivalent and when LFT returns to grade 1 or baseline, taper steroids over at least 1 month, consider prophylactic antibiotics for opportunistic infections, and resume I-O therapy per protocol
Grade 3-4 AST or ALT > 5 x ULN or T.bili >3 x ULN	• Discontinue I-O therapy* • Increase frequency of monitoring to every 1-2 days • 1.0 to 2.0 mg/kg/day methylprednisolone IV or IV equivalent* • Add prophylactic antibiotics for opportunistic infections • Consult gastroenterologist	If returns to grade 2: • Taper steroids over at least 1 month If does not improve in >3-5 days, worsens or rebounds: • Add mycophenolate mofetil 1 g BID • If no response within an additional 3-5 days, consider other immunosuppressants per local guidelines

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

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

Endocrinopathy Adverse Event Management Algorithm

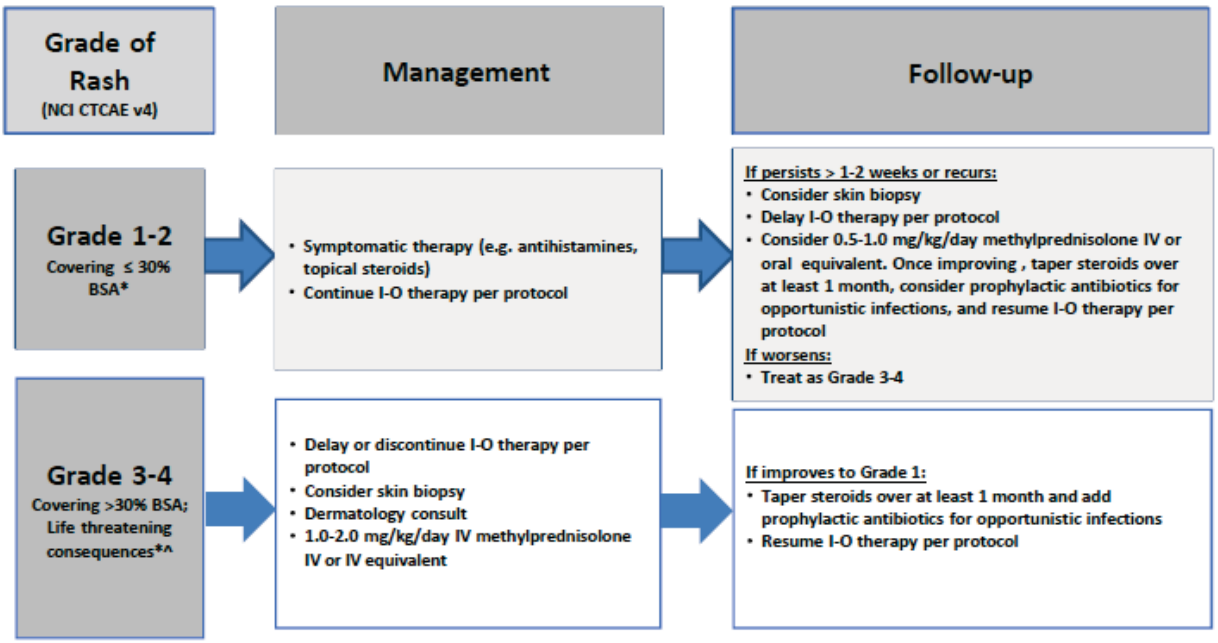
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy. Consider visual field testing, endocrinology consultation, and imaging.



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

Skin Adverse Event Management Algorithm

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



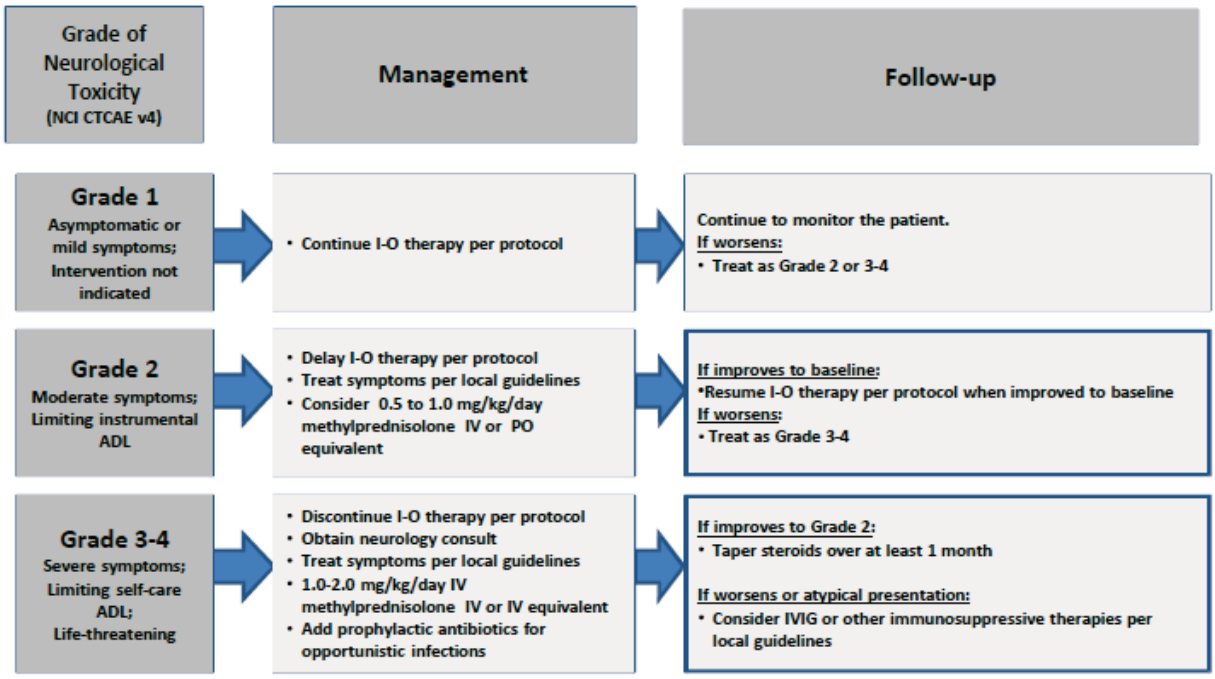
Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

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

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

Neurological Adverse Event Management Algorithm

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



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