

MD Anderson IND Sponsor Cover Sheet	
Protocol ID	2018-0381
Protocol Title	Phase 2 study (with safety lead in) of the safety, tolerability and efficacy of anti-CTLA4 (ipilimumab) and anti-PD-1 (nivolumab) in combination with radiation therapy to 50-66 Gy in low- intermediate volume, local-regionally advanced HPV-positive oropharyngeal squamous cell carcinoma (OPSCC)
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Clinical Protocol

Phase 2 study (with safety lead in) of the safety, tolerability and efficacy of anti-CTLA4 (ipilimumab) and anti-PD-1 (nivolumab) in combination with radiation therapy to 50-66 Gy in low- intermediate volume, local-regionally advanced HPV-positive oropharyngeal squamous cell carcinoma (OPSCC)

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SYNOPSIS

Title of Study: Phase 2 study (with safety lead in) of the safety, tolerability and efficacy of anti-CTLA4 (ipilimumab) and anti-PD-1 (nivolumab) in combination radiation therapy to 50-66 Gy in low- intermediate volume, local-regionally advanced HPV-positive oropharyngeal squamous cell carcinoma (OPSCC).

Investigational Product: Each subject will be administered two six week cycles of intravenous (IV) ipilimumab 1 mg/kg on day 1 and nivolumab 3 mg/kg on day 1, 15, and 29.

Study phase: 2

Research Hypothesis: The combination of ipilimumab, nivolumab and concurrent intensity modulated photon therapy (IMRT) with reduced field will demonstrate adequate safety, tolerability and clinical efficacy for treatment of subjects with low-intermediate volume, local-regionally advanced HPV-positive OPSCC.

Primary Objective 1: To evaluate the safety, tolerability and feasibility of ipilimumab and nivolumab when administered concurrently with reduced-field IMRT.

Primary Objective 2: To evaluate the clinical complete response rate to ipilimumab, nivolumab and IMRT with reduced field at six months as indicated by FDG-PET/CT post completion of RT.

Primary Objective 3: To evaluate the 2-year progression-free survival (PFS) rate of subjects with low-intermediate volume, local-regionally advanced, HPV-positive SCCHN treated with ipilimumab, nivolumab and reduced-field IMRT.

Principal Secondary Objectives:

To evaluate overall response rate to six weeks of induction immunotherapy (IO).

To evaluate the frequency of pharyngeal dysphasia as measured by DIGEST grade on modified barium swallow (MBS) and patient-reported symptoms (MDADI) at 6 months and 2 years after radiotherapy [IMRT].

Additional Secondary Objectives:

To measure acute and chronic toxicities per CTCAE v4;

To measure acute toxicity profiles at the end of radiation therapy and IO and at 6 months;

To measure late toxicity profiles at 1 and 2 years;

To determine local and regional control at 6 and 12 months;

To determine patterns of failure (local-regional relapse vs. distant) at 1 and 2 years;

To determine overall survival (OS) at 1 and 2 years;

Principal Correlative Objectives:

To evaluate associations between total mutational load, IFN γ score, T cell clonality at diagnosis with clinical response to induction, combination CTLA-4 PD-1 checkpoint blockade.

To evaluate changes in the tumor immune microenvironment (CD8 + IFN gamma score, T cell clonality, in tumor biopsy specimens pre and post induction immunotherapy (IO);

To evaluate dynamic changes in and clearance of oral HPV and cfDNA viral load during therapy

and to investigate associations with PFS and OS.

Additional Exploratory Objectives:

To evaluate changes in peripheral blood lymphocyte phenotypes and serum cytokine profiles before and after induction IO;

To evaluate changes in the T cell receptor repertoire in TIL and the peripheral blood in tumor biopsy specimens pre and post induction IO;

To determine the NPV and PPV of FDG-PET/CT 12-14 weeks after end of RT for 1 year and 2 year PFS and OS.

Study Design:

This is a phase II, open label, single arm study. The study is designed to evaluate the safety, feasibility and clinical efficacy of a treatment strategy of combination anti-CTLA4 (ipilimumab) and anti-PD-1 (nivolumab) IO with reduced dose and field radiation therapy to 50-66 Gy for patients with low-intermediate volume, local-regionally advanced HPV-positive OPSCC (AJCC 7th edition T1N2a-N2c, T3N0, T2-T3N1-N2C; AJCC 8th edition stage 1-2, excluding T1N0-1, T2N0). The primary objective of this study is to establish the efficacy of the new immunotherapy regimen such that it is non-inferior to the current standard therapy. Two co-primary endpoints are specified: (1) the complete response (CR) rate at 6 months and (2) the two-year progression-free survival (PFS) rate.

Based on the available data, the standard therapy yields a 6-month CR rate of 0.87 and a two-year PFS of 0.91. The non-inferiority margin is set at 0.05 for the 6-month CR rate and at 0.06 for the 2-year PFS. Thus, the new treatment is considered non-inferior to the standard therapy if the 6-month CR rate is at least 0.82 and the two-year PFS is at least 0.85. Otherwise, the new treatment is considered inferior to the standard therapy. The study comprises a three-year accrual period with 5 patient enrolled per month and additional two years of follow up. The maximum total sample size is 180 and the total study duration is up to 5 years. Assume that the 6-month response rate follows a binomial distribution and the PFS follows a Weibull distribution, given the parameters specified above, the study will have 82% power of establishing the non-inferiority if the efficacy of the new treatment is as good as the standard treatment. On the other hand, if the new treatment yields a 6-month response rate of 0.75 and a two-year PFS of 0.85, the early stopping probability is 0.93 with an average sample size of 127.6. The probability of claiming non-inferiority is 0.06 (type I error).

Interim Analysis:

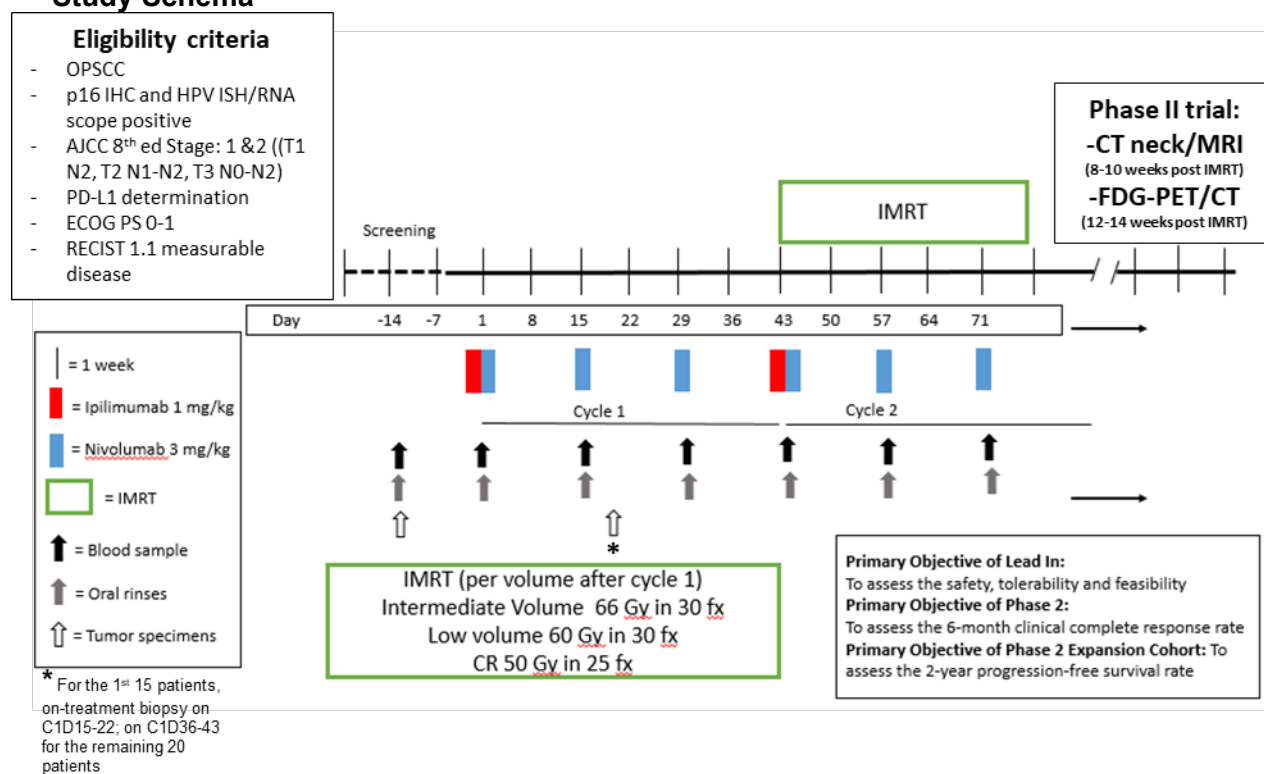
Futility early stopping rule will be implemented monthly starting month 7 after 35 patients are enrolled to protect patients from receiving inferior therapy. In order to assure that the new regimen is safe and efficacious, patient accrual will be paused after 35 patients are enrolled. After the toxicity data and the 6-month CR status are available, study statistician will perform the first interim analysis. The study PI will discuss with sponsor and make a decision to either resume accrual and expand the study size beyond 35 patients if the new regimen is deemed to be safe and efficacious or close the study otherwise. If the trial is not stopped early after the first interim analysis, patient accrual will resume and additional interim monitoring will be performed monthly. The non-inferiority boundary is evaluated at the end of study if the study is not stopped early. Patients in the lead in portion of the trial will be included in the phase 2. The maximum total sample size is 180 and the total study duration is up to 5 years.

Study Conduct:

Eligible subjects will include patients with newly diagnosed, low-intermediate volume local-

regionally advanced (AJCC 7th edition T1N2A-N2C, T2-T3N1-N2C, T3N0 or AJCC 8th edition stage T1 N2; T2 N1-N2 or T3 N0-N2), HPV-positive OPSCC. The study will be divided into four phases, including screening, treatment, clinical follow-up and survival follow-up. Patients will undergo screening (up to 1 month), treatment (12 weeks), clinical follow up (100 days) and survival follow-up (up to five years). The treatment period will include two, six-week cycles of ipilimumab 1 mg/kg day 1 and nivolumab 3 mg/kg on days 1, 15, and 29 starting six weeks before start of radiation therapy (50-66Gy) , equivalent to cycle 2 day 1 of the IO. On days when ipilimumab and nivolumab are given on the same day, nivolumab will be infused first over 30 minutes. A minimum of 30 minutes is required between infusions. Clinical response to induction therapy will be evaluated by repeat imaging after six weeks of IO and before start of radiotherapy. In the phase II trial, clinical response to treatment will be evaluated by physical exam and CT neck (or MRI) at eight-10 weeks and FDG-PET/CT at 12-14 weeks post completion of radiation therapy. For the first co-primary endpoint, the outcome of interest will be the proportion of patients who have a clinical complete response to therapy. Criteria for a clinical complete response include: (1) a metabolic complete response by FDG-PET/CT on week 12-14 post RT or (2) an indeterminant response by FDG-PET/CT on week 12-14 post RT followed by a complete metabolic response on week 24-28 or (3) an indeterminant or residual tumor FDG-PET/CT with no evidence of viable tumor on pathology from a salvage surgical procedure. The second co-primary endpoint of interest is 2-year progression-free survival, defined as the time from start of therapy to progression of disease or death from any cause.

Study Schema



1. RATIONALE

Platinum-based chemo-RT is the current standard of care for local-regionally advanced HPV-positive OPSCC and results in an approximate 8-year OS of 70.9% (Nguyen-Tan et al. 2014). Although platinum-based chemo-RT improves local-regional control and OS for SCCHN, acute and long-term toxicities (Trotti et al. 2007; Bentzen et al. 2007) as well as non-cancer associated deaths are increased (Kang et al. 2016). Accounting for total toxicity burden, concurrent chemo- RT has been estimated to increase the acute toxicity experienced by patients by 500% in comparison to

radiation therapy alone (Trotti et al. 2007). Given patients with HPV-positive OPSCC have a high probability of long-term survival, late toxicities of therapy are an increasing concern. Several recent trials have demonstrated that local-regional control (Chera et al. 2015) or progression-free survival (Marur et al, abstract 6005, ASCO 2016) may be maintained with reductions in intensity (e.g. total dose) of RT among patients with HPV-positive OPSCC. However, these studies maintained platinum chemotherapy (CT). In Checkmate 141, anti-PD1 (nivolumab) monotherapy reduced the risk of death by half in comparison to single-agent CT among patients with platinum-refractory, recurrent and metastatic HPV-positive OPSCC. This demonstrated clinical activity together with in vivo models of combination immunotherapy (IO)-RT support a hypothesis that neoadjuvant anti-CTLA4 and anti-PD1 IO followed by concurrent administration with RT would have substantial anti-cancer activity for patients with HPV-positive OPSCC. Therefore, we designed a phase 1/2 clinical trial to investigate combination IO-RT with anti-PD1 (Nivolumab) and anti-CTLA4 (Ipilimumab) with reduce field and dose of IMRT in patients with low-intermediate volume, local-regionally advanced HPV-positive OPSCC.

1.1 Head and neck cancer

Squamous cell carcinoma of the head and neck (SCCHN) is a major cause of cancer-associated morbidity, with 600,000 cases diagnosed annually worldwide (Ferlay et al. 2013). In the United States in 2013, there were 53,640 new cases and 11,520 deaths from SCCHN (Siegel et al 2013). Traditional risk factors include tobacco and alcohol use. However, HPV infection is now a major cause of OPSCC (Gillison et al. 2008; De Martel et al. 2012). Indeed, incidence rates for HPV-positive SCCHN increased by 225% (Chaturvedi et al. 2011) from 1988-2004 and are projected to continue to increase through 2060 (Maura L. Gillison et al. 2015)

1.2 HPV-positive oropharyngeal squamous cell carcinoma

In comparison to its HPV-negative counterpart, HPV-positive SCCHN is unique with regard to risk-factor profiles, clinical-pathological features, treatment response, prognosis and genetic profiles (Gillison et al. 2012; Gillison et al. 2015). It is now clear that tumor HPV status is a strong independent determinant of OS. Across numerous clinical trials, patients with HPV-positive SCCHN have been shown to have at least half the risk of death when compared to HPV-negative SCCHN (Ang et al. 2010). HPV-positive SCCHN has an improved response to platinum-based induction chemotherapy (Fakhry et al. 2008), RT (Gillison et al. 2015) and chemo-RT (Ang KK et al. 2010; Rischin et al. 2010) when compared to HPV-negative SCCHN. In an analyses of RTOG 0129, a combination of tumor HPV status, tobacco pack-years (<10 or ≥ 10), and T and N stage classified patients into low, intermediate, or high-risk of death (three-year OS rates 93% [95%CI, 88.3-97.7], 70.8% [95%CI 60.7-80.8] and 46.2% [95%CI 34.7-57.5], respectively) (Gillison et al. 2012). Notably, all HPV-positive SCCHN patients were included in the low-risk group (including T4 and N3), with the exception of those with the combination of >10 pack-years and N2b-N3 disease. This model was subsequently validated in RTOG 9003 and 0522 and O'Sullivan and colleagues confirmed the excellent 3-year local-regional and distant control rates of 93-95% for the low-risk subset (O'Sullivan et al. 2013). As a consequence, alternative pathways for clinical therapeutics for HPV-positive SCCHN have evolved, taking advantage of the increased sensitivity of the disease to chemotherapy and RT. Numerous clinical trials of reduce intensity of chemotherapy and/or RT are completed or ongoing, with a goal to reduce long-term toxicities while preserving disease control.

The current AJCC TNM staging system accurately discriminates subgroups of patients with HPV-negative, but not HPV-positive OPSCC (Maura L. Gillison 2016). Analyses of large datasets at Princess Margaret (O'Sullivan et al. 2013), MD Anderson (Sturgis et al. 2016) and additional institutions (O'Sullivan et al. 2016) have resulted in proposals for a new staging system specific to HPV-positive SCCHN. Across these analyses is a consistent pattern of high local-regional disease control and survival among patients with low-intermediate volume, HPV-positive SCCHN (<T4 and

<N3). In a Princess Margaret series, patients with <T4, <N3 HPV-positive OPSCC had 3-year disease control rate of 93% (95%CI, 89-95) and local-regional control of 95% (95%CI 91- 97%) (O'Sullivan et al. 2013). In a follow-up study, tobacco smoking was found to significantly affect OS for patients with low-intermediate volume HPV-positive OPSCC, with a cut-point of 20 pack-years. Five-year OS was 89% (95%CI, 85-93%) among those with ≤20 pack-years and 64% (95%CI 56-73%) for >20 pack-years (Huang et al. 2015). In the MD Anderson series, patients with low-intermediate volume HPV-positive SCCHN were classified as Stage 1A (T1<N3) and 1B (T2<N3) and had a 5-year survival of 94% (95%CI 87-97%) and 87% (95%CI 79-92%), respectively. Notably, 5-year survival for T1-T2N3 or T3N0-N3 was 76% (95%CI 65-84%). We note that, in contrast to prior models, smoking was not included in the final model. In the recent ICON-S stage validation analysis reported by O'Sullivan et al (O'Sullivan et al. 2016), five-year OS for patients with ICON-S stage 1 (T1-T2N0-N2b) was 85% (95% CI 81-90) and for ICON-S stage 2 (T1-T3N2c) was 78% (95%CI 73-84%). For patients who meet the specific eligibility criteria for this trial in the ICON-S dataset treated with chemoRT, 2-year PFS was 91%, local- regional control 97%, and distant control rate 94%. Notably, none of these ICON-S models included smoking history. Thus, patient with low-intermediate volume HPV-positive SCCHN (<T4,<N3) are an excellent clinical subgroup for treatment de-intensification strategies, given the consistently favorable outcomes across these studies.

1.3 De-escalation protocols and reduced dose RT.

Given patients with HPV-positive OPSCC are young and likely to survive, the long-term morbidity (i.e. xerostomia, dysphagia, hypothyroidism, atherosclerosis, radiation fibrosis, dental loss) associated with standard-of-care, high dose cisplatin-based chemo-RT to 70Gy has a significant clinical and economic impact (Gillison et al. 2012; Ang et al. 2010). "De-escalation" treatment strategies are therefore designed to investigate whether or not intensity of chemotherapy, radiotherapy or both can be reduced while preserving disease control and reducing long-term toxicities for the patient with HPV-positive SCCHN (Masterson et al. 2014).

Results of several of these trials have been reported. Based upon the increased response to induction chemotherapy for HPV-positive SCCHN demonstrated in a prospective ECOG trial (Fakhry et al. 2008), ECOG 1308 investigated reduced dose radiation to 54Gy among patients treated with three cycles of platinum-based induction chemotherapy (Cmelak et al. 2014). Sixty-seven of 80 patients received induction chemotherapy followed by reduced dose IMRT to 54Gy in 27 fractions concurrent with cetuximab. After a median follow-up of 35.4 months, 2-year PFS and OS were 81% and 93% for all patients treated with ≤54Gy and 96% for 27 patients with <T4, <N2C, <10 pack-years. Given the small subset, it could not be determined which of these factors (T4, N2C-N3, ≥ 10 pack-years) was most influential for the less successful disease control. Chen and colleagues reported similarly high 2-year PFS of 92% among patients with Stage 3-4 HPV- positive OPC when treated with two cycles of paclitaxel/carboplatin followed by 54 Gy IMRT with weekly paclitaxel among complete or partial responders (Chen AM 2017). Three of 4 patients with progression received standard dose RT due to a best response of stable disease during induction. A similar treatment algorithm is being investigated in the Quarterback Trial, a phase III clinical trial comparing induction chemotherapy followed by reduced dose chemo-RT in responding patients vs. standard dose RT.

Chera and colleagues reported the results of a phase II trial among 43 patients with low- volume HPV-positive SCCHN (<T4, <N3) treated with cisplatin 30 mg/m²/week X 6 and 60Gy IMRT, representing a 16% reduction in RT and a 60% reduction in cisplatin dose (Chera et al. 2015). The principal outcome of interest was pathological complete response (pCR) at a planned neck dissection nine weeks after RT. The pCR rate was 86%, just below the estimated 87% 3- year local-regional control rate achieved in RTOG 0129 with high-dose cisplatin and IMRT 70Gy. These results are encouraging, and the completed NRG-HN002 trial will be a more robust evaluation of a

similar approach. In that trial, patients with HPV-positive SCCHN (<T4, <N2C, <10 pack- years) were treated with cisplatin at 40/mg/m²/week X 6 and 60 Gy/30 fractions/6 weeks or accelerated reduced dose radiation therapy (60 Gy/30 fractions/5 weeks). The primary objective for this trial is to select the arm(s) achieving a 2-year PFS rate of $\geq 85\%$ without unacceptable swallowing toxicity at 1 year (ClinicalTrials.gov NCT: 02254278).

The radiation therapy alone arm in HN002 is based upon high rates of local-regional control for low volume OPSCC with IMRT given as a single modality. RTOG 0022 was a phase II of 69 patients with T1-2 N0-N1 M0 OPSCC. The protocol specified a prescribed dose to the high-dose planning target volume of 66 Gy at 2.2 Gy/fraction in 30 fractions delivered over 6 weeks. With a median follow up of 2.8 years, the 2-year local-regional failure rate was 9% (95% CI, 2.1-15.9), the disease-free survival (DFS) was 82% (95% CI, 72.7-91.2), and the OS was 95.5% (95% CI, 90.6-100.0). Notably, all cases of local-regional failure, metastasis, or second primary cancer occurred among patients identifiable as current or former smokers (54% of all enrolled), and no such events were seen among reported nonsmokers (defined as < 5 packs per lifetime, with a prevalence of 34% in this study) (Eisbruch et al. 2010)

A clinical precedent exists for treatment of HPV-positive OPSCC with reduced dose radiation to 60 Gy over five weeks. In the Princess Margaret Hospital series, 449 OPSCC were treated with RT alone on a variety of schedules (60-70 Gy over 4-7 weeks). Among 148 patients with p16-positive OPSCC, 82% were stage III-IVB. Three-year outcomes for disease, local and regional control were 92%, 93% and 88%, respectively. Patients with p16-positive OPSCC who had ≤ 10 pack-years (n = 37) had 3-year OS, cause-specific survival, local control, and regional control rates of 86%, 92%, 95% and 97%, with distant control rates of 92% (O'Sullivan et al. 2013). Additional analyses indicated high volume disease (T4 or N3) had a high-risk of disease progression, even if tobacco exposure is <10 pack-years (O'Sullivan et al. 2013). In a case series from Princess Margaret Hospital from 1985-1991, 228 patients with tonsillar cancer were treated with ipsilateral RT to a total dose of 50 Gy in 4 weeks (Withers et al, 1995) (O'Sullivan et al. 2001). The majority of patients had low-intermediate volume disease (<T4 and <N2C). Five-year local and nodal control rates were 77% and 81% overall.

Several trials of reduced dose RT for HPV-positive OPSCC in additional clinical settings are ongoing. This includes ECOG 3311, in which post-operative patients with intermediate risk features are randomized to adjuvant IMRT of 50Gy vs. 60Gy. A phase II clinical trial is ongoing in which post-operative adjuvant RT is reduced to 30 Gy. At Memorial Sloan Kettering, patients with early stage HPV-positive OPSCC without evidence of significant tumor hypoxia by FDG-PET/CT are undergoing TORS resection of the primary followed by IMRT 30 Gy to involved nodes and selective neck dissection. To date, 4 of 4 patients enrolled have had a pathological complete response to 30 Gy of RT (personal communication, Nancy Lee).

A common alternative de-escalation approach to RT dose reduction is replacement of cisplatin by cetuximab concurrent with IMRT to 68-72 Gy. Given cetuximab-RT did not increase acute toxicities over RT alone in the seminal trial led by Bonner and colleagues, three ongoing trials are based upon the hypothesis that cetuximab-RT will reduce acute and late toxicities in comparison to cisplatin-RT while preserving disease control. RTOG1016 is a non-inferiority study design, whereas the TROG-12.01 and De-Escalate trials have principal outcomes of acute and late toxicities. Results of RTOG1016 and De-Escalate trials identified similar rates of toxicity with cetuximab and cisplatin and inferior disease control with cetuximab (Gillison et al. 2019; Mehanna et al. 2019).

A radiation-based alternative to de-intensification of treatment is the use of proton beam therapy in OPC patients. An MD Anderson led multi-institution randomized Phase II/III radiation de-intensification trial (Frank-PI) is currently underway testing concurrent chemoradiation strategies

with IMRT vs. IMPT for patients with locally advanced head and neck cancer. IMPT significantly reduces the bystander radiation to non-clinical target volume structures in the head and neck that results in a decrease in acute and chronic toxicity without compromising disease control outcomes (Frank et al. 2012, Holliday et al. 2014, Gunn et al. 2016, McKeever et al. 2016, Blanchard et al. 2016, Leeman et al. 2017).

However, all the trials above treat the entire neck comprehensively, which may affect the lymphoid organs involved in priming and enhancing immune response. A differential radiation sensitivity of immune cells may have an effect on the anti-cancer response. T helper, T cytotoxic and monocytes have a radiation sensitive phenotype whereas regulatory T cells, macrophages, dendritic cells and NK cells have a relative radiation resistance (Heylmann et al. 2014). The University of Chicago has conducted a trial called Response Adapted Volume De-escalation (RAVD), wherein 2 cycles of TPC (cisplatin, paclitaxel and cetuximab) induction chemotherapy is followed by reduced radiation volume to treat mainly the gross disease with margins in patients with good response and to treat the neck comprehensively in nonresponders. For HPV-positive patients, this was associated with a 3-year local-regional control rate of 100% and 87%, respectively in good responders and non-responders. Reduced field in responders was associated with less long-term gastrostomy tube dependence (Melotek JM et al, Arizona meeting 2, 2016). Therefore, the combination of reduced-total dose RT and RT field size is expected to diminish both acute and long-term toxicity and maintain survival outcomes. In this trial there is interest in pursuing reduced field radiation therapy in combination with IO as a viable treatment option to offer to selected “low risk” oropharyngeal cancer patients.

1.4 Head and neck cancer and immunity

Cancer IO is based on the premise that tumors can be recognized as foreign rather than as self and can be effectively attacked by an activated immune system. Pathogenesis and progression of SCCHN may therefore be facilitated by local immunosuppressive alterations in the tumor microenvironment. Down-regulation of T cell function has been reported in SCCHN, and is mediated by multiple mechanisms including: reduced expression of co-stimulating molecules of the B7-CD28 family (Albers et al. 2005); increased expression of PD-L1 in tumor cells and tumor associated fibroblasts; and loss of HLA-class I and selective down-regulation of HLA-A, B, C locus expression resulting in defective antigen presentation (López-Albaitero et al. 2006; Leibowitz et al. 2013). Additionally, HPV-positive SCCHN patients have expanded populations of virus-specific T cells with an ineffective antitumor phenotype (Albers et al. 2005).

Programmed death receptor-1 (PD-1, CD279), a 55 kD type I transmembrane protein, is a member of the CD28 family of T-cell co-stimulatory receptors primarily expressed on activated T cells, B cells, and myeloid cells. Two ligands specific for PD-1 have been identified: PD-L1 (B7- H1/CD274) and PD-L2 (B7-DC/CD273). PD-L1 and PD-L2 have been shown to down-regulate T- cell activation upon binding to PD-1. PD-1 delivers a negative signal, suppressing the immune response away from a beneficial “type 1” response (Li et al. 2014). Existing literature supports a prevalence of PD-L1 expression in SCCHN of ~50-60% overall, with a slightly higher prevalence in HPV-positive SCCHN (Lyford-Pike et al. 2013). Ukpo and colleagues analyzed 181 OPSCC samples, 138 were HPV E6/E7 positive, and from those 68 (49.2%) expressed PD-L1. The authors found a correlation between the intensity of expression of PD-L1 and the development of distant metastasis ($p=0.03$) (Ukpo et al, 2013). More recently, Kim and colleagues evaluated 133 OPSCC, finding that the 71% of HPV-positive cases expressed PD-L1 (Kim et al. 2016). Concha-Benavente and colleagues studied 127 SCCHN for both HPV status and PD-L1 expression and observed PD-L1 expression to be more frequent in HPV-positive specimens (70% vs 43.3%) (Concha-Benavente et al. 2016). PD-L1 expression on tumor cells has been correlated with increased tumor aggressiveness and decreased survival (Cho et al. 2011). Additionally, tumor infiltration by PD-1+ Treg is more common

for HPV-positive than HPV-negative SCCHN (Badoual et al. 2013). Jie and colleagues observed higher expression of immune-checkpoint receptors (CTLA-4 and PD-1) in intratumoral Treg cells than on matched peripheral blood samples from 27 patients with SCCHN (H-B Jie et al. 2013).

CTLA-4 is a member of the immunoglobulin superfamily of receptors that is expressed on CTLs and Tregs. CTLA-4 is a co-inhibitory receptor that competes with the co-stimulatory molecule CD28 on CD8+ T cells to prevent binding to CD80 and CD86 on antigen presenting cells, thus suppressing the critical second signal and decreasing activation and proliferation of CTL. Montler and colleagues have reported co-expression of CTLA-4 and PD-1 in the Treg subset of TIL isolated from HNSCC (Montler et al. 2016)

In an analysis of transcriptome data from 280 HNSCC in TCGA, Mandal et al evaluated the immune landscape of HPV-positive vs. negative tumors (Mandal et al. 2016). Expression profiles were consistent with higher T cell infiltration in HPV-positive tumors, including both CD8+CTL and Tregs. Expression of negative regulators of both CD8+CTL (CTLA-4) and NK (Kir2DL1 and 3) function was higher in HPV-positive vs. negative HNSCC. Patients with high TIL had significantly improved OS. In a retrospective analysis published by Wad et al, 270 OPSCC the levels of tumor infiltrating lymphocytes (TILs) were dichotomized into two categories. Three-year survival in HPV-positive/high-TIL tumors was 96% vs. 59% in HPV-positive/low-TILs tumors (Ward et al. 2014). Circulating levels of T cells and NK cells that express detectable co-inhibitory checkpoint receptors may also correlate with disease stage and status (Badoual et al. 2013; H-B Jie et al. 2013; Hyun-Bae Jie et al. 2015; Lyford-Pike et al. 2013). In conclusion, HPV-positive HNSCC has a higher infiltration by TIL, consistent with an immunologically “hot” tumor indicative of likely benefit from IO.

1.5 Clinical trials of checkpoint inhibitors in SCCHN

Strome and colleagues originally demonstrated in animal models that PD-L1 blockade had therapeutic activity against PD-L1 positive SCCHN (Strome et al. 2003). Several clinical trials of single agent anti-PD1 or anti-PD-L1 therapy have demonstrated clinical activity of immunotherapy in patients with heavily pre-treated, recurrent/metastatic (R/M) SCCHN. A phase 1b clinical trial (Keynote 12) of single agent pembrolizumab (anti-PD1) demonstrated an ORR of 18% among 192 patients and 1-year OS of 38%. Response rates were slightly higher in HPV-positive vs negative patients (24 vs 16%) (Chow et al. 2016). A combined measure of PD-L1 expression in the tumor and inflammatory infiltrate identified a subset of patients with higher ORR (23% vs. 10%). Preliminary results of Keynote 55 including 92 of 171 patients with platinum- and cetuximab-refractory R/M SCCHN demonstrated an ORR of 18%, 22% in HPV-positive and 16% in HPV-negative SCCHN. ORR was also higher in PD-L1>1% vs. <1% (17% vs. 8%). Single- agent therapy with an anti-PD-L1 monoclonal (durvalumab) leads to an estimated ORR of 11% in RM SCCHN.

Importantly, data from a phase III trial (CheckMate 141) demonstrated that nivolumab improved survival of patients with platinum-refractory recurrent or metastatic SCCHN in comparison to standard of care therapy. Nivolumab monotherapy reduced the risk of death by 30% (HR 0.70, 95%CI 0.51-0.96) in comparison to single-agent methotrexate, docetaxel or cetuximab of investigator's choice (IC). Notably, one-year OS was more than doubled with nivolumab vs. IC (37% vs 17%) (Ferris et al. 2016). In a subset analysis, the risk of death was reduced by half (HR 0.56, 95% CI 0.32-0.99) with nivolumab vs. IC for patients with p16-positive (a surrogate for HPV) tumors, regardless of tumor PD-L1 expression. Similar to SCCHN, single agent nivolumab therapy has been shown to improve OS in patients with previously treated advanced non-small cell lung carcinoma (NSCLC) vs. docetaxel. In SQ-NSCLC, nivolumab therapy reduced the risk of death by 41% (HR 0.59, 95%CI 0.44-0.79). Keynote40 demonstrated similar results with single agent pembrolizumab (Cohen E et al. 2019).

1.6 Rationale for combination of Nivolumab and Ipilimumab

The combination of PD-1 and CTLA-4 receptor blockade has demonstrated improved clinical antitumor activity than either drug alone in clinical trials for patients with melanoma and lung cancer. The synergy between combined checkpoint inhibitor therapy is attributed to CTLA4 acting at early time points during T cell priming, activation and expansion versus PD-1 reactivation of exhausted T cells. In a phase II trial (CA209069), ORR for patients with BRAF wild type melanoma was improved with ipilimumab and nivolumab combination IO (ORR 61%, with 22% complete responses [CR]) in comparison to ipilimumab alone (ORR 11%, 0 CRs). In a subsequent randomized phase 3 trial (Checkmate 067), PFS was 11.5 months (95% CI, 8.9 to 16.7) in the nivolumab-plus-ipilimumab group, 6.9 months (95% confidence interval [CI], 4.3 to 9.5) in the nivolumab group, and 2.9 months (95% CI, 2.8 to 3.4) in the ipilimumab group. The PFS hazard ratio for the comparison between the nivolumab-plus-ipilimumab group and the nivolumab group was 0.74 (95% CI, 0.60 to 0.92) (Larkin et al. 2015). Notably, the combination lead to deep and durable responses in patients with melanoma with as estimated 2-year OS of 79%.

The clinical activity of nivolumab and ipilimumab combinations has been evaluated in patients with stage IIB-IV NSCLC as first line treatment in CheckMate 12 (ClinicalTrials.gov Identifier: NCT01454102) (Gettinger et al. 2012). Cohorts that evaluated nivolumab 1 mg/kg with ipilimumab 3 mg/kg every 3 weeks or nivolumab 3 mgs/kg with ipilimumab 1 mg/kg every 3 weeks resulted in ORR of 13-20% and 1-year OS of 44-65% but had significant toxicity in the non-small cell lung cancer (NSCLC) population (grade 3-4 treatment related adverse events (TRAEs) 44-58%), with 37% of patients discontinuing treatment due to a treatment-related adverse event. Thus, additional combination cohorts were initiated using lower doses of both nivolumab and ipilimumab, or the approved dose of nivolumab 3 mg/kg with less frequent dosing of ipilimumab. Numerically higher response rates were observed in cohorts evaluating the approved dose of nivolumab 3 mg/kg (with ipilimumab 1 mg/kg every 6 or 12 weeks), with confirmed response rates 38-47%. Median time to response was 8 weeks, and median number of doses was 8 for nivolumab and 2 for ipilimumab. Importantly, TRAEs grades 3-4 were reduced to ~28%, with treatment discontinuation of 10%. Most frequent TRAE of any grade were skin, gastrointestinal (diarrhea) and endocrine. Every six week ipilimumab 1 mg/kg scheduling thus improved ORR in comparison to nivolumab alone in SQ NSCLC and was more tolerable than every 3 week dosing. A phase 1-2 trial (Checkmate 032) among small cell lung cancer (SCLC) patients with progression after platinum chemotherapy investigated several combinations of nivolumab and ipilimumab (1mg/kg plus 1 mg/kg, 1 mg/kg plus 3 mg/kg or 3 mg/kg plus 1 mg/kg) every 3 weeks for 4 cycles, followed by nivolumab 3 mg/kg every 2 weeks. Among the 54 patients in the nivolumab 3 mg/kg and ipilimumab 1 mg/kg arm the 7% discontinued treatment because of toxicity related to the study drug (Helloman et al. 2017, Antonia et al. 2016).

There is an enlarging body of evidence of increased clinical benefit from dual PD-1/PD-L1 and CTLA-4 checkpoint blockade in comparison to either agent alone. Dual checkpoint blockade is now a SOC for patients with melanoma, renal cell carcinoma and non-small cell lung cancer (NSCLC, with high TMB). In NSCLC, dual checkpoint blockade significantly prolonged PFS and duration of response (DOR) in comparison to platinum-doublet chemotherapy in patients with high TMB, regardless of PD-L1 TPS (Hellmann et al. NEJM 2018). In metastatic melanoma, long-term follow up data from CheckMate 67 revealed dual checkpoint blockade significantly prolonged PFS versus nivolumab alone and also lead to numerically higher median and 4-year OS rates (Hodi et al. 2018). Benefit of the combination appeared independent of tumor PD-L1 status. Dual checkpoint blockade improved OS, PFS, ORR and DOR versus SOC sunitinib in patients with intermediate and high-risk renal cell carcinoma (Motzer et al. 2018). Relative to single agent checkpoint blockade, dual checkpoint blockade enhanced outcomes in small cell carcinoma high TMB (Hellmann et al. Cancer Cell 2018), improved ORR versus nivolumab in treatment-refractory

sarcoma (D'Angelo et al. 2018), and in DNA mismatch repair-deficient/microsatellite-high colorectal cancer (Overman et al. 2018). Preliminary results of clinical trials of the combination of durvalumab and tremelimumab in recurrent and metastatic head and neck cancer have been disappointing (Liu S. et al ASTRO/HNS/ASCO 2018), however, there is some concern regarding dose and efficacy of tremelimumab relative to ipilimumab. The synergy with dual checkpoint blockade is thought to be multifactorial, including induction of novel responses to neoantigens, decreased activity of Tregs, improved motility and cytotoxicity of activated CD8+ T cells and enhanced immunological memory (Grosso et al. 2013; Zhao et al. 2018).

Given the responses rates and toxicity profile, nivolumab 3 mg/kg every 2 weeks and ipilimumab 1 mg/kg every 6 weeks will be the treatment regimen chosen for this study.

In SCCHN, several ongoing phase 2 trials are investigating anti-PD1 or anti-PD-L1 in combination with anti-CTLA4 in patients with platinum-refractory R/M SCCHN or in first line. In the R/M SCCHN setting in first line (CheckMate 651) or platinum-refractory settings (CheckMate 714), the dose and schedule of nivolumab 3 mg/kg (or fixed dose equivalent) Q2w and ipilimumab 1 mg/kg Q6w is being utilized. Several phase 3 trials are comparing PFS and OS of anti-PD1 (or PD-L1) with or without anti-CTLA4 to standard of care platinum/5-FU/cetuximab ("extreme regimen"). A recent press release of Keynote 048 has reported that single agent pembrolizumab led to superior overall survival in comparison to triple agent platinum based chemotherapy in first line recurrent metastatic disease in patients with a CPS score of >20%, thus immediately changing the standard of care. A single, three-arm phase 3 trial is comparing anti-PD-1 + anti-CTLA4 (Checkmate 651) met accrual goals in December 2018.

A window of opportunity trial in patients with early stage, resectable oropharynx cancer at MDA has randomized 28 patients to anti-PD-L1 +/- anti-CTLA has demonstrated very strong activity in this patient population with the majority of patients experiencing a response at the primary site, and complete responses have been observed. No safety concerns have arisen. These data provide strong preliminary safety and efficacy data. In yet another window of opportunity trial of single agent anti_PD1 in 37 patients with advanced resectable oral cavity cancer has demonstrated a high pathological response rate to a single dose of pembrolizumab and safety of the addition of this agent to adjuvant (chemo)radiotherapy post-operative. All of these studies are currently undergoing intensive biomarker analysis and preparation for submission for publication.

In summary, in SQ-NSCLC the combination of nivolumab 3 mg/kg every two weeks and ipilimumab 1 mg/kg every six weeks led to grade 3-4 TRAE of ~28% with a median number of cycles similar to that proposed in this trial. However, it should be noted that standard of care cisplatin-based chemo-RT to ~70Gy is associated with grade 3-5 TRAE of 77-82% (Nguyen-Tan et al. 2014). IO and RT have minimal overlapping toxicities, with the exception of rash and hypothyroidism, and a total dose of RT to 60 Gy with reduced RT fields would be expected to significantly reduce mucosal and skin inflammation in comparison to 70Gy.

1.7 Checkpoint Inhibitors and RT

RT induces DNA damage and ER stress via reactive oxygen species (ROS), resulting in cell cycle arrest (Derer, Frey, et al. 2015). In addition to direct cytotoxic effects, RT may induce an immune effect important to tumor cell death (Demaria et al. 2005). RT can result in expression of activating cytokines and chemokines that may facilitate CD4+ and CD8+ T cell infiltration into the tumor as well as activation of dendritic cells, stimulating an immune response to the tumor. RT induced necroptosis of tumor may increase the immunogenicity of tumor cells. RT alone does not, however, induced anti-tumor immune responses outside of the radiation field. However, preclinical data support synergy between checkpoint inhibitors and RT (Table 1). Mouse models of poorly

immunogenic tumors have demonstrated that concomitant administration of anti-CTLA-4 antibodies and RT results in antitumor T cell responses both in the radiation field as well as outside of it (an abscopal effect) (Demaria et al. 2005; Dewan et al. 2009). PD-1 blockade after completion of RT also has been shown to induce rejection of persistent tumors in mouse models (Deng et al. 2014). Combination PD-1 blockade and anti-CD137 stimulation increased response to RT in a mouse model of triple negative breast cancer (Verbrugge et al. 2012) and PD-L1 blockade concomitant with RT improved survival in comparison to either therapy alone in mouse models of glioma (Zeng et al. 2013). Activation of dendritic cells (DCs) in response to radiation-induced tumor cell death may initiate innate and adaptive immune responses (Derer, Frey, et al. 2015). These data support a hypothesis that RT-induced cell death may result in alterations in the tumor immune environment (via upregulation of MHC class I, ICAM-1, CD80) as well as presentation of novel tumor antigens and generation of anti-tumor immune responses (Teng et al. 2015).

In addition to novel antigen presentation, recent in vivo data indicate that RT can induce increased PD-L1 expression in tumors and thereby inhibit activation of cytotoxic CD8⁺ T cell responses, thus reducing the efficacy of RT. Concurrent administration of anti-PD1 antibodies improved response to RT and survival in mouse models whereas sequential therapy did not (Dovedi et al. 2014).

There is preclinical and clinical data to support initiation of IO prior to RT for maximal synergy. In vivo models of sequencing of anti-PD-1 and RT have observed maximal anti-tumor effect when anti-PD-1 therapy is administered prior to and during RT (RL Ferris et al, personal communication 2016). In mouse models of colon and breast carcinoma, sequential (i.e. adjuvant) administration of anti-CTLA4 and radiation had reduced therapeutic efficacy relative to concurrent therapy (Dewan et al. 2009). More recent in vivo data support substantial synergy between the combination of anti-PD-1, anti-CTLA4 and RT. Tumor expression of PD-L1 was found to be a mechanism of resistance to anti-CTLA-4 and RT. Twyman-Saint Victor and colleagues demonstrated that genetic elimination of PD-L1 expression by CRISPR technology restored response to tumors that relapsed after RT and anti-CTLA4 therapy (Res 499 and Res 177). (Victor et al. 2015) Notably, in treatment-naïve tumors the combination of anti-PD-1/anti-CTLA4/RT markedly improved response and survival over anti-CTLA-4/RT. In this model, combination immunotherapy was administered prior, during and subsequent to RT. Each modality had a unique effect within the tumor microenvironment. Anti-CTLA4 reduced Tregs and reversed exhaustion of T cells, increasing Ki67+GzmB+CD8⁺ TIL whereas anti-PD-1 expanded CD8⁺ T cells in the tumor microenvironment and peripheral blood. Additionally, RT increased the diversity of the TCR repertoire of TILs in un-irradiated tumors (Victor et al. 2015). The results support combination IO with anti PD-1 and anti-CTLA4 together with RT as is proposed in this trial.

In human subjects, case-reports support the existence of a clinically significant abscopal effect for patients with melanoma who have received ipilimumab prior to RT (Grimaldi et al. 2014; Stameell et al. 2013; Postow et al. 2012). Moreover, induction IO with INF-alfa(2b) and immune- RT demonstrated efficacy in locally advanced melanomas (Hazard, Sause, and Noyes 2002; Conill et al. 2007) and neoadjuvant evaluation revealed a significant immunomodulating role for ipilimumab on Treg, MDSC and effector T cells in the circulation and tumor microenvironment in melanoma patients (Tahini et al. 2014).

Moreover, two trials have recently investigated the safety of anti-CTLA-4 (ipilimumab) in combination with cetuximab-IMRT to 68-70Gy (NCT01935921) or of anti-PD-1 (pembrolizumab) in combination with weekly cisplatin-IMRT to 70Gy in local-regionally advanced SCCHN (NCT02586207). In the former trial, the dose of ipilimumab was de-escalated from 3 to 1mg/kg for four doses Q3 weeks starting week 5 of RT. Two patients experienced a DLT of grade 4 radiation dermatitis at the dose of ipilimumab 3 mg/kg (J Bauman, personal communication). The dose of ipilimumab 1 mg/kg was recommended for future study. In the latter study, fixed-dose

pembrolizumab 200 mgs was started 7 days prior to RT and continued for 8 doses. Thirty patients have been enrolled to date and no unexpected toxicities have been observed (Powell J Clin Oncol 34, 2016, abstract TPS6107). A complete response rate of 100% has been observed in this study (J Lee, personal communication). Additionally, a recently completed safety evaluation trial (RTOG 3504) includes 4 treatment arms designed to evaluate the safety of nivolumab concurrent with cetuximab-IMRT 68-70Gy, high-dose cisplatin 100 mgs/m² X 3-IMRT 68-70 Gy, weekly cisplatin 40 mg/m²/week X 7 and IMRT 68-70GY and IMRT 68-70Gy. No DLTs or other safety concerns were identified. Disease control has also been excellent with a median follow-up of over 12 months.

Johnson and colleagues at Jefferson University presented safety data of the combination of nivolumab, ipilimumab and radiotherapy at ASCO 2019. Eligible patients included those with local-regionally very advanced Stage IVA-B HNSCC and ECOG PS 0-1. Patients received nivolumab 3 mgs/kg every 2 weeks for 17 doses and ipilimumab 1 mg/kg every 6 weeks for 6 doses, starting 14 days prior to start of 70Gy RT (2 Gy per fraction/35 fractions). DLT was defined as any grade >3 in radiation field toxicity within two weeks after completion of radiotherapy. Safety data for a total of 12 patients were presented. Three of 12 patients experienced grade 3 immune mediated events, including colitis, lipase increase or hyperglycemia. Rates of grade 3 dysphagia (4 of 12), oral mucositis (3 of 12), odynophagia (2 of 12) and radiation dermatitis (1 of 12) were similar to that expected with radiotherapy alone. No DLT events were observed. However, 2 of 12 patients had radiation ulcer with or without bleeding more than three months after completion of RT. In one patient, the bleeding event was fatal (carotid rupture). Ten of 12 patients are alive without evidence of disease after 10 to 21 months of follow-up. To date, no emergent safety signals have been observed and disease control is very promising. Accrual of an additional 12 patients is ongoing.

Table 1: Systemic effects observed in preclinical studies after multimodal treatment of RT and anti-PD1/PDL-1 or anti-CTLA4 (Modified from Derer et al, Frontiers in Immunology 2015) (Derer, Deloch, et al. 2015)

Checkpoint	Tumor type	Treatment	Systemic effect
PD-1	Melanoma (B16), renal cortical adenocarcinoma (RENCA) ¹	SABR (15Gy) + anti-PD-1 mAb (5x)	Near complete-regression of primary tumor, 66% size reduction of non-irradiated tumor, increase CD8+ CTLs
	Glioma (GL261) ²	RT (10Gy)+ anti-PD-1 mAb i.p.	Tumor regression and long-term survival, decrease Tregs, increase CD8+ CTLs and INFgamma
	Melanoma (B16), Breast carcinoma (4T1-HA) ³	RT (12Gy)+ anti-PD-1 mAb i.p. (x3)	Tumor regression and tumor control, decrease Tregs, increase CD8+ CTLs
PD-L1	Mammary Carcinoma (TUBO) ⁴	SABR (12Gy) + anti-PD-L1 mAb (4x)	Side reduction of primary and abscopal tumors, decrease MDCS, increase CD8+ CTLs
PD-1 and CD137	Triple negative breast Cancer: AT-3 tumors ⁵	RT (4 X 4 Gy or 4 X 5 Gy)+ anti PD-1 + anti-(α)-CD137	Therapy in combination with either 4 X 4 Gy or 4 X 5 Gy was more effective in controlling tumor outgrowth than either treatment alone; achieving rejection rates of 40% and 80%, respectively, increase CD8+ CTLs

CTLA4	Metastatic mammary carcinoma ⁶	RT (2x12 Gy) primary tumor + anti-CTLA4 (x3)	Inhibition of lung metastases, increase CD8+ CTLs
	B16-F10 melanoma mouse model ⁷	Anti-CTLA4 (before or concurrent) + RT	Complete responses were CD8 T-cell-dependent.
	Cell lines that relapse after RT+ anti-CTLA4 (Res 499 and Res 177) ⁷	Resistance study	Best predictor of resistance CD8/Treg ratio. Genetic elimination of PD-L1 on Res 499 by CRISPR restored response by increasing survival from 0 to 60%

1. Park SS et al, Cancer Immunol Res 2015. 2. Zeng J et al, Int J Radiat Oncol Biol Phys 2013 3. Sharabi AB et al, Cancer Immunol Res 2015 4. Deng L et al, J Clin Invest 2014 5. Verbrugge et al, Cancer Research 2012. 6. Demaria S, Clin Cancer Res 2005. 7. Twyman-Saint Victor, Nature 2015.

These data support a hypothesis that combination IO concurrent with RT will be safe, feasible and synergistic and will induce clinically significant anti-tumor immune responses induced by “vaccination” to tumor-specific antigens exposed during radiation-induced cell death (Demaria and Formenti 2012). Such a phenomenon may be particularly relevant to viral-induced tumors, such as HPV-positive SCCHN. An advantage of “neoadjuvant” or “induction” IO is the ability to perform tumor biopsy before and after exposure in previously untreated patients in order to perform exploratory biomarker studies to identify immunological and histological correlates of tumor response.

Table 2: Systemic effects observed in clinical trials after multimodal treatment of RT and anti-CTLA4 (Modified from Derer et al, Frontiers in Immunology 2015) (Derer, Deloch, et al. 2015)

Checkpoint	Tumor type	Treatment	Systemic effect
CTLA4	Melanoma with brain metastasis (n=21) ¹	Ipilimumab x4 + loco-regional RT	13/21 local responses, 11/21 local responses with abscopal effect and 2/21 stable disease
	Metastatic castration-resistant prostate cancer (n=799) (NCT00861614) ²	RT (1x8Gy) per lesion =1-4 doses of ipilimumab (n=399) or placebo (n=400)	Improve median OS
	Metastatic melanoma (phase I) (NCT01497808) ³	SBRT plus Ipilimumab (Escalating dose)	Major tumor regressions

1. Grimaldi AM, Oncoimmunology 2014. 2. Known ED, Lancet Oncol 2014. 3. Twyman-Saint Victor C, Nature 2015.

1.8 Rationale for using the FDG-PET/CT as a predictive imaging marker in HPV-positive OPSCC.

In this trial we will monitor FDG-PET CT response at 12-14 weeks after completion of radiotherapy as an early surrogate of long-term disease control in the study population. This FDG-PET/CT evaluation is included in the National Comprehensive Cancer Center Guidelines and is considered within the standard of care. This evaluation is utilized to guide need for salvage surgical resection of persistent disease (Loo et al. 2011; Nayak et al. 2007; Martin et al. 2009). A recently reported

randomized clinical trial (PET-NECK) demonstrated equivalent OS for FDG- PET/CT surveillance vs. planned neck dissection after chemo-RT for local-regionally advanced SCCHN.

The literature provides criteria for interpretation and estimates for FDG-PET/CT metabolic complete response (CR) rates obtained for HPV-positive oropharyngeal cancer patients when treated with standard of care chemoradiotherapy. Marcus et al have developed and validated a 5-point scoring system for PET-CT interpretation that has high inter-reader agreement and that strongly stratifies risk for cancer progression (Marcus et al. 2014). Among 123 HPV-positive cases, the metabolic CR by PET at ~12 weeks was 87%. Investigators at the University of Michigan reported an analysis of FDG-PET/CT response among 101 patients with Stage 3-4 (94% stage 4) HPV-positive oropharyngeal cancer treated with chemoradiation (Vainshtein JM Oral Oncol 2014). SUVmax thresholds of 6.5 for the primary tumor and 2.8 for the lymph nodes were used as cut-points to distinguish metabolic CR from less than CR, a cut-point established by discrimination of patients who had subsequent disease progression (Moeller B et al J Clin Oncol 2009). At 3-months, 92% of cases achieved a CR. Chen and colleagues utilized a lower threshold of SUVmax of 2.0 among 67 patients with HPV-positive oropharynx cancer treated with chemoradiotherapy. The lower threshold resulted in a lower metabolic CR rate of 70% (Chen JY Arch Otolaryngol Head Neck Surg 2012).

In the PET NECK trial, 75% of patients enrolled in the trial had HPV-positive OPSCC (Mehanna et al. 2016). A metabolic CR (interpreted per local practice without central review) was documented in 69% of patients, however, 25% of patients had FDG-PET/CT performed 10 or fewer weeks post completion of RT. The sensitivity and specificity of FDG-PET/CT for persistent disease after chemo-RT strongly depend upon the time interval between the completion of therapy and FDG-PET/CT, with both improved when performed at least 12 weeks from RT (Yao et al. 2009; Sandro V. Porceddu et al. 2011). Residual uptake prior to 12 weeks is attributable to treatment-related inflammation.

Importantly, a negative FDG-PET/CT at 12-14 weeks has a very high negative predictive value (NPV) for the presence of persistent disease (S Porceddu et al. 2014; Sandro V. Porceddu et al. 2011). A meta-analysis of 2335 patients estimated post-treatment FDG-PET/CT >12 weeks post RT to have a 91.9% sensitivity and 86.7% specificity for residual disease at the primary site and 90.4% and 94.3% for nodal disease (Gupta et al. 2011).

Several studies have indicated that a negative FDG-PET/CT post RT has a high predictive value for long-term local-regional disease control. Bird and colleagues recently reported performance characteristics of FDG-PET/CT for residual disease in 146 OPSCC patients, the majority (92%) of which were treated with platinum or cetuximab together with IMRT 65Gy in 30 fractions. A positive post-treatment FDG-PET/CT was vaguely defined as “suspicious for residual or regional tumor”. In this study, sensitivity, specificity, positive predictive-value (PPV) and NPV for detection of residual disease were estimated as 92%, 85%, 56% and 98%, respectively. Only 9.6% of patients in this study underwent neck dissection as a result of an abnormal FDG-PET/CT, and 36% were positive for cancer. Thus, only 5 (3.4%) of 146 patients had pathologically confirmed persistent disease. Most importantly, the investigators observed a 92% 3-year DFS among patients with HPV-positive OPSCC who had a 12 week FDG-PET/CT with either a complete metabolic response (CMR) or an equivocal metabolic response followed by a CMR at a repeat FDG-PET/CT 12 weeks later. Additional studies have reported NPV of ~98% associated with negative FDG-PET/CT scans post treatment (Yao et al. 2009; Ryan et al. 2005; Moeller et al. 2009). Therefore, in HPV-positive OPSCC, a CR on FDG-PET/CT is a reasonable surrogate biomarker for 3-year local-regional and overall disease control.

Residual treatment-related inflammatory response is thought to account for the reduced specificity of FDG-PET/CT scans performed prior to 12 weeks after RT. In this trial it is possible that the

performance characteristics of post-treatment FDG-PET/CT could be altered by immunotherapy. No formal studies have yet evaluated this concern in any tumor type, including melanoma. However, FDG-PET/CT is commonly utilized to assess treatment response to immune modulation and used for follow-up to detect recurrence in melanoma (Perng, Marcus, and Subramaniam 2015). It has been noted, however, that pseudo progression, immune-related toxicities (e.g. colitis, hypophysitis), and mild inflammatory FDG uptake in lymph nodes can be detectable by FDG-PET/CT in patients on IO. In the latter case, SUV uptake is generally equivocal and is noted to resolve on repeat FDG-PET/CT.

As noted above, a scoring system for post-treatment FDG-PET/CT for SCCHN patients was recently validated by Marcus et al (The Hopkins Criteria). The five-point scoring system indicated in the Table below had high inter-rater agreement (kappa ~0.70) and high AUC (0.98) in comparison to 6 month clinical follow-up for local-regional disease progression (Marcus et al. 2014). To align with NRG HN002 interpretation, a score of 1 or 2 will be considered negative, a score of 3 indeterminate, and a score of 4 or 5 will be positive. The standard of care for individuals with a positive FDG-PET/CT is further evaluation with ultrasound and fine needle aspiration biopsy followed by salvage surgery at the primary site and/or lymph nodes. Because of moderate PPV and sensitivity of FDG-PET/CT for residual disease, however, histopathological confirmation of residual disease is considered necessary for documentation of treatment “failure.”

Five-Point Qualitative Post therapy Assessment Scoring System (Hopkins Criteria) for Head and Neck FDG-PET/CT/CT (Marcus et al. 2014)

Score	FDG uptake pattern	Response category
1	FDG uptake at the primary site and nodes less than IJV.	Complete metabolic response
2	Focal F-FDG uptake at the primary site and nodes greater than IJV but less than liver.	Likely complete metabolic response
3	Diffuse F-FDG uptake at the primary site or nodes is greater than IJV or liver.	Likely post-radiation inflammation
4	Focal F-FDG uptake at the primary site or nodes greater than liver.	Likely residual tumor
5	Focal and intense F-FDG uptake at the primary site or nodes.	Residual tumor

IJV: Internal Jugular Vein. Scores 1, 2, and 3, which represent complete metabolic response, likely complete metabolic response, and likely post-radiation inflammation, respectively, were considered negative for tumor. Note, a score of 3 requires repeat PET in 12 weeks per protocol. Scores 4 and 5, which represent likely residual tumor and residual tumor, respectively, were considered positive for tumor. New lesion would be considered as progressive disease.

In summary, in this trial we will monitor metabolic CR rate as measured by FDG-PET/CT at 12- 14 weeks post treatment as defined by the Hopkins Criteria and validated by Marcus et al. Prospective studies have established that a metabolic CR has a high predictive value (~95%) for 3-year progression-free survival. An overall metabolic CR rate of 87% would be expected in the patient population when treated by standard chemoradiotherapy.

1.9 Rationale for assessment of tumor HPV status by p16 IHC and HPV DNA in situ hybridization detection for HPV Testing.

Tumor p16 expression as measured by immunohistochemistry (IHC) is a common clinical surrogate for tumor HPV status and is scored as positive if strong and diffuse nuclear and cytoplasmic staining is present in $\geq 70\%$ of tumor cells (Jordan et al. 2012). The p16 IHC assay is readily available, inexpensive, and has excellent interrater agreement on interpretation (Jordan et al. 2012). Moreover, the laboratory methods used for p16 IHC and HPV16 ISH have demonstrated good prognostic value on formalin fixed, paraffin-embedded (FFPE) material (Ang KK et al. 2010).

When restricted to testing of OPSCC, the assay has high sensitivity ($\geq 90\%$) but only moderate ($>80\%$) specificity when compared to the gold standard of high-risk HPV mRNA expression (Thavaraj et al. 2011). Despite being the gold standard for causality, HPV E6/E7 RNA detection is difficult to reproduce on a clinical setting. Therefore, to improve specificity of testing a common algorithm recommends p16 IHC as a first step due to its high sensitivity, followed by HPV DNA ISH methods for use as confirmation of the viral aetiology, leading to less equivocal molecular classification (Smeets et al. 2007). The combination of p16 IHC and HPV DNA ISH has demonstrated 98% specificity in comparison to HPV mRNA expression (Jordan et al. 2012)(Thavaraj et al. 2011).

An alternative to confirmation with HPV DNA ISH is HPV RNA ISH with the RNAscope HPV test. High concordance between RNA ISH and p16 IHC of 96.4% or DNA ISH of 83.5% has been observed (Ukpo et al. 2011; Bishop et al. 2012). In comparison to the gold standard of HPV E6/E7 mRNA by reverse transcriptase PCR, RNAscope had a sensitivity of 93-97%, specificity of 93- 94%, positive predictive-value of 91-96% and negative predictive value of 88-98% (Mirghani H. et al. 2015; Schache et al. 2013).

Clinical trials investigating “de-intensification” strategies for patients with HPV-positive OPSCC should require high specificity to avoid false positives and consequent under treatment of patients with true HPV-negative OPSCC. Therefore combined positivity for both p16 IHC and HPV ISH is necessary to provide the high specificity required (Jordan et al. 2012). The combination of p16 IHC and RNAscope is a reasonable clinical alternative to p16 IHC and HPV DNA ISH.

Rationale for Principal Secondary Outcome of Pharyngeal Dysphagia

Fortunately, survival rates from HPV-positive oropharyngeal cancer are high, but as a consequence long-term toxicities of radiotherapy in this patient population have become problematic. The most frequent high-grade (CTCAE grade 3-4) long-term toxicity reported with standard of care chemoradiotherapy is dysphagia, traditionally measured by g-tube dependence. G tube dependence at 1 and 5 years is $\sim 26\text{-}28\%$ and $6\text{-}13\%$ with cisplatin-based chemoradiotherapy (Nguyen_tan JCO 2014). Rates appear slightly lower among p16-positive patients ($\sim 17\%$ and 5%), likely due to lower T stage and thus treatment volumes to the oropharynx. However, the effect on quality of life for patients from chronic swallowing dysfunction is underrepresented by g-tube dependence alone and should include dysphagia that can result in life threatening complications (aspiration pneumonia), nutritional deficiencies, and psychosocial morbidity. Hutcheson and colleagues at MD Anderson have developed and validated a 5-point grading system (dynamic imaging grade of swallowing toxicity or DIGEST) for interpretation of modified barium swallow studies that combines an assessment of safety and efficiency of swallowing function (Hutcheson Cancer 2017). Additionally, pharyngeal dysphagia DIGEST grade inversely correlated with patient perception of swallowing dysfunction as measured by MDADI. Approximately 31% of patients with any stage oropharynx cancer treated with IMRT experience Grade 2 or greater dysphagia 3-6 months after radiotherapy as measured by DIGEST (Kamal 2018). Sixteen percent (16%) of low to intermediate risk oropharyngeal carcinoma patients (AJCC 7th ed. T1-2 N0-2b, T3N0) treated with

primary displayed pharyngeal dysphagia DIGEST grade 2 or higher (Hutcheson, manuscript under review). Rates of pharyngeal dysphagia are affected by the total dose of radiotherapy (in particular to laryngeal, submental and pharyngeal constrictors), field size and exacerbated by concurrent chemotherapy. Alterations in radiation dose to 55-60 Gy and to treatment volume as proposed in this trial have the potential to reduce the frequency and severity of pharyngeal dysphagia as measured by DIGEST by ~25% (from 40% to 30%).

Summary of Rationale

- Long-term toxicities of platinum-based chemo-RT are a concern for patients with HPV-positive OPSCC given they are young at diagnosis and have high survival rates.
- Recent trials have demonstrated that local-regional control and progression-free survival can be maintained with CT and reduced dose IMRT among patients with low-intermediate volume (T4, <N3) HPV-positive OPSCC.
- Anti-PD1 therapy with nivolumab reduced the risk of death by ~50% in patients with platinum-refractory HPV-positive OPSCC in comparison to standard of care single agent chemotherapy, regardless of PD-L1 expression, indicating responsiveness to IO even when refractory to CT and RT.
- Combination IO with anti-CTLA4 (ipilimumab) and anti-PD1 (nivolumab) increases durable response rates in patients with melanoma and NSCLC in comparison to anti-PD-1 therapy along and is currently under investigation in phase 3 trials for first line therapy of R/M SCCHN.
- Ongoing clinical trials of the addition of anti-PD1 (Pembrolizumab) to platinum-based chemo-RT and anti-CTLA4 to cetuximab-based chemo-RT for patients with local-regionally advanced SCCHN have demonstrated no safety concerns to date.
- Preclinical models demonstrate substantial synergy between anti-PD-1 and anti-CTLA-4 and RT.
- HPV-positive OPSCC is an excellent candidate for IO given higher TIL, higher interferon-associated inflammation gene signature and higher PD-L1 expression in comparison to HPV-negative SCCHN.
- Therefore, we designed a phase 1/2 clinical trial to investigate combination immuno-RT with anti-PD1 (Nivolumab) and anti-CTLA4 (Ipilimumab) with reduce field and dose of intensity modulated radiation therapy (IMRT) in patients with low-volume (T1 N2, T2 N1- 2, T3 N0-2), local-regionally advanced HPV-positive OPSCC.

2. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

2.1 Patient Selection Guidelines

Investigators should consider all relevant medical and non-medical factors and the risks and benefits of study therapy when deciding if a patient is an appropriate candidate for this trial.

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

Women of childbearing potential and men who are sexually active should be willing and able to use medically acceptable forms of contraception throughout the treatment phase of the trial and until at least 23 weeks (161 days) for women and 31 weeks (217 days) for men following the last dose of study treatment (nivolumab or ipilimumab).

Submission of biospecimens (tumor) is mandatory for this trial. Therefore, investigators should consult with pathology departments about availability and release of specimens before discussing enrollment with a patient.

Subjects must have signed and dated the approved written informed consent form in accordance with regulatory and institutional guidelines. This must be obtained before the performance of any protocol related procedures that are not part of normal subject care.

2.2 Eligibility Criteria

- 2.2.1** Histologically or cytologically newly confirmed diagnosis of squamous cell carcinoma (including the histological variants of papillary or basaloid) of the oropharynx (tonsil, base of tongue, soft palate, or oropharyngeal walls).
- 2.2.2** Clinical AJCC 7th edition stage T1N2a-N2cM0, T2N1-N2cM0, T3N0-N2cM0, excluding T1N0-N1 and T2N0, equivalent to AJCC 8th edition stage 1 and 2 (T1 N1-N2, T2 N1-N2, T3 N0-N2) (Brian O'Sullivan et al. 2016).
- 2.2.3** Tumor positive for p16 IHC (defined as greater than 70% strong nuclear or nuclear and cytoplasmic staining of tumor cells) (Jordan et al. 2012) and HPV DNA in situ hybridization or HPV mRNA RNAScope. Repeat samples may be required if adequate diagnostic tissue is unavailable for testing.
Note: Although confirmation of tumor HPV-positive status via DNA ISH or RNAScope is preferred, cobas HPV testing may be performed for patients who only have banked tissue from FNA biopsy.
- 2.2.4** PD-L1-positive status as determined by an immunohistochemistry assay.
- 2.2.5** Zubrod Performance Status of 0-1
- 2.2.6** Age ≥ 18 years
- 2.2.7** Patients must have radiographically evident measurable disease at the primary site or at nodal stations per RECIST 1.1 documented by diagnostic quality CT or MRI of the neck with contrast within 28* days prior to registration; a FDG-PET/CT of the neck performed for the purposes of radiation planning is acceptable as a substitute if the CT is of diagnostic quality
- 2.2.8** Diagnostic quality cross sectional imaging of the thorax within 28* days prior to registration. A 18-FDG-PET/CT or conventional CT are acceptable.
- 2.2.9** FDG-PET/CT of the neck is required within 28* days prior to registration for comparison to post treatment FDG-PET/CT. Note: Repeat imaging for variability within 96 hours of this time frame should be allowed to avoid unnecessary re-imaging and its financial potential physical consequences for patients.
- 2.2.10** History and physical exam within 1 month prior to registration.
- 2.2.11** Fiberoptic exam with laryngopharyngoscopy (mirror and/or fiberoptic and/or direct procedure) by Radiation Oncologist, Medical Oncologist or ENT/Head and neck surgeons within 28 days prior to registration;
- 2.2.12** Adequate hematologic function within 2 weeks prior to registration, defined as follows:
- Absolute neutrophil count (ANC) ≥ 1,500 cells/mm³;
 - Platelets ≥ 100,000 cells/mm³;
 - Hemoglobin ≥ 8.0 g/dl; Note: The use of transfusion or other intervention to achieve Hgb ≥ 8.0 g/dl is acceptable.
- 2.2.13** Adequate renal function within 2 weeks prior to registration, defined as follows:
- Serum creatinine < 1.5 mg/dl or creatinine clearance (CC) ≥ 50 ml/min determined by 24-hour collection or estimated by Cockcroft-Gault formula:

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

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

2.2.14 Adequate hepatic function within 2 weeks prior to registration defined as follows:

- Bilirubin < 2 mg/dL;
- AST or ALT < 3 x the upper limit of normal

2.2.15 Na, K, Cl, glucose, Ca, Mg, albumin, amylase, lipase, TSH within 2 weeks prior to registration

2.2.16 Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential;

2.2.17 Seronegative for active Hepatitis-B or hepatitis-C infection and seronegative for HIV.

2.2.18 Mandatory submission of hematoxylin and eosin (H&E) and paraffin-embedded tumor block or unstained slides.

**Note: 4 day window allowed for the 28 day-window assessments*

2.3 Exclusion Criteria

2.3.1 Cancers of the oral cavity (oral tongue, floor mouth, alveolar ridge, buccal or lip), or the nasopharynx, hypopharynx, or larynx, even if p16 positive;

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

2.3.3 Definitive clinical or radiologic evidence of metastatic disease or adenopathy below the clavicles;

2.3.4 Gross total excision of both primary and nodal disease with curative intent; this includes tonsillectomy, local excision of primary site, and nodal excision that removes all clinically and radiographically evident disease;

2.3.5 Simultaneous primary cancers or separate bilateral primary tumor sites;

2.3.6 Prior invasive malignancy (except non-melanomatous skin cancer) unless disease free for a minimum of 1095 days (3 years) (for example, carcinoma in situ of the breast, oral cavity, or cervix are all permissible);

2.3.7 Prior systemic chemotherapy for the study cancer; note that prior chemotherapy for a different cancer is allowable; patients who have received PD-1/PD-L1 or CTLA4 therapy for a previous malignancy are not eligible;

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

2.3.9 Severe, active co-morbidity defined as any of the following:

- Unstable angina and/or congestive heart failure requiring hospitalization 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;
- A diagnosis of immunodeficiency or use of any form of systemic immunosuppressive therapy. The use of physiologic doses of corticosteroids may be approved after consultation with the Sponsor.

2.3.10 Active autoimmune disease that has required systemic treatment in past 2 years (i.e. with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (e.g., thyroxine, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency, etc.) is not considered a form of systemic treatment. Steroid premedications for contrast allergy allowed (see below).

2.3.11 Has evidence of active, non-infectious pneumonitis.

2.3.12 Has received a live vaccine within 30 days of planned start of study therapy.

2.3.13 Pregnancy or breast-feeding; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

2.3.14 History of severe hypersensitivity or contraindication to CT or PET contrast material uncontrolled

with pre-medications (steroids, antihistamines).

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

3.1 Assessments pre-treatment:

Assessments	Days prior to C1D1 (unless specified)**
Informed Consent	28
Patient's smoking history	28
History and physical examination included height & weight ^A	28
Fiberoptic exam with laryngopharyngoscopy	28
CT/MRI of neck	28
Chest imaging (CT or FDG-PET/CT/)	28
FDG-PET/CT of neck*	28
Zubrod Performance Status	14
Cell blood count/differential	14
Bilirubin, AST or ALT	14
Serum creatinine or creatinine clearance	14
HIV testing	14
Hepatitis B and C testing	14
T3 (total or free), T4 and TSH	14
Serum pregnancy test, if applicable	14 days prior to ipi/nivo
Na, K, Cl, glucose, Ca, Mg, and albumin	14
Hepatic function panel, lipase, amylase	14
EKG	28
Modified Barium Swallow	any time before treatment start
MDASI/MDADI***	any time before treatment start
Tumor Specimen	28
Oral rinse sample	14
Blood biospecimens****	day 1 prior to ipi/nivo

*NOTE: Use of the same PET/CT scanner is strongly recommended for each on-protocol assessment.

**4 day window allowed for the cut-point for the 28 day window assessments

*** See Appendix II

****Collection of blood biospecimens will be obtained 1 day prior to ipi/nivo and as follows:

- 2 x 10 cc red top tubes for serum, WBC

- 2 x 10 cc Streck tubes for plasma

^A Concomitant medications will be captured in the participants' medical record.

3.2 Assessments during treatment:

Assessments	Prior to each dose of IO ^B
Physical examination including height & weight ^{A,C}	X (height only at baseline)
Fiberoptic exam with laryngopharyngoscopy	Within 7 days of start of radiation therapy
Adverse events evaluation ^C	X
Zubrod Performance Status ^C	X
Cell blood count/differential ^C	X
Bilirubin, AST or ALT ^{**}	X
Serum creatinine or creatinine clearance ^{**}	X
T3 (total or free), T4 and TSH ^{**}	Prior to start of every cycle
Na, K, Cl, glucose, Ca, Mg, and albumin ^{**}	X
Lipase, amylase, hepatic function panel ^{**}	X
Serum pregnancy test, if applicable	Within 24 hours of first ipi/nivo and every 4 weeks until end of therapy
Tumor biopsy	Cycle 1 Days 15-22 for first 15 patients that have started on therapy OR Cycle 1 Days 36-43 for the remainder of eligible participants that have started therapy
Oral rinse collection ^C	X
Blood biospecimen collection ^{***, C}	X ^{***}
MDASI/MDADI	Within 7 days after last day of radiotherapy
CT/MRI of Neck [*]	Within 7 days before first dose of radiotherapy

*Chosen imaging modality should be same as baseline

**Blood work window may be within 48 hours of each dose of immunotherapy

***Collection of blood biospecimens will be as follows:

- 2 x 10 cc red top tubes for serum, WBC
- 2 x 10 cc Streck tubes for plasma

^A Concomitant medications will be captured in the participants' medical record.

^B Subjects may be dosed with nivolumab no less than 12 days from the previous dose.

Ipilimumab dosing should occur within a +/- 3 day window.

^C These assessments should be performed relative to IO dosing within 48 hours prior to IO dose, including collection of oral rinses and blood correlative samples.

3.3 Assessments post treatment, follow-up:

Assessments	Timing post treatment		
	4 weeks after the last dose of Nivolumab	3 months from the end of IMRT (12-14 weeks)	Every 3 months from the end of IMRT during first 2 years; every 6 month for 3 years, after annually
Physical examination included height & weight ^A	X	X	X
CT/MRI of neck*	8-10 weeks after RT	X	At 6, 9, and 12 mon after RT then every 6 mon X 1 year.
FDG-PET/CT of neck and chest +/- contrast**		X	At 6 mon after RT in patients with an equivocal FDG-PET/CT at 12- 14 weeks, then only in the event of suspicion of disease
Chest CT			12 and 24 months from end of RT
Modified Barium Swallow			3- 6 months from end of RT (+/- 6 week window)
MDADI/MDASI			18-24 months from end of RT (+/- 2 month window)
Adverse events evaluation	X	X	
Treatment related late toxicity			X
Zubrod Performance Status	X	X	X
Cell blood count/differential	X	X	
Bilirubin, AST or ALT	X	X	
Serum creatinine or creatinine clearance	X	X	
T3 (total or free), T4 and TSH	X	X	
Na, K, Cl, glucose, Ca, Mg, and albumin	X	X	
Serum pregnancy test, if applicable	X	X	
Oral rinse collection	X	X	X

Blood biospecimen collection	X***	X	
Biopsy	If suspicious of tumor recurrence		

*Chosen imaging modality should be same as baseline

**NOTE: Use of the same PET/CT scanner is strongly recommended for each on-protocol assessment.

***Collection of blood biospecimens will be performed 4 weeks after the last dose of Nivolumab and as follows:

- 2 x 10 cc red top tubes for serum, WBC
- 2 x 10 cc Streck tubes for plasma

^A Concomitant medications will be captured in the participants' medical record.

^B For patients requiring FDG-PET/CT at 6 months (due to an equivocal FDG-PET/CT at 12-14 weeks), a CT/MRI of neck is not required at 6 months after RT.

4. DRUG INFORMATION

Investigational Study Agent

Study drug includes Investigational [Medicinal] Product (IP/IMP) and can consist of the following:

Product Description / Class and Dosage Form	Potency	Blinded or Open Label	Packaging / Appearance	Storage Conditions (per label)
Nivolumab Injection ^a	100 mg/vial (10 mg/mL)	Open Label	10mL vial containing a clear to opalescent, colorless to pale yellow liquid; may contain particulates	Store 2 to 8°C. Store in original package. Do not freeze. Protect from light.
Ipilimumab Injection	200 mg/vial (5 mg/mL)	Open Label	40mL vial containing a clear, colorless liquid; may contain particulates	Store 2 to 8°C. Store in original package. Do not freeze. Protect from light.

^a May be labeled as either "BMS-936558-01" or "Nivolumab".

4.1 Treatment plan/regimen description

4.1.1 Nivolumab and Ipilimumab dosing

Subjects will receive a total of two, six-week cycles starting 6 weeks prior to start of RT.

Intravenous nivolumab 3 mg/kg will be administered over 30 minutes on day 1, 15, and 29 and ipilimumab 1 mg/kg over 30 minute on day 1 of a six week cycle.

When nivolumab and ipilimumab are administered on the same day, separate infusion bags and filters must be used for each infusion. Nivolumab is to be administered first. The second infusion will always be ipilimumab and will start no sooner than 30 minutes after completion of the nivolumab infusion. Subjects who require small volumes may infuse over < 30 minutes but no less than 20 minutes.

Nivolumab and ipilimumab may be diluted in 0.9% Sodium Chloride Solution or 5% Dextrose solution.

Dosing calculations should be based on the actual body weight. If the subject's weight on the day of dosing differs by >10% from the weight used to calculate the prior dose, the dose must be recalculated. All doses should be rounded to the nearest milligram. There will be no dose reductions allowed for toxicity both nivolumab and ipilimumab.

Subjects may be dosed with nivolumab no less than 12 days from the previous dose. Ipilimumab dosing should occur within a +/- 3 day window. There are no premedications recommended.

Doses of nivolumab and/or ipilimumab may be interrupted, delayed, or discontinued depending on how well the subject tolerates the treatment. No dose de-escalations will occur.

Dosing Schedule

	Week 1 (C1D1)	Week 3 (C1D15)	Week 5 (C1D29)	Week 7 (C2D1) (Start IMRT)	Week 9 (C2D15)	Week 11 (C2D29)
Nivolumab 3 mg/kg	X	X	X	X	X	X
Ipilimumab 1 mg/kg	X			X		
Ipilimumab 1 mg/kg (Alternate schedule if DLT observed)	X					X

Definition of dose limiting toxicity

The period of observation for a DLT is from the first dose of nivolumab/ipilimumab through to 28 days after the completion of RT.

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

- Any \geq grade 3 adverse event (CTCAE, v. 4) that is related to nivolumab/ipilimumab that does not resolve to grade 1 or less within 28 days;
- A delay in RT of >1 week due to toxicity related to nivolumab/ipilimumab; Inability to complete RT due to toxicity related to nivolumab/ipilimumab;

- Grade 3 or greater radiation mucositis that does not resolve to <3 within 28 days from end of RT.

Note: Toxicity related to nivolumab/ipilimumab that does not affect delivery of RT is not a dose limiting toxicity unless it satisfies criteria 1 noted above. In the event of 0-2 nivolumab/ipilimumab attributable DLT events, the study will proceed to phase 2. In the event of >2 of 8 nivolumab/ipilimumab attributable DLT, a second cohort of 8 patients will be enrolled at an alternate schedule in which ipilimumab will be administered on cycle 2 day 29, equivalent to an every 12 week schedule of ipilimumab. This alternate schedule is chosen due to the possibility of increased inflammation within the RT field, as indicated by the two grade 4 radiation dermatitis events in the completed trial of the addition of ipilimumab to cetuximab-RT at the University of Pittsburgh. We note, however, that this occurred with concomitant cetuximab and a total RT dose to 68-70 Gy.

5. TREATMENT MODIFICATIONS/MANAGEMENT

Nivolumab and ipilimumab should be administered only if all hematological and non-hematological toxicity criteria are met.

There will be no dose modifications for nivolumab or ipilimumab. Instead, the dose will be delayed or discontinued as specified below.

Nivolumab may be continued in the event of a toxicity that in the opinion of the investigator is attributable to ipilimumab after review with the principal investigator.

Radiation therapy may continue at the discretion of the treating physician if nivolumab and/or ipilimumab are held unless specific criteria to hold RT are met.

If RT is delayed due to technical or scheduling constraints, the schedule of nivolumab and/or ipilimumab administration should not be altered.

Tumor assessments for all subjects should continue as per protocol even if nivolumab and/or ipilimumab dosing is delayed (FDG-PET/CT will be performed 12 to 14 weeks from the end of IMRT).

5.1 IO Dose Modifications

5.1.1 Dose Delay criteria for Nivolumab and Ipilimumab

Dose delay criteria apply for all TRAEs. Treatment delay may be up to 6 weeks for nivolumab and up to 12 weeks for ipilimumab from the last dose.

Nivolumab/Ipilimumab administration should be delayed for CTCAE, version 4, toxicities as indicated in the tables below that in the opinion of the treating physician are related to the study drug. Please note nivolumab and or ipilimumab therapy will not be delayed for the following:

- Grade 2 weight loss;
- Grade 2 nausea that in the opinion of the investigator is related to radiation;
- Grade 3 radiation dermatitis;
- Any Grade 2-3 mucositis, dysphasia, or pharyngolaryngeal pain that in the opinion of the treating physician is related to radiation therapy for head and neck cancer;
- Grade 3 or 4 isolated lymphopenia;
- Grade 3 asymptomatic elevation of lipase or amylase

- Grade 3 isolated anemia if, in the opinion of the treating physician, the anemia is not related to the study drug (e.g. related to chronic disease, iron deficiency, RT)

Bleeding from the tumor site may occur at any time in head and neck cancer patients receiving therapy. Appropriate clinical management of bleeding per standard of care is up to the patient's treating physician. There is no evidence that immunotherapy increases rates or severity of bleeding (in the absence of drug induced thrombocytopenia), and therefore therapy should be continued after the patient has been stabilized and bleeding controlled.

For immunotherapy-induced lymphedema or edema of the head and neck of grade 1, continue without change, for grade 2 without airway or swallowing compromise, hold until resolved to \leq grade 1. Oral steroids may be used if clinically appropriate. For grade 3 or with any airway compromise, stabilize the airway per the standard of care and initiate oral or IV steroids (per Appendix 1) and taper as clinically appropriate.

<u>Skin Rash and Oral Lesions</u>	Management/Next Dose for Ipilimumab/Nivolumab
\leq Grade 1	No change. Resume treatment. See guidelines for management in Appendix I.
Grade 2	No change*. Resume treatment. See guidelines for management in Appendix I.
Grade 3	Hold* until \leq Grade 1; see guidelines for management in Appendix I. Resume at same level at investigator discretion
Grade 4	Off protocol therapy
<p>*Patients with grade 2 or greater purpuric or bullous lesions must be evaluated for vasculitis, Steven-Johnson syndrome, drug rash with eosinophilia and systemic symptoms (DRESS), toxic epidermal necrolysis (TEN), and autoimmune bullous disease including oral lesions of bullous pemphigus/pemphigoid by a specialist. 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. Note this does not apply to oral mucositis due to radiation.</p> <p>Recommended management: TRAEs management guidelines (in Appendix I)</p>	

<u>Liver Function</u> <u>AST/ALT/T. Bili *</u>	Management/Next Dose for Ipilimumab/Nivolumab
\leq Grade 1	No change. Resume treatment.
Grade 2	Hold until UNL or baseline. See guidelines for management in Appendix I.
Grade 3	Off protocol therapy. See guidelines for management in Appendix I.

Grade 4	Off protocol therapy. See guidelines for management in Appendix I.
<p>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.</p> <p>Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.</p> <p>Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.</p>	

<u>Renal Function</u> <u>Serum Creatinine</u>	Management/Next Dose for Ipilimumab/Nivolumab
≤ Grade 1	Resume treatment.
Grade 2	Hold until UNL or baseline. See guidelines for management in Appendix I.
Grade 3	Hold until UNL or baseline. See guidelines for management in Appendix I.
Grade 4	Off protocol therapy
For Grade 2 or greater, consider renal biopsy.	

<u>Diarrhea/ Colitis</u>	Management/Next Dose for Ipilimumab/Nivolumab
≤ Grade 1	No change. See guidelines for management in Appendix I.
Grade 2	Hold until Grade 0 or baseline. See guidelines for management in Appendix I.
Grade 3	Permanently discontinue Ipilimumab; may continue Nivolumab if diarrhea/colitis resolves to grade 1 or less at the discretion of the study PI.
Grade 4	Off protocol therapy. See guidelines for management in Appendix I.

See GI TRAE Algorithm for management of symptomatic colitis (in IB). Patients with grade 2 symptoms but normal colonoscopy and biopsies may be retreated after resolution. Patients with persistent symptoms greater than 14 days who require 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.

<u>Pancreatitis Amylase/Lipase</u>	Management/Next Dose for Ipilimumab/Nivolumab (See Note)
≤ Grade 1	If symptomatic, hold dose until Grade 0. Resume if asymptomatic.
Grade 2	If symptomatic, hold until Grade 0. Resume if asymptomatic.
Grade 3*	If symptomatic, hold until Grade 0. Resume if asymptomatic. Patients who develop symptomatic pancreatitis or DM should be taken off treatment.
Grade 4**	Off protocol therapy
<p>Patients may develop symptomatic and radiologic evidence of pancreatitis as well as DM and 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 Adverse Event Management Algorithm (in Appendix I).</p> <p>* Patients with Grade 3 asymptomatic lipase or amylase elevation (2-5 X ULN) may receive ipi or nivo treatment at the discretion of the treating physician.</p> <p>**Excluding asymptomatic amylase and lipase increases</p> <p>NOTE: RT to the head and neck is associated with transient elevations in salivary amylase that can be of any grade. In the event of asymptomatic solitary amylase elevation, the investigator should consider fractionation of salivary vs. pancreatic amylase. The investigator may attribute</p>	

<u>Pneumonitis</u>	Management/Next Dose for Ipilimumab/Nivolumab
≤ Grade 1	Hold dose pending evaluation and resolution to ≤ Grade 0 or baseline including baseline pO ₂ . Resume after pulmonary and/or ID consultation.
Grade 2	Hold dose pending evaluation. Resume after pulmonary and/or ID consultation if lymphocytic pneumonitis is excluded. Off study if grade 2 symptoms do not improve or worsen after 2 weeks of steroids and dose delay; see guidelines for management in Appendix I.

Grade 3	Hold dose pending evaluation. Resume after pulmonary and/or ID consultation only if lymphocytic pneumonitis is excluded. Off protocol therapy if attributed to nivolumab/ipilimumab; see guidelines for management in Appendix I.
Grade 4	Off protocol therapy. See guidelines for management in Appendix I.
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.	

<u>Other GI N-V</u>	Management/Next Dose for Ipilimumab/Nivolumab
≤ Grade 1	No change. Resume treatment.
Grade 2	Hold pending evaluation for gastritis duodenitis and other immune adverse events or other causes. Resume after resolution to ≤ Grade 1.
Grade 3	Hold pending evaluation. Resume after resolution to ≤ Grade 1. 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.	

<u>Fatigue</u>	Management/Next Dose for Ipilimumab/Nivolumab
≤ Grade 1	No change. Resume treatment.
Grade 2	No change. Resume treatment.
Grade 3	Hold until ≤ Grade 2.
Fatigue is the most common adverse event 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. G2	

<u>Neurologic events</u>	Management/Next Dose for Ipilimumab/Nivolumab
≤ Grade 1	No change in dose.

Grade 2	Hold dose pending evaluation and observation. Hold until \leq Grade 1; see guidelines for management in Appendix I. Resume for peripheral isolated n. VII (Bell's palsy); see guidelines for management in Appendix I.
Grade 3	Off protocol therapy. See guidelines for management in Appendix I.
Grade 4	Off protocol therapy. See guidelines for management in Appendix I.
*Patients with any CNS events including aseptic meningitis, encephalitis, or myopathy, peripheral demyelinating neuropathy, cranial neuropathy (other than peripheral n. VII), GB syndrome, myasthenia gravis should be off study.	

<u>Endocrine Hypophysitis Adrenal Insufficiency</u>	Management/Next Dose for Ipilimumab/Nivolumab
Note that protocol-specific actions and management are not strictly by CTCAE grade; see guidelines for management in Appendix I for recommendations on IO and management of TRAEs.	

<u>Fever</u>	Management/Next Dose for Ipilimumab/Nivolumab
\leq Grade 1	Hold until \leq Grade 1. Resume treatment.
Grade 2	Hold until \leq Grade 1. Resume after.
Grade 3	Hold until \leq Grade 1. Resume after.
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	

ALL OTHER EVENTS	Management/Next Dose for Ipilimumab/Nivolumab
\leq Grade 1	No change .
Grade 2	Hold until \leq Grade 1 OR baseline.** When resolved or following steroids, resume.

Grade 3	Any grade 2 or 3 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 requires treatment discontinuation. Any other immune-related grade 3 toxicity not covered in the tables above would require that the patient go off protocol therapy with the following exceptions: Any grade 3 or 4 drug-related laboratory abnormality or electrolyte abnormality, not associated with underlying organ pathology, that does not require treatment except for electrolyte replacement OR hormone/steroid replacement does not require treatment discontinuation.
Grade 4	Off protocol therapy (except for drug-related laboratory abnormality or electrolyte abnormality, not associated with underlying organ pathology, that does not require treatment except for electrolyte replacement OR hormone/steroid replacement does not require treatment discontinuation).
** Immunologically mediated	
Recommended management: As clinically indicated	

5.1.2 Dose reductions for Nivolumab and Ipilimumab

There will be no dose reductions for nivolumab or ipilimumab.

5.1.3 Criteria to Resume Nivolumab and Ipilimumab Dosing

Subjects may resume treatment with nivolumab or ipilimumab when the TRAE(s) resolve(s) to Grade \leq 1 or baseline, with the following exceptions:

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

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

Subjects with baseline Grade 1 AST/ALT or total bilirubin who require dose delays for reasons other than a 2-grade shift in AST/ALT or total bilirubin may resume treatment in the presence of Grade 2 AST/ALT or total bilirubin.

Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.

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

Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone \leq 10 mg/day.

Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.

Dose delay of ipilimumab which results in no ipilimumab dosing for > 12 weeks requires ipilimumab discontinuation.

Ipilimumab may not be resumed sooner than 6 weeks (\pm 5days) after the prior ipilimumab dose.

Nivolumab may be delayed until the next planned nivolumab (every two weeks) to be synchronized with nivolumab and ipilimumab dosing. If one nivolumab dose is missing due to toxicity during IMRT period, it will be administrated after finishing IMRT, until a maximum of 6 doses of nivolumab are administrated.

In general, subjects who meet criteria to resume ipilimumab will also have met criteria to resume nivolumab, so it should be feasible to synchronize dosing of both drugs when resuming ipilimumab. In order to facilitate this, the dosing days of nivolumab and ipilimumab may be adjusted within the permitted \pm 5 day window, as long as consecutive nivolumab doses are given at least 12 days apart.

Investigator attribution of this toxicity to the ipilimumab dosing must be clearly noted in the subject's medical chart.

5.2 IO treatment Discontinuation Criteria

NOTE: In the event of clinical disease progression during the first six week cycle of IO, the patient may be withdrawn from therapy at the discretion of the treating physician to receive standard of care therapy off protocol. The patient will continue to be followed per protocol and will remain evaluable for DLT.

The assessment for discontinuation of ipilimumab should be made separately from the assessment made for discontinuation of nivolumab. Although there is overlap among the discontinuation criteria, if discontinuation criteria are met for ipilimumab but not for nivolumab, treatment with nivolumab may continue if ipilimumab is discontinued at the study PI's discretion. If a subject meets criteria for discontinuation and investigator is unable to determine whether the event is related to both or one study drug, the subject should discontinue both nivolumab and ipilimumab and be taken off the treatment phase of the study.

Collection of data and biospecimens for correlative studies from patients that are withdrawn from therapy due to progression or toxicities will continue as per protocol (see Oral Rinse collection, Blood biospecimen collection, and biopsy under Section 3.3 Assessments post-treatment, follow-up)

5.2.1 Nivolumab and Ipilimumab Discontinuation

Treatment should be permanently discontinued for any of the following:

Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment, unless attributed to (an) alternative diagnosis(es) by a referring ophthalmologist;

Any Grade \geq 2 drug-related pneumonitis or interstitial lung disease that does not resolve with dose delay and systemic steroids;

Any Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction, regardless of duration;

Any Grade 3 non-skin, drug-related adverse event lasting $>$ 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reactions, infusion reactions, endocrinopathies, and laboratory abnormalities;

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

For patients with Grade 3 or higher diarrhea/colitis, the investigator can discontinue ipilimumab and continue nivolumab on study after discussion with the study PI once the symptoms have resolved to ≤ grade 1 if patient is still in treatment window;

Any Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation;

Any Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except: Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.

Any drug-related LFT abnormality that meets the following criteria require discontinuation (also see Hepatic Adverse Event Management Algorithm):

- AST or ALT > 5-10x ULN for > 2 weeks
- AST or ALT > 10x ULN
- Total bilirubin > 5 x ULN
- Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN

Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:

- Grade 4 neutropenia ≤ 7 days
- Grade 4 lymphopenia or leukopenia
- Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset.
The Monitor should be consulted for Grade 4 amylase or lipase abnormalities
- Isolated Grade 4 electrolyte imbalances/abnormalities that are not associated with clinical sequelae and are corrected with supplementation/appropriate management within 72 hours of their onset
- Grade 4 drug-related endocrinopathy adverse events such as adrenal insufficiency, ACTH deficiency, hyper- or hypothyroidism, or glucose intolerance, which resolve or are adequately controlled with physiologic hormone replacement (corticosteroids, thyroid hormones) or glucose controlling agents, respectively, may not require discontinuation after discussion with and approval from the Monitor.

Periodic study visits to assess safety and laboratory studies should also continue every 6 weeks or more frequently if clinically indicated during such dosing delays.

5.3 Treatment of Infusion Reactions

5.3.1 Nivolumab or Ipilimumab Infusion Reactions

Since nivolumab and ipilimumab contain only human immunoglobulin protein sequences, they are unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours to the Medical Monitor and reported as an SAE if

criteria are met. Infusion reactions should be graded according to NCI CTCAE (Version 4.0) guidelines.

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

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

Remain at bedside and monitor subject until recovery from symptoms. The following prophylactic premedications are recommended for future infusions: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg at least 30 minutes before additional nivolumab or ipilimumab administrations.

For Grade 2 symptoms: (moderate reaction requires therapy or infusion interruption but responds promptly to symptomatic treatment [eg, antihistamines, non-steroidal anti-inflammatory drugs, narcotics, corticosteroids, bronchodilators, IV fluids]; prophylactic medications indicated for ≤ 24 hours)

-Stop the nivolumab or ipilimumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab or ipilimumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms.

-For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen/paracetamol 325 to 1000 mg should be administered at least 30 minutes before nivolumab or ipilimumab infusions. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

For Grade 3 or 4 symptoms: (severe reaction, Grade 3: prolonged [ie, not rapidly responsive to symptomatic medication and/or brief interruption of infusion]; recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae [eg, renal impairment, pulmonary infiltrates]. Grade 4: Life threatening; pressor or ventilatory support indicated)

- Immediately discontinue infusion of nivolumab or ipilimumab. Begin an IV infusion of normal saline and treat the subject as follows: Recommend bronchodilators, epinephrine 0.2 to 1 mg of a 1:1000 solution for subcutaneous administration or 0.1 to 0.25 mg of a 1:10,000 solution injected slowly for IV administration, and/or diphenhydramine 50 mg IV with methylprednisolone 100 mg IV (or equivalent), as needed. Subject should be monitored until the investigator is comfortable that the symptoms will not recur. Nivolumab or ipilimumab will be permanently discontinued. Investigators should follow their institutional guidelines for the treatment of anaphylaxis. Remain at bedside and monitor subject until recovery of the symptoms.

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

Preparation/Handling/Storage/Accountability

Please refer to the current version of the Investigator Brochure (IB) and/or pharmacy manual for complete storage, handling, dispensing, and infusion information for nivolumab and ipilimumab. Any unused portion of the infusion solution cannot be stored for reuse, and any unused medicine or waste should be disposed of in accordance with local requirements.

6. RADIATION THERAPY

6.1 Radiation Therapy

All patients will receive an initial plan of 20 fractions (4 weeks) followed by a boost plan of either 5 or 10 fractions. Volume will be assessed independently for the primary and nodal disease.

Note that overall interpretation of response to induction will be based upon RECIST 1.1 on week 5-6 imaging. However, radiation treatment planning will be stratified by primary site and nodal disease.

Primary disease volume $\geq 3\text{cm}$ and/or nodal disease volume $\geq 2\text{cm}$ (intermediate volume) will receive a final dose of 63-66 Gy in 30 fractions (intermediate volume).

Primary disease volume $< 3\text{cm}$ and/or nodal disease volume $< 2\text{cm}$ will receive a final dose of 60 Gy in 30 fractions (low volume).

Primary and/or nodal disease with CR ($< 10\text{ mm}$ in short axis) after induction IO will receive a final dose of 50 Gy in 25 fractions (CR).

Full details of radiation dose prescriptions are provided in Section 6.1.6 - 6.1.7.

- Intermediate volume defined as: primary $\geq 3\text{cm}$; node $\geq 2\text{cm}$
- Low volume primary defined as: primary $< 3\text{cm}$; node $< 2\text{cm}$
- CR determined via RECIST 1.1 on restaging imaging.

Initial plan: All patients will receive an initial plan of 20 fractions (4 weeks). Intermediate volume primary/nodal disease will receive 42-44 Gy at 2.1-2.2 Gy per fraction. Small volume gross primary/nodal disease and/or primary/nodal disease with CR after induction IO will receive 40 Gy at 2.0 Gy per fraction. High risk subclinical sites will receive 36 Gy at 1.8 Gy per fraction.

Boost plan: Intermediate volume primary/nodal disease will receive a boost of 21-22 Gy at 2.2 Gy per fraction (total dose of 63-66 Gy in 30 fractions). Small volume gross primary/nodal disease will receive a boost of 20 Gy at 2.0 Gy per fraction (total dose of 60 Gy in 30 fractions). Primary and/or nodal disease with CR after induction IO will receive a boost of 10 Gy in 5 fractions (total dose of 50 Gy in 25 fractions). No boost will be given to high risk subclinical sites.

Baseline imaging will be utilized to guide radiotherapy volume for high-risk subclinical sites. In instances of partial or complete response, radiation planning will be based upon determination of volume on post-induction CT imaging at 5-6 weeks.

Unilateral radiation will be permitted in selected patients; see Section on target volume below

6.1.1 Treatment Technology

All patients will be managed with radiation therapy using IMRT (static-beam IMRT and volumetric

arc therapy technique allowed) delivered with megavoltage photons.

6.1.2 Immobilization and Simulation

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. It is strongly encouraged to also include an oral stent with bite-block attachment to further ensure accurate patient set-up on a daily basis.

The treatment planning CT scan should be obtained in the immobilization device and in the treatment position with a slice thickness of 3 mm or less. The use of IV contrast with planning CT is recommended unless contraindicated but not required.

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

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

6.1.3 Definition of Target Volumes and Margins

All specified target volumes and organs-at-risk (OAR) will be contoured on the planning CT scan data sets and named according to the nomenclature described below. For the purposes of contouring, MRI and PET images, if available and clinically indicated, may be fused with the planning CT data set. Target volumes and OARs will be labeled according to published guidelines (Santanam 2012).

Gross Tumor Volume (GTV)

The GTV represents clinically or radiographic grossly involved regions of primary tumor designated GTVp_66 for intermediate volume disease, GTVp_60 for low volume disease, or GTVp_50 for CR disease, or involved nodes designated GTVn_66 for intermediate volume disease, GTVn_60 for low volume disease, or GTVn_50 for disease with CR. These volumes are defined based on physical exam and review of available imaging. FDG-PET and/or MRI may assist in GTV identification but GTV border delineation should not rely exclusively on PET signal given the known variable association between gross tumor extent and PET signal cutoff. CR will be determined per RECIST 1.1.

Post-Biopsy GTV

Patients undergoing gross total excision of both primary and gross nodal disease with curative intent are not eligible for this study. Patients undergoing diagnostic procedures at the primary site, such as simple/diagnostic tonsillectomy or excisional biopsy, are eligible but are not considered to have had an oncologically therapeutic surgical procedure even in the absence of clinically or radiologically appreciable gross residual disease at the primary site. As such, these patients require full radiation dose (60 Gy) to be delivered to a volume immediately adjacent to the tissues removed at the time of the biopsy. For purposes of planning, this volume will be labeled GTVp_60 and it should be defined relative to the extent of disease prior to removal. This GTVp_60 may be defined by fusion of pre-biopsy imaging studies (CT, MRI) with the planning CT data set. The gross primary tumor on the pre-biopsy imaging may be projected on the planning CT and defined as the intersection with the residual tissues. If there is not such an intersection or the residual tissues lie in a different anatomic orientation post-biopsy, the GTVp_60 may be defined as a 5 mm expansion into the residual tissues circumferential to the area of the biopsy. In the event that

pre-biopsy imaging is not available the GTVp_60 must be defined relative to the clinical exam of the biopsy site and normal anatomic landmarks. For instance, in the specific case of tonsillectomy the GTVp_60 will include, at a minimum, the tonsillar bed to include anterior and posterior tonsillar pillars up to the level of the soft palate and inferiorly to the pharyngoepiglottic fold; the GTVp should be expanded superiorly or inferiorly if the pre-biopsy tumor extended past these landmarks. A CTV_60 is then defined for this GTVp_60 according to methods defined below.

Nodal Definitions

- Grossly Positive Nodes (GTVn_60) are defined as those greater than 1.5 cm in long axis and/or > 1 cm in short axis, a cluster of 3 or more borderline size nodes, radiographic evidence of extracapsular extension (ECE), or a node of any size with evidence of necrosis. Smaller nodes may be determined to be gross disease objects depending on clinical suspicion (based on proximity to the primary site or other involved nodes) or demonstration of significant uptake of FDG on PET scanning. Intermediate volume nodes (GTVn_66) are defined as an individual or cluster of matted node(s) ≥ 4 cm
- Extracapsular extension (ECE): is defined as radiographic evidence of irregular borders and/or perinodal fat stranding, invasion of adjacent structures, or both. Any areas of potential involvement should be included within the GTV. Clinicians are highly encouraged to request radiologist review if the determination is unclear.

Clinical Target Volume (CTV)

- CTVs are defined and contoured in relation to the targets they are intended to encompass and the dose they are intended to receive. For gross targets (GTVs), the CTVs are defined by 3D isotropic expansions that should then be limited by potential barriers to tumor spread such as air cavities, external contours and bony or fascial planes through which tumor spread is not possible or apparent. CTV must be determined by the treating physician with quality assurance from the head and neck radiation oncology team. This margin can be reduced as needed for tumors in close proximity to critical structures in order to meet their dose constraint at discretion of treating radiation oncologist. Similarly, CTVs may be expanded beyond the limits defined in this protocol in order to cover areas deemed at risk of tumor extension (e.g. neck musculature invaded by nodal disease, or pterygoid regions of infratemporal fossa in superiorly extending tonsillar cancers). For nodal regions of potential microscopic involvement CTVs are defined according to normal anatomic landmarks (Gregoire 2014).
- **CTV_66: Intermediate Volume Primary Tumor and Involved Nodes**
A CTV_66 will be defined for primary tumor and involved nodes as up to 0.5 cm expansion of the GTVs defined for these structures. When defined for nodes, the CTV_66 should be suffixed as CTVn_66 to distinguish this from the primary, CTVp_66, for the purposes of plan evaluation. CTV_66 is the sum of CTVp_66 and CTVn_66.
- **CTV_60: Small Volume Primary Tumor and Involved Nodes**
A CTV_60 will be defined for primary tumor and involved nodes as up to 0.5 cm expansion of the GTVs defined for these structures. When defined for nodes, the CTV_60 should be suffixed as CTVn_60 to distinguish this from the primary, CTVp_60, for the purposes of plan evaluation. CTV_60 is the sum of CTVp_60 and CTVn_60.
- **CTV_50: Primary Tumor and Involved Nodes with CR**
A CTV_50 will be defined for primary tumor and involved nodes as up to 0.5 cm expansion of the GTVs defined for these structures. When defined for nodes, the CTV_50 should be suffixed as CTVn_50 to distinguish this from the primary, CTVp_50, for the purposes of plan evaluation. CTV_50 is the sum of CTVp_50 and CTVn_50.
- **CTV_36: High-Risk Subclinical Sites**

High-risk subclinical sites are defined as areas of potential subclinical tumor infiltration beyond the primary site CTVp. In the event of a node excision that occurred at time of diagnosis, the node levels that contained grossly involved adenopathy should be included in CTV_36, even if there is no residual post excision adenopathy. In patients with a CR to induction, the first echelon node levels to the primary site may be omitted from CTV_36.

A CTV_36 will be defined for these sites and include the following:

- i) An up to 0.5 cm expansion on the CTVp_60 and/or CTVp_66
- ii) All node levels containing a CTVn_60 and/or CTVn_66 that has been assigned to involved nodes (all grossly involved nodal levels). Coverage of these sites are required.
- iii) Other high-risk subclinical sites may include nodes < 1cm 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, an expansion up to 0.5 cm on these nodes can be added to the CTV_36 at the discretion of the treating clinician.
- iv) 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 can include bilateral level II. In cases with soft palate or posterior pharyngeal wall involvement this should include the lateral retropharyngeal lymph nodes. Coverage of these sites will be determined by the treating physician with quality assurance from the head and neck radiation oncology team.
- v) CTV_36 may be omitted in patients with CR of primary and nodal sites

Contralateral Neck.

Groups of Patients with Regard to Unilateral or Bilateral Neck Irradiation

Group 1: Unilateral treatment is recommended.

T1 to T2 tonsil primaries with < 0.3cm clinical or radiographic extension into tongue base and/or <1cm clinical or radiographic extension into palate, no posterior pharyngeal wall extension, N0-N2a.

Group 2: Unilateral treatment is optional.

T1 to T3 tonsil primaries with < 1cm clinical or radiographic extension into tongue base and/or palate, no posterior pharyngeal wall extension, N2b with involved adenopathy confined to ipsilateral level 2 of the neck

Group 3: Bilateral treatment is mandatory.

Tongue base, soft palate or posterior pharyngeal wall primaries or tonsil primaries with > 1cm soft palate and/or tongue base extension or any posterior pharyngeal wall extension.

Prior to enrollment, oncologists will declare their intention to treat unilaterally or bilaterally. Exploratory analyses adjusted for unilateral vs. bilateral radiotherapy will be conducted when the results are available.

Management of the Low Neck (levels III, IV, V)

The low and posterior neck will only be treated if there is evidence of nodal involvement in these level or suspicious nodes < 1cm, 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 or the involved nodes. For example, if there is involved node in the level II and small < 1cm suspicious nodes in level III, then the level III nodes will be treated to 36 Gy.

Table 6.1.4: Clinical Target Volume Nomenclature and Description.

Note: All structures marked as **Required** in the table below must be contoured, and labeled as listed under “Standard Name” for digital RT data submission. All structures marked as **Required if applicable** must be contoured and labeled as listed under “Standard Name” for digital data submission **IF** they are applicable to the patient’s plan. Resubmission of data is necessary when labeling of structures does not conform to the DICOM Standard Name listed.

Standard Name	Description	Detailed Specification
GTVp_66	GTV to receive 63-66 Gy at the primary site Required if applicable	Equivalent to GTVp as defined above
GTVn_66	GTV to receive 63-66 Gy at involved nodes Required if applicable	Equivalent to GTVn as defined above
CTVp_66	CTV to receive 63-66 Gy at the primary site Required if applicable	Up to 0.5 cm isotropic expansion of GTVp_66 limited by potential anatomic barriers to tumor spread
CTVn_66	CTV to receive 63-66 Gy at involved nodes Required if applicable	Up to 0.5 cm isotropic expansion of GTVn_66 limited by potential anatomic barriers to tumor spread
CTV_66	CTV to receive 63-66 Gy Required if applicable	Sum of CTVp_66 and CTVn_66
GTVp_60	GTV to receive 60 Gy at the primary site Required if applicable	Equivalent to GTVp as defined above
GTVn_60	GTV to receive 60 Gy at involved nodes Required if applicable	Equivalent to GTVn as defined above
CTVp_60	CTV to receive 60 Gy at the primary site Required if applicable	Up to 0.5 cm isotropic expansion of GTVp_60 limited by potential anatomic barriers to tumor spread

CTVn_60	CTV to receive 60 Gy at involved nodes Required if applicable	Up to 0.5 cm isotropic expansion of GTVn_60 limited by potential anatomic barriers to tumor spread
CTV_60	CTV to receive 60 Gy Required if applicable	Sum of CTVp_60 and CTVn_60
GTVp_50	GTV to receive 50 Gy at the primary site Required if applicable	Equivalent to pre-induction GTVp as defined above
GTVn_50	GTV to receive 50 Gy at involved nodes Required if applicable	Equivalent to pre-induction GTVn as defined above
CTVp_50	CTV to receive 50 Gy at the primary site Required if applicable	Up to 0.5 cm isotropic expansion of pre-induction GTVp_50 limited by potential anatomic barriers to tumor spread
CTVn_50	CTV to receive 50 Gy at involved nodes Required if applicable	Up to 0.5 cm isotropic expansion of pre-induction GTVn_50 limited by potential anatomic barriers to tumor spread
CTV_50	CTV to receive 50 Gy Required if applicable	Sum of CTVp_50 and CTVn_50
CTV_36	CTV to receive 36 Gy at high risk volume at the primary site and applicable node levels Required if applicable	<ul style="list-style-type: none"> i) Up to 0.5 cm expansion on the CTVp_60 or CTVp_66 ii) node levels containing involved nodes <p>Recommended but not required:</p> <ul style="list-style-type: none"> iii) First echelon nodes (unilateral or bilateral) iv) Up to 0.5 cm expansion on nodes < 1 cm thought to be at risk of containing more than subclinical disease. v) Nodal level outside of level II (level III, IV or V) only if they contain < 1 cm nodes thought to be at risk of containing more than subclinical disease

6.1.4 Definition of Organs at Risk

Note: All structures marked as **Required** in the table below must be labeled as listed under “Standard Name” for digital RT data submission. Resubmission of data is necessary when labeling of structures does not conform to the DICOM Standard Name listed.

Table 6.1.5: Organ at Risk Nomenclature

For detailed descriptions see below.

OAR Standard Name	Description
SpinalCord	Spinal cord Required
SpinalCord_05	PRV = 5 mm expansion on spinal cord Required
BrainStem	Brain stem Required
BrainStem_03	PRV= 3 mm expansion on brainstem Required
Lips	Lips Required
OralCavity	Oral cavity Required
Parotid_R	Right parotid gland Required
Parotid_L	Left parotid gland Required
Submandibular_R	Right submandibular gland Required, if applicable
Submandibular_L	Left submandibular gland Required, if applicable
Pharynx	Non-treated pharynx Required

Esophagus_Up	Cervical esophagus Required
Larynx	Larynx Required
Mandible	Mandible Required
Thyroid	Thyroid gland Required
NonPTV	Unspecified tissue, External minus all PTVs Required
External	External border of the patient Required

- **Spinal Cord:** The cord begins at the cranial-cervical junction (ie, the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The spinal cord must be contoured at least 1 cm below the lowest extent of the neck PTVs. The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined as: SpinalCord_05 = cord + 5 mm in each dimension.
- **Brain Stem:** The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined as: BrainStem_03 = brainstem + 3 mm in each dimension.
- **Lips:** The definition of lips is self-explanatory.
- **Oral Cavity:** The oral cavity will be defined as a composite structure posterior to lips consisting of the anterior ½ 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.
- **Parotid Glands:** Parotid glands will be defined in their entirety (superficial and deep lobes) based on the treatment planning CT scan.
- **Submandibular Glands:** Submandibular glands will be defined in their entirety based on treatment planning CT scans.
- **Pharynx:** This will be defined as the pharyngeal 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 (level of the posterior cricoid cartilage).
- **Esophagus:** This will be defined as the cervical (upper) esophagus, a tubular structure that starts at the bottom of pharynx (cricopharyngeal inlet) and extends to the thoracic inlet.
- **Larynx:** This will be defined as the glottic and supraglottic larynx, the aryepiglottic folds, arytenoids, false cords, and true cords, bounded by the thyroid cartilage laterally, anteriorly including the anterior edge of the pre-epiglottic fat, and posteriorly bounded by the anterior

edge of the pharyngeal wall or the posterior edge of the arytenoid and/or cricoid cartilage. Inferiorly, bottom of cricoid cartilage.

- **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 CTVs and PTVs.
- **Thyroid:** This includes both lobes (left and right) of the thyroid gland
- **Unspecified Tissue Outside the Targets (NonPTV):** This will be defined as tissue located between the skull base and thoracic inlet external to all PTVs and defined normal structures within the external contour of the patient.

6.1.5 Planning Target Volumes

All CTVs will have associated PTVs which represent the volumes to which radiation dose will be prescribed, delivered and evaluated. The PTVs are isotropic expansions of the CTVs to account for internal motion and residual set-up error.

PTVs are defined as 2-5 mm expansion of the CTV in all planes, depending on the frequency of IGRT (see IGRT Section below), except when the isotropic expansion results in the following dosimetric challenges:

- when the CTV expansion results in a PTV that overlaps a critical OAR or its PRV, hence dose delivered to this PTV will exceed the acceptable dose limits for the OAR;
- and when the CTV expansion results in PTVs extending beyond the patient external contour, making PTV dose calculation and evaluation unreliable.
- In such instances, the PTVs may be modified in the following manner:
 - When a PTV overlaps a critical OAR (e.g. spinal cord, brainstem and/or larynx) and its associated PRV, the PTV should be modified to exclude the PRV.
 - The PTVs should be constrained to be within the external contour. For situations where gross disease is external to the external contour (disease at or through the skin surface), the use of 3-5 mm tissue equivalent material (bolus) is recommended, and no PTV constraint should be used underneath the bolus.

Table 6.1.6: Planning Target Volume Nomenclature and Description

Note: All structures marked as **Required** in the table below must be contoured and labeled as listed under “Standard Name” for digital RT data submission. All structures marked as Required if applicable must be contoured and labeled as listed under “Standard Name” for digital data submission **IF** they are applicable to the patient’s plan. Resubmission of data is necessary when labeling of structures does not conform to the DICOM Standard Name listed.

Standard Name	Description	Detailed Description
PTVp_66	PTV to receive 63-66 Gy at the primary site Required if applicable	2-5mm expansion of CTVp_66
PTVn_66	PTV to receive 63-66 Gy at involved nodes Required	2-5mm expansion of CTVn_66

PTV_66	PTV to receive 63-66 Gy Required if applicable	Sum of PTVp_66 and PTVn_66
PTVp_60	PTV to receive 60 Gy at the primary site Required if applicable	2-5mm expansion of CTVp_60
PTVn_60	PTV to receive 60 Gy at involved nodes Required if applicable	2-5mm expansion of CTVn_60
PTV_60	PTV to receive 60 Gy Required if applicable	Sum of PTVp_60 and PTVn_60
PTVp_50	PTV to receive 50 Gy at the primary site Required if applicable	2-5mm expansion of CTVp_50
PTVn_50	PTV to receive 50 Gy at involved nodes Required if applicable	2-5mm expansion of CTVn_50
PTV_50	PTV to receive 50 Gy Required if applicable	Sum of PTVp_50 and PTVn_50
PTV_36	PTV to receive 36 Gy at the primary site and applicable node levels Required if applicable	2-5mm expansion of CTV_36

6.1.6 **Dose Prescription**

All PTVs are to be treated at 1.8-2.2 Gy/Fx . In the initial plan, prescribed dose to both PTV_30 and PTV_60 will be 30 Gy in 15 fractions at 2 Gy/fraction. After that PTV_60 will be boosted with an addition 30 Gy in 15 fractions at 2 Gy/fraction. The total number of fractions to PTV_30 will therefore be 30 fractions over 6 weeks. Unilateral radiation will be permitted in selected patients; see Section 6.1.3. Doses prescribed are indicated in Table 6.1.7 below.

Table 6.1.7: Doses Prescribed to PTVs

Target Standard Name	Dose (Gy)	Fraction Size (Gy)	# of fractions	Dose specification technique
PTV_66	63-66	2.1-2.2	30	Covering ≥ 95% of PTV_66
PTV_60	60	2.0	30	Covering ≥ 95% of PTV_60

PTV_50	50	2.0	25	Covering $\geq 95\%$ of PTV_50
PTV_36	36	1.8	20	Covering $\geq 95\%$ of PTV_36

6.1.7 **Treatment Planning Priorities and Instructions**

IMRT Dose Prescription to PTVs

Doses are prescribed to PTVs as outlined in Table 6.1.7. The treatment goal is that 95% of the volume of all PTVs must receive the prescribed dose with a minimum dose (defined as dose to 99% of PTVs) greater than 93% of the prescription dose and a maximum dose (defined as dose encompassing 0.03 cc of the PTV) less than 110-115% of the highest prescription dose.

It is recognized that portions of PTVs close to the skin or critical PRVs (spinal cord and brainstem) may receive significantly less than the prescription doses. This is acceptable in these regions as long as cold spots within these PTVs do not exist within the GTV. In cases of PTVs close to skin, tissue equivalent bolus must be utilized to ensure adequate dose.

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.

Prioritization for IMRT Planning

- 1) Spinal Cord
- 2) Brainstem
- 3) PTV_66 and/or PTV_60 and/or PTV_50
- 4) PTV_36
- 5) a. Parotid gland contralateral to primary tumor site
b. Larynx
- 6) a. Pharynx
b. Contralateral submandibular
- 7) a. Oral Cavity
b. Lips
c. Esophagus
d. Thyroid
- 8) a. Parotid gland ipsilateral to primary tumor site
b. Mandible

9) Unspecified tissue outside the targets

6.1.8 Doses to Normal Structure

Dose limitations to normal structures are described below. For the critical structures of spinal cord and brainstem these are mandatory. For other structures recommended limits are provided, but the doses delivered should always be as low as reasonably achievable without compromising doses to PTVs.

- **Spinal Cord:** The PRV for spinal cord (SpinalCord_05) should not exceed 48 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the spinal cord PRV should be given the highest priority.
- **Brainstem:** The PRV for brainstem (BrainStem_03) should not exceed 50 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the BrainStem_03 should be given less priority than the SpinalCord_05, but more than the critical structures listed below.
- **Lips:** Reduce the dose as much as possible. The mean dose should be < 20 Gy.
- **Oral Cavity:** Reduce the dose as much as possible. The mean dose should be < 30 Gy for the oral cavity. Efforts should also be made to avoid hot spots (> 50 Gy) within the non-involved oral cavity.
- **Parotid Glands:** In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of < 26 Gy but efforts should be made to reduce this further if possible without compromising dose to PTVs.
- **Contralateral submandibular gland:** If contralateral level Ib is not a target, aim to reduce mean contralateral submandibular gland to < 39 Gy.
- **Pharynx:** Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include:
 - 1) No more than 33% of the Pharynx exceeds 45 Gy;
 - 2) Mean dose < 35-40 Gy;
 - 3) No more than 15% of the Pharynx exceeds 50 Gy.
- **Esophagus:** Reduce the dose as much as possible; recommended (but not mandatory) treatment goal: mean dose < 30 Gy.
- **Larynx:** Reduce the dose as much as possible. The larynx mean dose is recommended to be ≤ 30-35 Gy if whole-neck IMRT is used.
- **Thyroid:** Mean dose should be < 30 Gy.
- **Mandible:** Reduce the dose as much as possible. Hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 50 Gy.
- **Unspecified Tissue Outside the Targets (NonPTV):** No more than 1cc of unspecified tissue outside the targets can receive ≥ 50 Gy.

6.1.9 Dose Compliance Criteria

The compliance criteria listed in Table 6.1.10 will be used to evaluate each case. 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 to avoid protocol deviation.

Table 6.1.10: Planning Target Volume and Critical OAR Constraints and Compliance Criteria

Name of Structure	Dosimetric parameter*	Per Protocol Dose (Gy)	Variation Acceptable
PTV_66	D95%*(Gy) D99%(Gy) Dmax**(Gy)	63-66	≥ 63 and < 70
CTV_66	V63-66 Gy (%)	≥ 99 %	95 to 99 %
PTV_60	D95%*(Gy) D99%(Gy) Dmax**(Gy)	60	> 60 and ≤ 63
CTV_60	V60 Gy (%)	≥ 99 %	95 to 99 %
PTV_50	D95%*(Gy) D99%(Gy) Dmax**(Gy)	50	>50 and ≤ 53
CTV_50	V50 Gy (%)	≥ 99 %	95 to 99 %
PTV_36	D95%*(Gy) D99%(Gy)	≥ 30 ≥ 28	≥ 28.5 ≥ 27
CTV_36	V36 Gy (%)	≥99 %	95 to 99 %
SpinalCord_05	Dmax**(Gy)	≤48	≤50
Spinal Cord	Dmax**(Gy)	≤45	≤48
BrainStem_03	Dmax**(Gy)	≤ 50	≤52

A **Deviation Unacceptable** will be scored when the Variation Acceptable limits are not met.

*D_{95%}(Gy) = dose to 95% of volume; **Dmax = maximum dose to 0.03 cc of the volume

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

Structure	Recommended dose acceptance criteria
Parotid	Mean dose to one parotid ≤ 26 Gy
Larynx	Mean dose ≤ 30 Gy

Pharynx	Mean dose \leq 35-40 Gy
Submandibular_R or Submandibular_L (contralateral)	Mean Dose \leq 39 Gy
Oral Cavity (excluding PTV's)	Mean dose \leq 30 Gy
Esophagus_Up	Mean dose \leq 30 Gy
Thyroid	Mean dose $<$ 30 Gy
NonPTV	D1cc $<$ 50 Gy
Mandible	D0.03cc $<$ 50 Gy

6.1.10 Radiation Delivery Compliance Criteria

Radiation should begin on day 1 of cycle 2 of immunotherapy. 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 2 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 inter-fraction 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 below.

Table 6.1.11: Delivery Compliance Criteria

	Per Protocol	Variation Acceptable	Deviation Unacceptable
Overall Treatment time	$<$ 49 days	50-54 days	$>$ 55 days without a medically appropriate indication for delay
Interruptions (without medical indication)	0-2 days	2-4 days	$>$ 4 days

6.1.11 Dose Calculations

The primary data set for dose calculation is CT. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density. The dose grid size should be \leq 3 mm in all directions, which means that the CT slice thickness should be \leq 3 mm.

6.1.12 Daily Treatment Localization/IGRT

Daily image guidance (IGRT) of IMRT is required if PTV margins of ≤ 0.3 cm are used. If using PTV margins of 0.4-0.5 cm, a minimum of weekly IGRT will be required, and the imaging alignment must be approved by the attending physician on the first day of treatment and weekly thereafter

IGRT may be achieved using any one of more of the following techniques:

- Orthogonal kilovoltage (KV) images, ExacTrac;
- Linear-accelerator mounted kV and MV conebeam CT images;
- Linear-accelerator mounted MV CT images;
- Other mechanism, after discussion with the Radiation Oncology Co-Chair and/or Medical Physics Co-chair.

The institution's procedure to register the treatment day imaging dataset with the reference dataset is suggested to include the following recommendations:

- Region-of-interest (ROI) or "clip box" for fusion should be set to encompass the high dose target volumes and adjacent critical structures such as spinal cord when applicable;
- 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 surgical clips and 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 (this typically corresponds to one half of the usual PRV margin), 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, reimaging 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.

6.1.13 Replanning

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. Whether or not a new IMRT plan will be generated is at the discretion of the treating physician. The new CT dataset should be used for IGRT image registration when the patient's shape changes significantly.

6.1.14 Radiation Therapy Adverse Events

Grade 3-4 (CTCAE, v. 4) therapy-induced mucositis and/or dysphagia are expected to develop in about two thirds of patients. Nutritional evaluation prior to the initiation of therapy to decide on the use of a prophylactic gastrostomy (PEG) tube placement is recommended, but in the absence of significant pretreatment dysphagia and associated weight loss of $< 10\%$ body weight, the insertion of a prophylactic PEG is not recommended. If done the placement of a feeding tube should be

recorded, as should proportion of use of a feeding tube during and after treatment (e.g. greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields.

Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis (< 5% incidence with attention to the dental recommendations provided in Appendix I, "Dental Assessment and Management Document"), and cervical myelopathy (< 1% with restriction of spinal cord dose to \leq 45 Gy).

6.1.15 Radiation Discontinuation

Radiation is the primary treatment for these patients and should not be discontinued for any reason. If radiation is discontinued due to toxicity concerns, this is considered to be a dose limiting toxicity of the study.

7. SURGERY

Surgery is expected to play only a limited role in the favorable risk HPV-associated cancers included in this study. Locoregional progression is expected in <10% of patients. The role of neck dissection has been declining in recent years, in part due to a high rate of negative specimens when planned neck dissections are performed in cancers of the oropharynx.

8. POST-TREATMENT ASSESSMENT OF CLINICAL RESPONSE TO THERAPY

Patient's response will be followed with both clinical and radiographic assessment as indicated in the table of assessments. Clinical response at the primary site and nodal regions will be evaluated after six weeks of induction IO and 8-10 weeks after completion of RT by physical exam and CT/MRI of neck (modality should be the same as baseline). Treatment response will be evaluated by RECIST v1.1 and scored as indicated in the table 1 below. If unequivocal signs of persistent disease are demonstrated by clinical exam or imaging studies, histological or cytological pathological confirmation of persistent disease at the primary or nodal sites should be obtained. Patient should be evaluated for salvage surgery. Patients with persistently enlarged lymph nodes at 8-10 weeks post RT may be observed or undergo ultrasound with fine-needle aspiration at the discretion of the treating physician and evaluation by FDG-PET/CT 12-14 weeks from the end of RT (see table 2 for FDG-PET/CT criteria evaluation). An algorithm for clinical management of findings on the 12-14 week FDG-PET/CT scan is provided in Figure 1. If residual tumor is demonstrated by FDG-PET/CT, histological or cytological pathological confirmation of persistent disease at the primary or nodal sites should be obtained. Patient should be evaluated for salvage surgery. If response per FDG-PET/CT is indeterminate (PET/CT interpretation score of 3), FDG-PET/CT should be repeated at 3 months and evaluated for continued resolution versus evidence of persistent disease. A patient will be considered to have persistent disease after completion of RT only if histopathological or cytological confirmation of squamous cell carcinoma is confirmed by biopsy or is present within the resection specimen. Table 3 described failure response criteria.

Table 1: RECIST 1.1 response criteria.

Complete Response (CR)	Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to < 10 mm.
Partial Response (PR)	At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum diameters.
Progressive Disease (PD)	At least a 20% increase in the sum of diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm. (Note: the appearance of one or more new lesions is also considered progression).
Stable Disease (SD)	Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

Table 2: FDG-PET/CT Five-Point Qualitative Post therapy Assessment Scoring System

Score	FDG uptake pattern	Response category
1	FDG uptake at the primary site and nodes less than IJV.	Complete metabolic response
2	Focal F-FDG uptake at the primary site and nodes greater than IJV but less than liver.	Likely complete metabolic response
3	Diffuse F-FDG uptake at the primary site or nodes is greater than IJV or liver.	Likely postradiation inflammation
4	Focal F-FDG uptake at the primary site or nodes greater than liver.	Likely residual tumor
5	Focal and intense F-FDG uptake at the primary site or nodes.	Residual tumor

IJV: Internal Jugular Vein. Scores 1, 2, and 3, which represent complete metabolic response, likely complete metabolic response, and likely postradiation inflammation, respectively, were considered negative for tumor. Score of 3 requires further investigation with either ultrasound and FNA and/or repeat PET in 12 weeks. Scores 4 and 5, which represent likely residual tumor and residual tumor, respectively, were considered positive for tumor. New lesion would be considered as progressive disease.

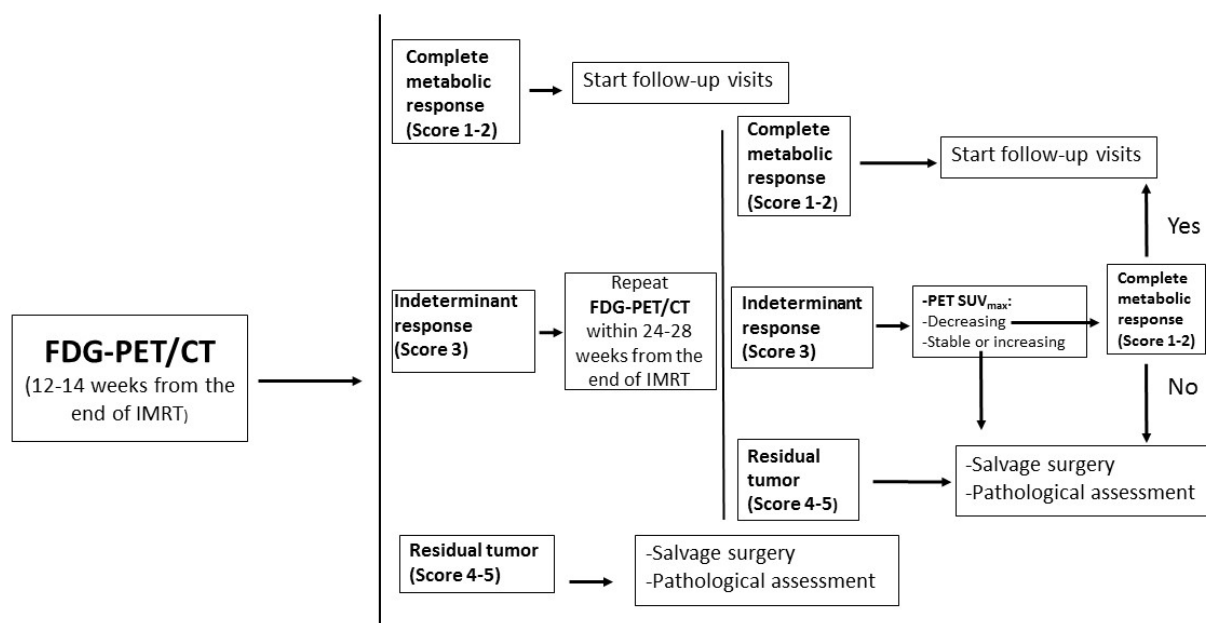
Table 3: Failure response criteria

For the purposes of this protocol, failure response criteria will be defined as follows:
Clinical or image evidence of persistent disease pathologically confirmed
Clinical or image evidence of progression disease pathologically confirmed.
Pathological evidence of invasive squamous cell carcinoma after salvage surgery.

Appearance of one or more new lesions pathologically confirmed.

Any other reason which may lead to abandoned the study treatment.

Evaluation Response Schema



8.1.1 Post-Treatment Surgical Salvage of Residual Disease

The standard of care for management of residual disease at the primary site or at the cervical nodal basin based upon an abnormal physical exam or imaging evaluation by FDG-PET/CT is surgical salvage if feasible. The extent of neck dissections performed for nodal persistence or recurrence or salvage of disease at the primary site ultimately will be determined by the treating surgeon. In the case of negative FDG-PET/CT in patients who did not achieve clinical nodal complete response, a minimum of careful clinical examination is required at 3 months.

9. ADVERSE EVENT REPORTING FOR INTERVENTIONAL PROTOCOLS

- All Serious Adverse Events (SAEs) that occur following the subject's first protocol specific intervention through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).
- The MD Anderson IRB SAE form for Unexpected and Related SAE should be used to report SAEs. The BMS protocol ID number must be included on the form submitted by the Sponsor/Investigator.
- Following the subject's first protocol specific intervention, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these time periods that is believed to be related to study drug or protocol-specified procedure. The duration of SAE collection should be extended to 100 days.

- The drug supporter company will reconcile the clinical database AE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms.com). The Investigator will request from BMS GPV&E (aepbusinessprocess@bms.com) the SAE reconciliation report and include the BMS protocol number every 3 months and prior to data base lock or final data summary. GPV&E will send the investigator the report to verify and confirm all SAEs have been transmitted to BMS GPV&E. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS (Worldwide.Safety@bms.com).

- In accordance with local regulations, BMS will notify investigators of all reported SAEs that are suspected (related to the investigational product) and unexpected (ie, not previously described in the IB). In the European Union (EU), an event meeting these criteria is termed a Suspected, Unexpected Serious Adverse Reaction (SUSAR). Investigator notification of these events will be in the form of an expedited safety report (ESR).
 - Other important findings which may be reported by BMS as an ESR include: increased frequency of a clinically significant expected SAE, an SAE considered associated with study procedures that could modify the conduct of the study, lack of efficacy that poses significant hazard to study subjects, clinically significant safety finding from a nonclinical (eg, animal) study, , or sponsor decision to end or temporarily halt a clinical study for safety reasons.
 - Upon receiving an ESR from BMS, the investigator must review and retain the ESR with the IB. Where required by local regulations or when there is a central IRB/IEC for the study, the sponsor will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
 - In addition, suspected serious adverse reactions (whether expected or unexpected) shall be reported by BMS to the relevant competent health authorities in all concerned countries according to local regulations (either as expedited and/or in aggregate reports).

SAEs, whether related or not related to study drug, and pregnancies must be reported to BMS within 24 hours. SAEs must be recorded on BMS or an approved form; pregnancies must be reported on a Pregnancy Surveillance Form.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: 609-818-3804

If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)

If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS (or designee) using the same procedure used for transmitting the initial SAE report.

All SAEs should be followed to resolution or stabilization.

- An SAE report should be completed for any event where doubt exists regarding its seriousness.
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If only limited information is initially available, follow-up reports are required. (Note: Follow-up SAE reports should include the same investigator term(s) initially reported.)
- If an ongoing SAE changes in its intensity or relationship to study drug or if new information becomes available, a follow-up SAE report should be sent within 24 hours to BMS using the same procedure used for transmitting the initial SAE report. All SAEs should be followed to resolution or stabilization. All SAEs should be followed to resolution or stabilization.

MD Anderson Serious Adverse Event (SAE) Reporting

An adverse event or suspected adverse reaction is considered “serious” if, in the view of either the investigator or the sponsor, it results in any of the following outcomes:

- Death
- A life-threatening adverse drug experience – any adverse experience that places the patient, in the view of the initial reporter, at immediate risk of death from the adverse experience as it occurred. It does not include an adverse experience that, had it occurred in a more severe form, might have caused death.
- Inpatient hospitalization or prolongation of existing hospitalization
- A persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions.
- A congenital anomaly/birth defect.

Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32).

- Important medical events as defined above, may also be considered serious adverse events. Any important medical event can and should be reported as an SAE if deemed appropriate by the Principal Investigator or the IND Sponsor, IND Office.
- All events occurring during the conduct of a protocol and meeting the definition of a SAE must be reported to the IRB in accordance with the timeframes and procedures outlined in “The University of Texas M. D. Anderson Cancer Center Institutional Review Board Policy for Investigators on Reporting Serious Unanticipated Adverse Events for Drugs and Devices”. Unless stated otherwise in the protocol, all SAEs, expected or unexpected, must be reported to the IND Office, regardless of attribution (within 5 working days of knowledge of the event).

- **All life-threatening or fatal events**, that are unexpected, and related to the study drug, must have a written report submitted within **24 hours** (next working day) of knowledge of the event to the Safety Project Manager in the IND Office.
- Unless otherwise noted, the electronic SAE application (eSAE) will be utilized for safety reporting to the IND Office and MDACC IRB.
- Serious adverse events will be captured from the time of the first protocol-specific intervention, until 100 days after the last dose of drug, unless the participant withdraws consent. Serious adverse events must be followed until clinical recovery is complete and laboratory tests have returned to baseline, progression of the event has stabilized, or there has been acceptable resolution of the event.
- Additionally, any serious adverse events that occur after the 100 day time period that are related to the study treatment must be reported to the IND Office. This may include the development of a secondary malignancy.

Reporting to FDA:

- Serious adverse events will be forwarded to FDA by the IND Sponsor (Safety Project Manager IND Office) according to 21 CFR 312.32.

It is the responsibility of the PI and the research team to ensure serious adverse events are reported according to the Code of Federal Regulations, Good Clinical Practices, the protocol guidelines, the sponsor's guidelines, and Institutional Review Board policy.

The Case Report Form (CRF) for this study is DMI. The PI and designee will be responsible for assigning attribution to study drug, and record AEs in Adverse Event Logs.

9.1 DEFINITIONS

The protocol must include a definition for Serious Adverse Events (SAE).

9.1.1 SERIOUS ADVERSE EVENTS

A **Serious Adverse Event (SAE)** is any untoward medical occurrence that at any dose:

- results in death
- is life-threatening (defined as an event in which the participant was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe)
- requires inpatient hospitalization or causes prolongation of existing hospitalization (see NOTE below)
- results in persistent or significant disability/incapacity
- is a congenital anomaly/birth defect

- is an important medical event (defined as a medical event(s) that may not be immediately life-threatening or result in death or hospitalization but, based upon appropriate medical and scientific judgment, may jeopardize the subject or may require intervention [eg, medical, surgical] to prevent one of the other serious outcomes listed in the definition above.) Examples of such events include, but are not limited to, intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.)
- Suspected transmission of an infectious agent (eg, pathogenic or nonpathogenic) via the study drug is an SAE.

Although pregnancy, overdose, potential drug-induced liver injury (DILI) and cancer are not always serious by regulatory definition, these events must be handled as SAEs.

Any component of a study endpoint that is considered related to study therapy should be reported as an SAE (eg, death is an endpoint, if death occurred due to anaphylaxis, anaphylaxis must be reported).

NOTE: (PI determines if this information regarding hospitalizations are considered SAEs and should be included in the protocol. This is supplemental information that is included in BMS-sponsored trials)

The following hospitalizations are not considered SAEs in BMS clinical studies:

- a visit to the emergency room or other hospital department < 24 hours, that does not result in admission (unless considered an important medical or life-threatening event)
- elective surgery, planned prior to signing consent
- admissions as per protocol for a planned medical/surgical procedure
- routine health assessment requiring admission for baseline/trending of health status (eg, routine colonoscopy)
- Medical/surgical admission other than to remedy ill health and planned prior to entry into the study. Appropriate documentation is required in these cases
- Admission encountered for another life circumstance that carries no bearing on health status and requires no medical/surgical intervention (eg, lack of housing, economic inadequacy, caregiver respite, family circumstances, administrative reason).
- Admission for administration of anticancer therapy in the absence of any other SAEs (applies to oncology protocols)

9.1.2 ADVERSE EVENTS

An Adverse Event (AE) is defined as any new untoward medical occurrence or worsening of a preexisting medical condition in a clinical investigation participant administered study drug and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (such as an abnormal laboratory finding), symptom, or disease temporally associated with the use of investigational product, whether or not considered related to the investigational product.

The causal relationship to study drug is determined by a physician and should be used to assess all adverse events (AE). The casual relationship can be one of the following:

Related: There is a reasonable causal relationship between study drug administration and the AE.

Not related: There is not a reasonable causal relationship between study drug administration and the AE.

The term "reasonable causal relationship" means there is evidence to suggest a causal relationship.

Adverse events can be spontaneously reported or elicited during open-ended questioning, examination, or evaluation of a subject. (In order to prevent reporting bias, subjects should not be questioned regarding the specific occurrence of one or more AEs.)

9.2 NONSERIOUS ADVERSE EVENT

- Nonserious Adverse Events are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [e.g. IND US trial] as part of an annual reporting requirement.
- Nonserious AE information should also be collected from the start of a placebo lead-in period or other observational period intended to establish a baseline status for the subjects.

A **nonserious adverse event** is an AE not classified as serious.

9.2.1 Nonserious Adverse Event Collection and Reporting

The collection of nonserious AE information should begin at first protocol specific intervention. All nonserious adverse events (not only those deemed to be treatment-related) should be collected continuously during the treatment period and for a minimum of 100 days following the last dose of study treatment.

The drug supporter company will reconcile the clinical database AE cases (case level only) transmitted to BMS Global Pharmacovigilance (Worldwide.Safety@bms). Frequency of reconciliation should be every 3 months and prior to the database lock or final data summary. BMS GPV&E will email, upon request from the Investigator, the GPV&E reconciliation report. Requests for reconciliation should be sent to aepbusinessprocess@bms.com. The data elements listed on the GPV&E reconciliation report will be used for case identification purposes. If the Investigator determines a case was not transmitted to BMS GPV&E, the case should be sent immediately to BMS.

Nonserious AEs should be followed to resolution or stabilization, or reported as SAEs if they become serious. Follow-up is also required for nonserious AEs that cause interruption or discontinuation of study drug and for those present at the end of study treatment as appropriate.

Recommended Adverse Event Recording Guidelines

Attribution	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5
Unrelated	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III

Unlikely	Phase I	Phase I	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III
Possible	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Probable	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III
Definitive	Phase I Phase II	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III	Phase I Phase II Phase III

9.3 Laboratory Test Abnormalities

All laboratory test results captured as part of the study should be recorded following institutional procedures. Test results that constitute SAEs should be documented and reported as such.

The following laboratory abnormalities should be documented and reported appropriately:

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

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

9.3.1 Potential Drug Induced Liver Injury (DILI)

Specific criteria for identifying potential DILI have not been identified for this protocol. Standard medical practice in identifying and monitoring hepatic issues should be followed.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

Potential drug induced liver injury is defined as:

- 1) AT (ALT or AST) elevation > 3 times upper limit of normal (ULN)
AND
- 2) Total bilirubin > 2 times ULN, without initial findings of cholestasis (elevated serum alkaline phosphatase),
AND
- 3) No other immediately apparent possible causes of AT elevation and hyperbilirubinemia, including, but not limited to, viral hepatitis, pre-existing chronic or acute liver disease, or the administration of other drug(s) known to be hepatotoxic.

Wherever possible, timely confirmation of initial liver-related laboratory abnormalities should occur prior to the reporting of a potential DILI event. All occurrences of potential DILIs, meeting the defined criteria, must be reported as SAEs.

9.4 Pregnancy

If, following initiation of the investigational product, it is subsequently discovered that a study participant is pregnant or may have been pregnant at the time of investigational product exposure, including during at least 5 half-lives after product administration, the investigational product will be permanently discontinued in an appropriate manner (eg, dose tapering if necessary for participant).

The investigator must immediately notify Worldwide.Safety@bms.com of this event via the Pregnancy Surveillance Form in accordance with SAE reporting procedures.

Protocol-required procedures for study discontinuation and follow-up must be performed on the participant.

Follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome and, where applicable, offspring information must be reported on the Pregnancy Surveillance Form [provided upon request from BMS]

Any pregnancy that occurs in a female partner of a male study participant should be reported to BMS. Information on this pregnancy will be collected on the Pregnancy Surveillance Form. In order for Sponsor or designee to collect any pregnancy surveillance information from the female partner, the female partner must sign an informed consent form for disclosure of this information.

9.5 Overdose

An overdose is defined as the accidental or intentional administration of any dose of a product that is considered both excessive and medically important. All occurrences of overdose must be reported as an SAE.

9.6 Other Safety Considerations

Any significant worsening noted during interim or final physical examinations, electrocardiograms, x-rays, and any other potential safety assessments, whether or not these procedures are required by the protocol, should also be recorded as a nonserious or serious AE, as appropriate, and reported accordingly.

9.7 Data management and monitoring plan

We will build an integrated database for web-based clinical trial data collection, trial monitoring, reporting, and data quality assurance. Patient medical-demographic information, treatment course, toxicity, and efficacy outcomes will be entered into the database in a timely fashion. A monthly report of study enrollment will be generated automatically and distributed to the study team. Toxicity, response status, and PFS will also be monitored via an integrated statistical program to check against the stopping boundaries. At the time when the stopping boundary is crossed, the study statistician and the PI will be notified by an e-mail generated by the statistical program automatically. The study team will check the data quality to affirm the finding.

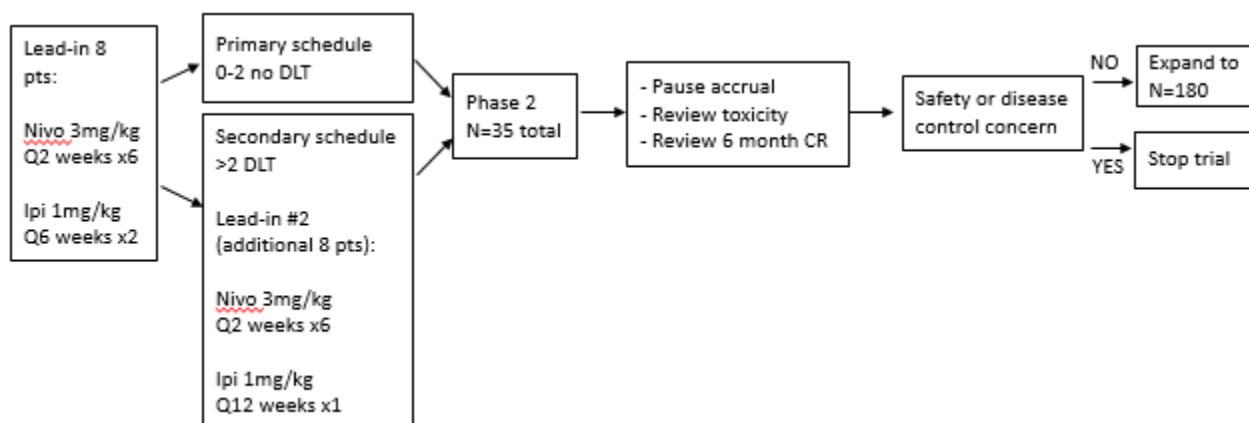
STUDY MONITORING AND EARLY STOPPING RULES

As a single-arm Phase II trial, the study will not be monitored by the MD Anderson Data Safety and Monitoring Board (DSMB). Toxicity monitoring will include grade ≥ 2 toxicities, attribution (e.g., possibly related, probably related or definitely related), whether the toxicity is expected vs. not expected, or whether the toxicity is an SAE vs. not an SAE. All grade immunotherapy-related

toxicities will be reported. SAE reporting will follow standard clinical trial guidelines.

10. STATISTICAL CONSIDERATIONS

10.1 Study Design and Study Endpoints



10.1.1 Safety lead in:

Primary Endpoint:

Dose limiting toxicity for the addition of anti-CTLA4 (ipilimumab) and anti-PD-1 (nivolumab) to IMRT 60 Gy and reduced fields in patients with low-volume, HPV-positive OPSCC.

Secondary Endpoints:

- Number of patients who experience a \geq grade 3 treatment-related adverse event
- Number of patients who tolerated protocol therapy, including completion of radiotherapy without a treatment break and who were administered IO per protocol

- Number of patients who achieve a clinical complete response

Safety lead in design:

The dose finding study will include the dose and schedule of the nivolumab/ ipilimumab combination that was observed to provide clinical efficacy and reduced toxicity in patients with NSCLC. Patients will be administered two cycles of ipilimumab 1 mg/kg on day 1 and nivolumab 3 mgs/kg on day 1, 15 and 29 of a six week schedule, starting 6 weeks prior to day 1 of RT. A cohort of 8 patients will be enrolled. The period of observation for DLT is from the start of IO through 28 days post-completion of radiotherapy. In the event of 0-2 DLT events in the lead-in phase of the protocol, the study will proceed to phase 2. In the event of >2 treatment- attributable DLTs in a cohort of 8 patients, an alternative schedule may be considered in which the second dose of ipilimumab is administered on day 29 cycle 2 and if additional DLT are observed, only one dose of ipilimumab may be administered to prime to T cell response. Observation of the last patient for the period of DLT (28 days post-completion of RT) is mandatory. A DLT will be defined as: (1) Any \geq grade 3 adverse event (CTCAE, v. 4) that is related to IO that does not resolve to grade 1 or less within 28 days; (2) A delay in radiotherapy of >1week due to toxicity related to IO; (3) Inability to complete radiotherapy due to toxicity related to IO; (4) \geq Grade 3 radiation-induced mucositis that does not resolve to < grade 3 within 28 days after radiotherapy. With a cohort of 8 patients, the probability of the combination IO being judged to be too toxic when the true toxicity rate is 45% or higher is at least 78%. If the true toxicity rate is 20% or lower, the probability that the therapy will be safe is 80%. Should schedule adjustment be necessary, given a signal of safety concern, the second cohort of patients will include 8 patients. The phase 2 trial will proceed based upon the DLT data from the first 8 (schedule 1) and first 8 (schedule 2, if necessary) patients. However, data from all patients will be evaluated when available. The principal investigators and BMS will review this data to determine if the study design will need to be adjusted.

10.1.2 Phase II:

Primary endpoint: Two co-primary endpoints are specified: (1) the complete response (CR) rate at 6 months and (2) the two-year progression-free survival (PFS) rate.

Secondary endpoints:

- acute and chronic toxicities per CTCAE v4;
- acute toxicity profiles per CTCAE v4 at the end of radiation therapy, end of IO and 6 months;
- \geq grade 3 treatment-related adverse events at end of radiotherapy, end of IO and 6 months;
- late toxicity profiles per CTCAE v 4 at 1 and 2 years;
- patient-reported, swallowing outcomes at 1 and 2 years;
- patterns of failure (local-regional relapse vs. distant) at 1 and 2 years;
- overall survival (OS) at 1 and 2 years.

10.2 Exploratory Objectives:

To measure changes in the tumor microenvironment in tumor biopsy specimens pre and post induction IO.

To measure changes in serum cytokine profiles before and after induction IO;

To measure alterations in PD-L1 expression in tumor biopsy specimens pre and post induction IO and at progression;

To perform T cell receptor repertoire analysis of TIL in tumor biopsy specimens pre and post induction IO;

To evaluate changes in HPV viral load in plasma and oral rinses during primary therapy and follow-up;

To determine the NPV and PPV of FDG-PET/CT 12-14 weeks after end of RT for 6 month, 1 year and 2 year PFS and OS.

10.3 Study Design:

This is a phase II, open label, single arm study. The study is designed to evaluate the safety, feasibility and clinical efficacy of a treatment strategy of combination anti-CTLA4 (ipilimumab) and anti-PD-1 (nivolumab) IO with reduced dose and field IMRT to 60 Gy for patients with low volume, local-regionally advanced HPV-positive OPSCC (AJCC 7th edition T1N2a-N2c, T3N0, T2-T3N1-N2C; AJCC 8th edition stage 1-2, excluding T1N0-1, T2N0). Treatment will include two, six-week cycles of ipilimumab 1 mg/kg day 1 and nivolumab 3 mg/kg on days 1, 15, and 29 starting 6 weeks before start of IMRT (60 Gy; 2 Gy/fx, 6 fx/week), equivalent to cycle 2 day 1 of the IO.

The statistical considerations for the Phase II design are described as follows. The primary objective of this study is to establish the efficacy of the new immunotherapy regimen such that it is non-inferior to the current standard therapy. Two co-primary endpoints are specified: (1) the complete response (CR) rate at 6 months and (2) the two-year progression-free survival (PFS) rate. Time 0 is defined at start of treatment. Based on the available data (reference), the standard therapy yields a 6-month CR rate of 0.87 and a two-year PFS of 0.91. The non-inferiority margin is set at 0.05 for the 6-month CR rate and at 0.06 for the 2-year PFS. Thus, the new treatment is considered non-inferior to the standard therapy if the 6-month CR rate is at least 0.82 and the two-year PFS is at least 0.85. Otherwise, the new treatment is considered inferior to the standard therapy.

The study comprises a three-year accrual period with 5 patient enrolled per month and additional two years of follow up. Futility early stopping rule will be implemented monthly starting month 7 to protect patients from receiving inferior therapy. In order to assure that the new regimen is safe and efficacious, patient accrual will be paused after 35 patients are enrolled. After the toxicity data and the 6-month CR status are available, study statistician will perform the first interim analysis. The study PI will discuss with sponsor and make a decision to either resume accrual and expand the study size beyond 35 patients if the new regimen is deemed to be safe and efficacious or close the study otherwise. If the trial is not stopped early after the first interim analysis, patient accrual will resume and additional interim monitoring will be performed monthly. If the trial is not stopped early, the non-inferiority boundary is evaluated at the end of study. Patients in the safety evaluation will be included in the phase 2 trial. The maximum total sample size is 180 and the total study duration is up to 5 years.

Assume that the 6-month response rate follows a binomial distribution and the PFS follows a Weibull distribution, given the parameters specified above, the study will have 82% power of establishing the non-inferiority if the efficacy of the new treatment is as good as the standard treatment. In this case, the early futility stopping probability is 0.12 with an average sample size of 170.2. On the other hand, if the new treatment yields a 6-month response rate of 0.75 and a two-

year PFS of 0.85, the early stopping probability is 0.93 with an average sample size of 127.6. The probability of claiming non-inferiority is 0.06 (type I error). If the new treatment is apparently worse than the standard treatment with a 6-month response rate of 0.70 and a two- year PFS of 0.79, the early stopping probability is 1 with an average sample size of 57.0, and a probability of 0 claiming non-inferiority. Detailed model specification, hypothesis testing framework, derivation of test statistics and stopping boundaries can be found in the Appendix. The results were based on simulation studies with 1,000 runs.

The Investigator is responsible for completing safety/efficacy summary reports and submitting them to the IND office Medical Affairs and Safety Group for review. These should be submitted as follows:

- **Lead-In Phase:**
A toxicity summary will be submitted after the first 8 evaluable subjects enrolled in Schedule 1, complete 28 days post radiotherapy, and if required, after the first group of 8 evaluable patients enrolled in Schedule 2, complete the same toxicity monitoring timeline. IND Office approval must be obtained prior to advancing/changing dose levels.
- **Phase II:**
An efficacy/toxicity summary will be submitted after the first 5 evaluable subjects complete 6 months of study treatment, and every 5 patients thereafter. The study enrollment must be paused after 35 patients are enrolled, when study statistician will perform the first interim analysis. Subsequently, summaries submission to IND Office will continue every 5 evaluable subjects until the study is complete. Best response information must be assess after 6 months of initiation of study treatment, and toxicity information after 28 days post radiotherapy.

A copy of the cohort summary should be placed in the Investigator's Regulatory Binder under "sponsor correspondence".

11. CORRELATIVE STUDIES

11.1 Rationale for PD-L1 detection

In CheckMate 141, response rate to single agent nivolumab increased with PD-L1 expression cut-point, but OS did not. As noted in the table below, PD-L1 expression has been associated with efficacy of PD-1/PD-L1 checkpoint blockade (Table 1).

Table 1: Association of PD-L1 expression on tumor cells with immune response of anti-PD-1 antibody Nivolumab. (Modified from X. Meng et al. (Meng et al. 2015))

Tumor	Cut off values	PD-L1 + (%)	Anti-body	ORR PD-L1+	ORR PD-L1-	p-val	Conclusion
Melanoma¹	5%	35.4	Dako	52.7%	33.1%	NR	No sig. association
NSCLC squamous²	1%	83	Dako	18%	17%	0.94	No association
	5%			21%	15%	0.29	
	10%			19%	16%	0.64	
RCC³	5%	27	28-8	31%	18%	NR	No sig. association
NSCLC non-squamous⁴	1%	78	Dako	31%	9%	0.0019	PD-L1 expression sig. associated with ORR
	5%			36%	10%	0.0020	
	10%			37%	11%	0.0021	

Melanoma⁵	5%	46	Dako	43.6%	20.3%	NR	No sig. association
Melanoma, NSCLC RCC CRC⁶	5%	53 53 89 13	5H1	39%	6%	0.0025	PD-L1 expression sig. associated with ORR
Melanoma, RCC, NSCLC, CRC, Prostate⁷	5%	60	5H1	36%	0%	0.006	PD-L1 expression sig. associated with ORR
Melanoma⁸	1%	52	28-8	39%	23%	0.004	PD-L1 expression sig. associated with ORR
	5%	27		67%	19%		

Abbreviations: PD-1, programmed death-1; PD-L1, programmed death-ligand 1; RCC, renal cell cancer; NSCLC, non-small cell lung cancer; CRC, colorectal cancer; NR, not reported; TC, tumor cells.

1. Robert C, et al. N Engl J Med 2015; 2. Brahmer J, et al. N Engl J Med 2015; 3. Motzer RJ, et al. JCO 2015; 4. Borghaei H, et al. N Engl J Med 2015; 5. Weber JS, et al. Lancet Oncol 2015; 6. Taube JM, Clin Cancer Res 2014; 7. Topalian SL, et al. N Engl J Med 2012; 8. Weber JS, et al. JCO 2013.

PD-L1 expression appears associated with ORR (Taube et al. 2014). Nevertheless, patients with PD-L1 negative HNSCC still derive clinical benefit with regard to ORR. This clinical trial design will allow for the evaluation of changes in PD-L1 expression before and after IO among previously untreated patients as well as associations with clinical outcomes.

11.2 HPV-positive head and neck cancer and response to IO: neoantigens and T cell repertoire

Studies first carried out in the 1980s demonstrated murine T cells recognize mutated gene products, known as neoantigens, and that these T cells are capable of mediating tumor rejection (Lu and Robbins 2016). Thus, mutational burden may be related to response to immune checkpoint blockade. For example, neoantigen burden was positively correlated with the clinical benefit and progression-free survival in patients with NSCLC receiving the anti-PD-1 antibody pembrolizumab (Rizvi et al. 2015).

Tumors with an immune-active microenvironment (so called “hot tumors”) are more likely to respond to IO agents targeting key immunosuppressive pathways (Denkert et al. 2010). Tumor regression in response to IO may be mediated in part by CTLs and NK cells that recognize neoepitopes expressed by tumors. HPV E6 and E7 proteins are tumor-specific, foreign neoantigens that can be recognized by T cells, thus inducing tumor rejection. Moreover, high levels of TILs in a diagnostic specimen among HPV-positive patients treated primarily with RT was associated with a high 3-year OS of 96% (Ward et al. 2014). Moreover, as a response to viral infection, HPV associated tumors display evidence of induction of a component of innate immunity known as the apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like (APOBEC) family of proteins, leading to high potential for generation of neoantigens (Cleary et al. 2016). As an example, two specific codons (E542K and E545K) within the helicase domain of PIK3CA are frequently mutated in HPV-positive SCCHN due to C>T transitions in a T*pC context (Hayes, Van Waes, and Seiwert 2015). We note that smoking is a negative prognostic factor for HPV-positive HNSCC. However, higher tobacco-signature mutations may result in neoantigen generation. We will perform WES and RNAseq on tumor biopsies at baseline to determine mutational burden and resulting expressed neoantigen generation and frequency distribution. Somatic mutations in DNA repair proteins (eg. FA, POLE) and their association with mutational burden will also be of

interest.

11.3 Changes in the microenvironment among HPV-positive OPSCC treated with IO:

The study design provides an opportunity to evaluate the effect of dual IO checkpoint blockade with ipilimumab and nivolumab on the tumor microenvironment among previously untreated patients. We will explore T cell receptor diversity and expansion in the peripheral blood and tumor microenvironment before and after neoadjuvant ipi/nivo, if feasible, by means of targeted T cell sequencing and presence and phenotype distribution of the inflammatory infiltrate by multi-spectral immunofluorescence and possibly single cell RNAseq in before and after biopsies. We will explore associations between biomarkers of interest and 6-months CR and 2-year PFS outcomes. For example, alterations that will be evaluated include the frequency and phenotype distribution of TIL in the tumor microenvironment (e.g. CTLA-4, PD-L1 expressing CD8+ and CD4+FoxP3+Treg and associated ratios; NKp46 CD56dim NK cells).

12. Appendices

APPENDIX I: Nivolumab and Ipilimumab TOXICITY MANAGEMENT ALGORITHMS

These general guidelines constitute guidance to the Investigator and may be supplemented by discussions with Prof. Dr. Ferrarotto. The guidance applies to all immune-oncology agents and regimens.

A general principle is that differential diagnoses should be diligently evaluated according to standard medical practice. Non-inflammatory etiologies should be considered and appropriately treated.

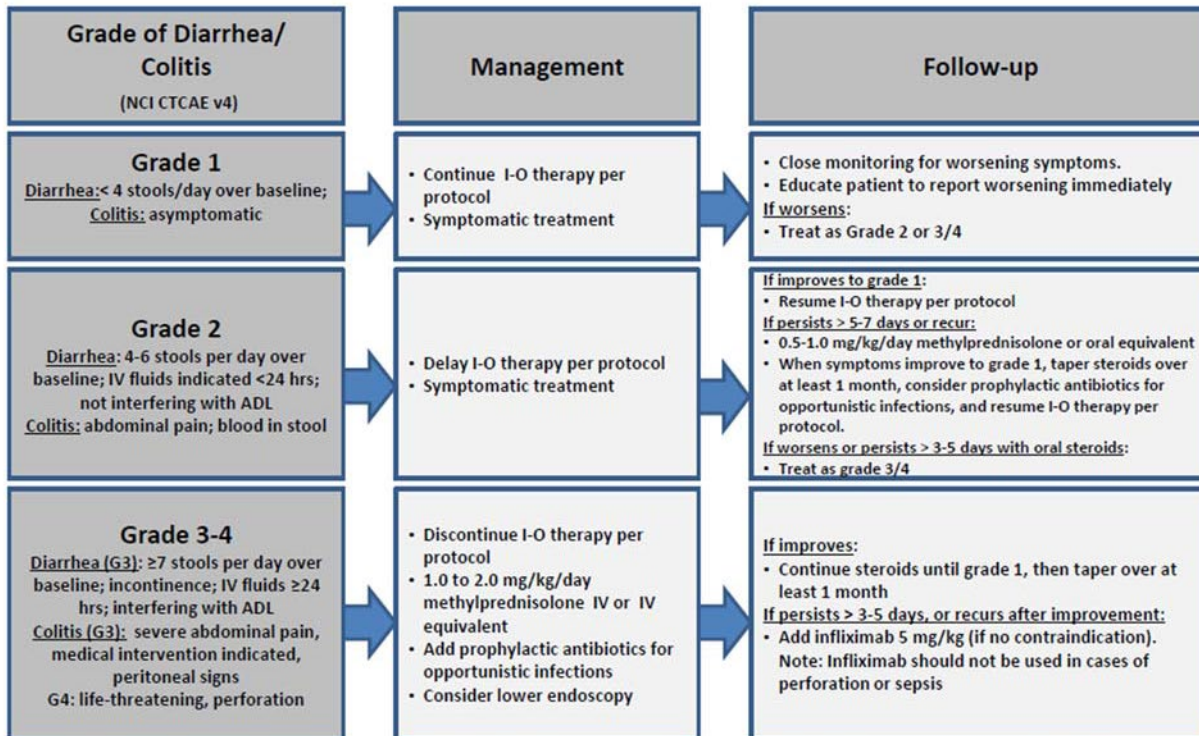
Corticosteroids are a primary therapy for immuno-oncology drug-related adverse events. The oral equivalent of the recommended IV doses may be considered for ambulatory patients with low-grade toxicity. The lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of oral corticosteroids.

Consultation with a medical or surgical specialist, especially prior to an invasive diagnostic or therapeutic procedure, is recommended.

The frequency and severity of the related adverse events covered by these algorithms will depend on the immuno-oncology agent or regimen being used.

GI Adverse Event Management Algorithm

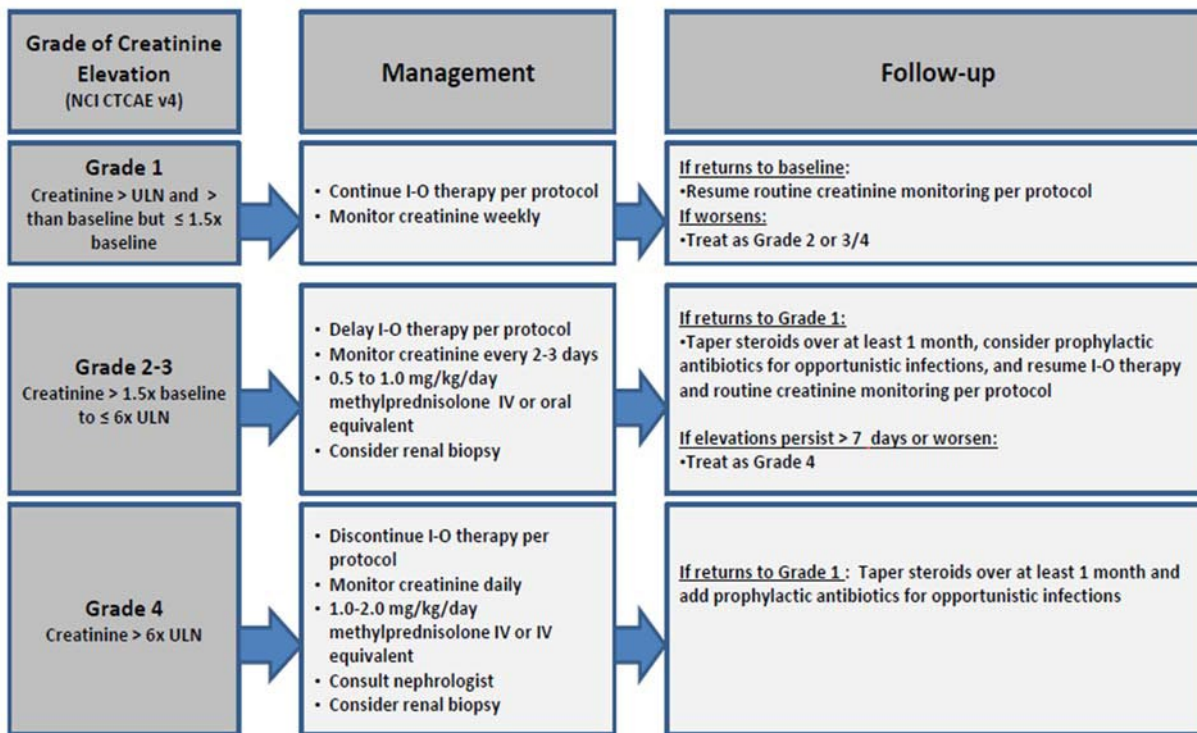
Rule out non-inflammatory causes. If non-inflammatory cause is identified, treat accordingly and continue I-O therapy. Opiates/narcotics may mask symptoms of perforation. Infliximab should not be used in cases of perforation or sepsis.



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

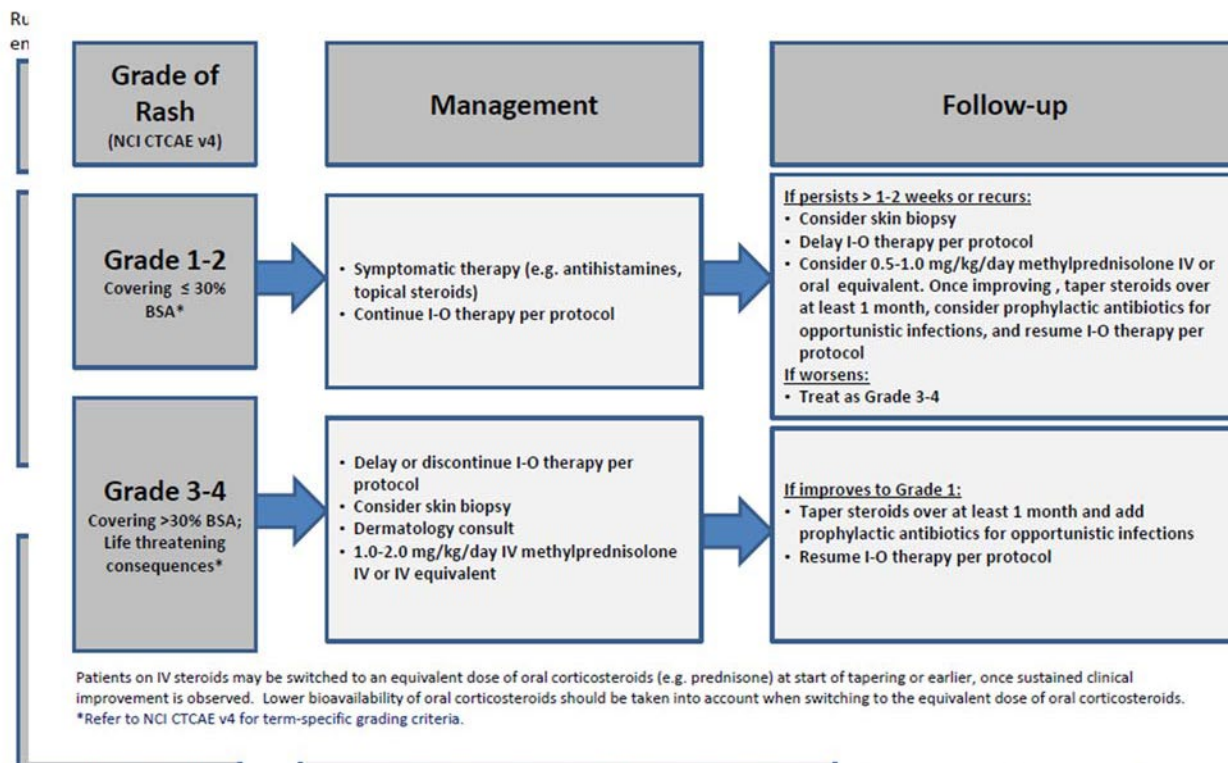
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy



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.

Skin Adverse Event Management Algorithm

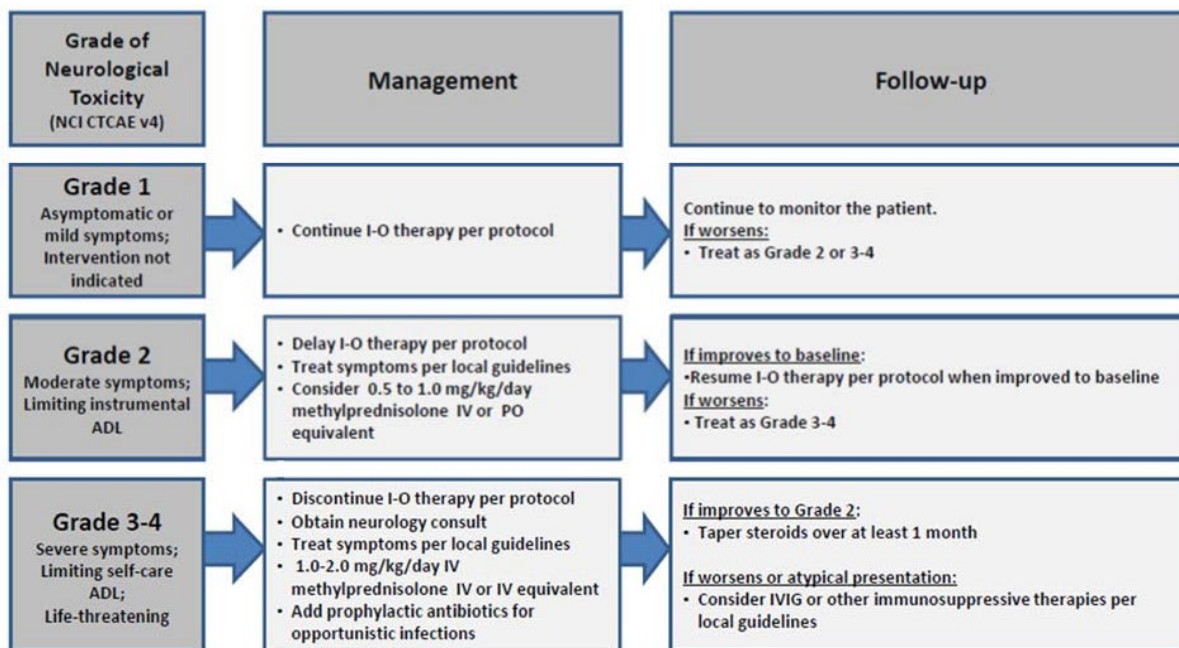
Rule out non-inflammatory causes. If non-inflammatory cause, treat accordingly and continue I-O therapy.



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.

Neurological Adverse Event Management Algorithm

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

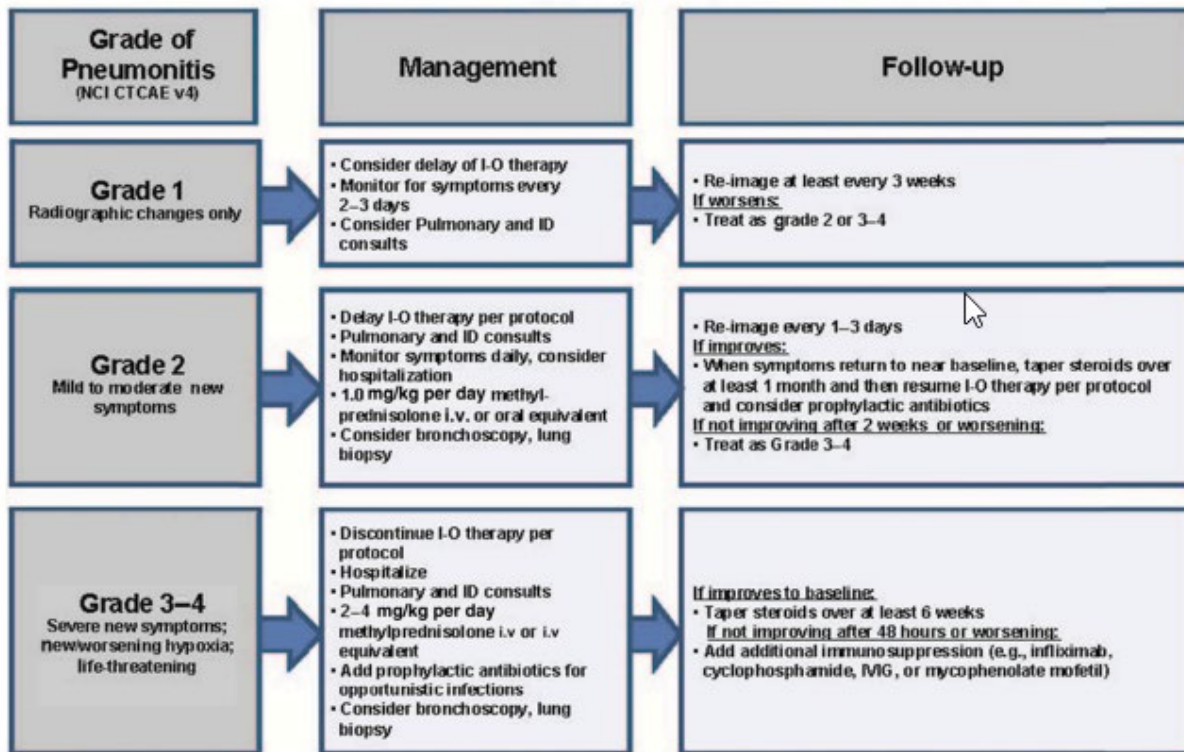


Patients on IV steroids may be switched to an equivalent dose of oral corticosteroids (e.g. prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose of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

D

Pulmonary Adverse Event Management Algorithm

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

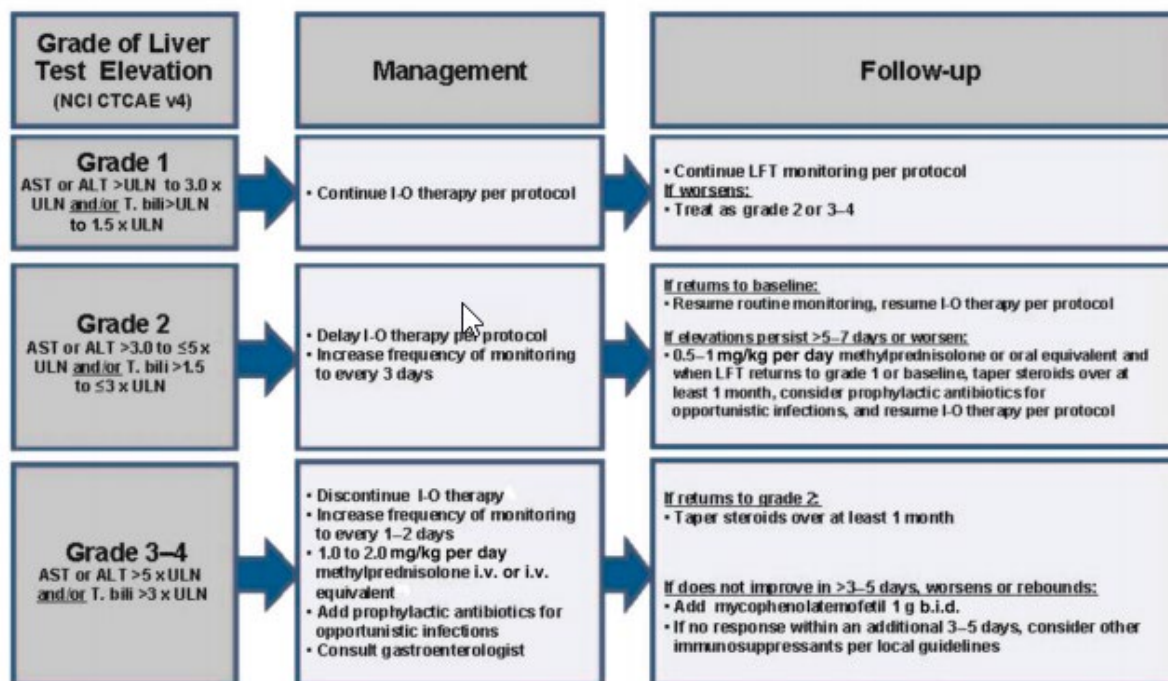


Patients on i.v. steroids may be switched to an equivalent dose of oral corticosteroids (e.g., prednisone) at start of tapering or earlier, once sustained clinical improvement is observed. Lower bioavailability of oral corticosteroids should be taken into account when switching to the equivalent dose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

C

Hepatic Adverse Event Management Algorithm

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



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

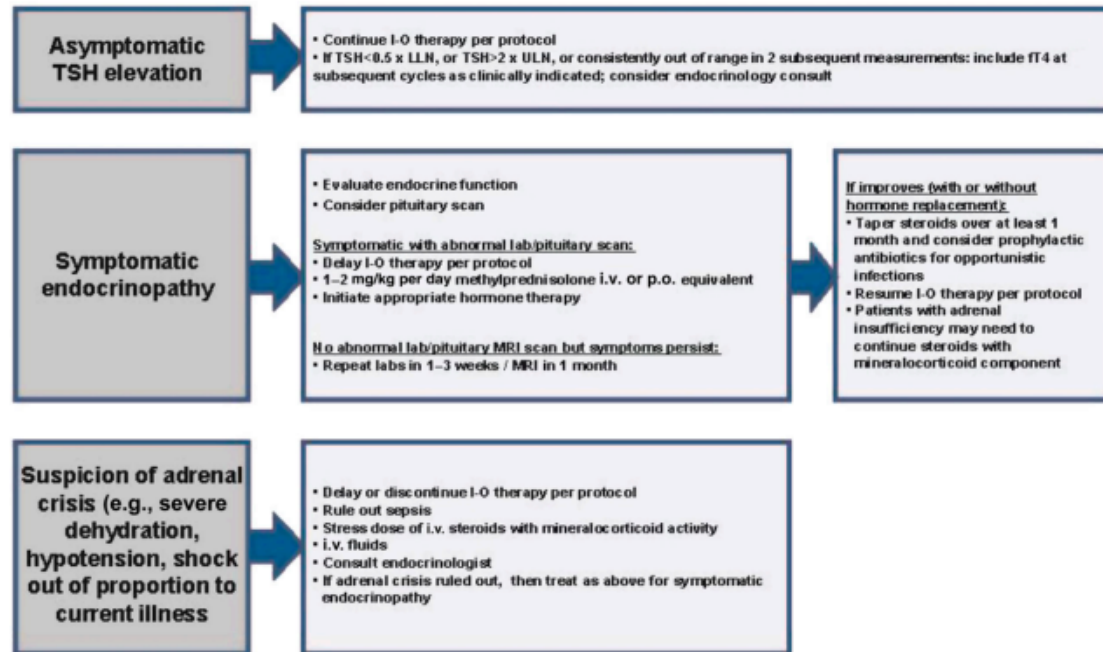
I-O therapy may be delayed rather than discontinued if AST/ALT ≤8 x ULN and T. bili ≤5 x ULN.

The recommended starting dose for grade 4 hepatitis is 2 mg/kg per day methylprednisolone i.v.

B



Endocrine Adverse Event Management Algorithm

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



Patients on i.v. 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.

APPENDIX II: MADSI/MDAMI

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Date: / /
(month) (day) (year)

Subject's Initials:

Study Subject #

Study Name:

Protocol #:

Pt:

Revision: 07/01/05


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M. D. Anderson Symptom Inventory - Head & Neck (MDASI-HN)

Part I. How severe are your symptoms?

People with cancer frequently have symptoms that are caused by their disease or by their treatment. We ask you to rate how severe the following symptoms have been *in the last 24 hours*. Please fill in the circle below from 0 (symptom has not been present) to 10 (the symptom was as bad as you can imagine it could be) for each item.

	NOT PRESENT	0	1	2	3	4	5	6	7	8	9	10	AS BAD AS YOU CAN IMAGINE
1. Your pain at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
2. Your fatigue (tiredness) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
3. Your nausea at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
4. Your disturbed sleep at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
5. Your feeling of being distressed (upset) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
6. Your shortness of breath at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
7. Your problem with remembering things at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
8. Your problem with lack of appetite at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
9. Your feeling drowsy (sleepy) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
10. Your having a dry mouth at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
11. Your feeling sad at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
12. Your vomiting at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
13. Your numbness or tingling at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
14. Your problem with mucus in your mouth and throat at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	
15. Your difficulty swallowing/chewing at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	

 35625
 Date: / /
 (month) (day) (year)

Study Name: _____
 Protocol #: _____
 PI: _____
 Revision: 07/01/05

Subject's Initials: _____
 Study Subject #

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	NOT PRESENT	1	2	3	4	5	6	7	8	9	10
16. Your choking/coughing (food/liquids going down the wrong pipe) at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
17. Your difficulty with voice/speech at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
18. Your skin pain/burning/rash at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
19. Your constipation at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
20. Your problem with tasting food at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
21. Your mouth/throat sores at their WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
22. Your problem with your teeth or gums at its WORST?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>

Part II. How have your symptoms interfered with your life?

Symptoms frequently interfere with how we feel and function. How much have your symptoms interfered with the following items in the last 24 hours:

	Did not interfere	1	2	3	4	5	6	7	8	9	10	Interfered Completely
23. General activity?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
24. Mood?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
25. Work (including work around the house)?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
26. Relations with other people?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
27. Walking?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>
28. Enjoyment of life?	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>	<input type="radio"/>



M.D. Anderson Dysphagia Inventory



PATIENT:
MDA MRN:
ACCT#:
ADM DATE:
DISCHARGE DATE:
PRINT DATE: 8/27/2018;

CSN:
DOB:
LOCATION:
SEX: FC:

English Version

Head & Neck Center and Diagnostic Imaging A

Please complete this form and return it to your Speech Pathologist at the time of your Modified Barium Swallow. This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing. The following statements have been made by people who have problems with their swallowing. Some of these statements may apply to you.

Please read each statement and choose which response best reflects your experience in the past week.

	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
G1. My swallowing ability limits my day-to-day activities.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
E2. I am embarrassed by my eating habits.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
F1. People have difficulty cooking for me.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
P2. Swallowing is more difficult at the end of the day.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
E7. I do not feel self-conscious when I eat.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
E4. I am upset by my swallowing problem.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
P6. Swallowing takes great effort.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
F5. I do not go out because of my swallowing problems.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
F5. My swallowing difficulty has caused me to lose income.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
P7. It takes me longer to eat because of my swallowing problem.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

M.D.A. Dysphagia Inventory (English Version)
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(Form Review: 3/10/2016)

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M.D. Anderson Dysphagia Inventory



PATIENT:
MDA MRN:
ACCT#:
ADM DATE:
DISCHARGE DATE:
PRINT DATE: 8/27/2018;

CSN:
DOB:
LOCATION:
SEX: FC:

English Version

Head & Neck Center and Diagnostic Imaging A

Please complete this form and return it to your Speech Pathologist at the time of your Modified Barium Swallow. This questionnaire asks for your views about your swallowing ability. This information will help us understand how you feel about swallowing. The following statements have been made by people who have problems with their swallowing. Some of these statements may apply to you.

Please read each statement and choose which response best reflects your experience in the past week.

	Strongly Agree	Agree	No opinion	Disagree	Strongly Disagree
P3. People ask me, "Why can't you eat that?"	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
E3. Other people are irritated by my eating problem.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
P8. I cough when I try to drink liquids.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
F3. My swallowing problems limit my social and personal life.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
F2. I feel free to go out to eat with my friends, neighbors, and relatives.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
P5. I limit my food intake because of my swallowing difficulty.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
P1. I cannot maintain my weight because of my swallowing problem.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
E5. I have low self-esteem because of my swallowing problem.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
P4. I feel that I am swallowing a huge amount of food.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
F4. I feel excluded because of my eating habits.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Patient Signature: _____ Date Signed: _____

MDA Dysphagia Inventory (English Version)
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