TITLE: Phase II Study of IMRT Re-Irradiation with concurrent/adjuvant Nivolumab in patients with locoregionally recurrent or second primary squamous cell cancer of the head and neck (BMS Protocol CA209-9KY)

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BMS supplied agent: Nivolumab

PROTOCOL SYNOPSIS

Title of study	**Phase II Study of IMRT Re-Irradiation with concurrent/adjuvant Nivolumab in patients with locoregionally recurrent or second primary squamous cell cancer of the head and neck**
Investigational drugs	Nivolumab
Protocol Date and Version	Version 11.0 July 27, 2023
Protocol number	Winship 4221-17; BMS CA209-9KY
Principal Investigators	1. Nabil Saba, M.D. (Emory) 2. Shlomo Koyfman (Cleveland Clinic)
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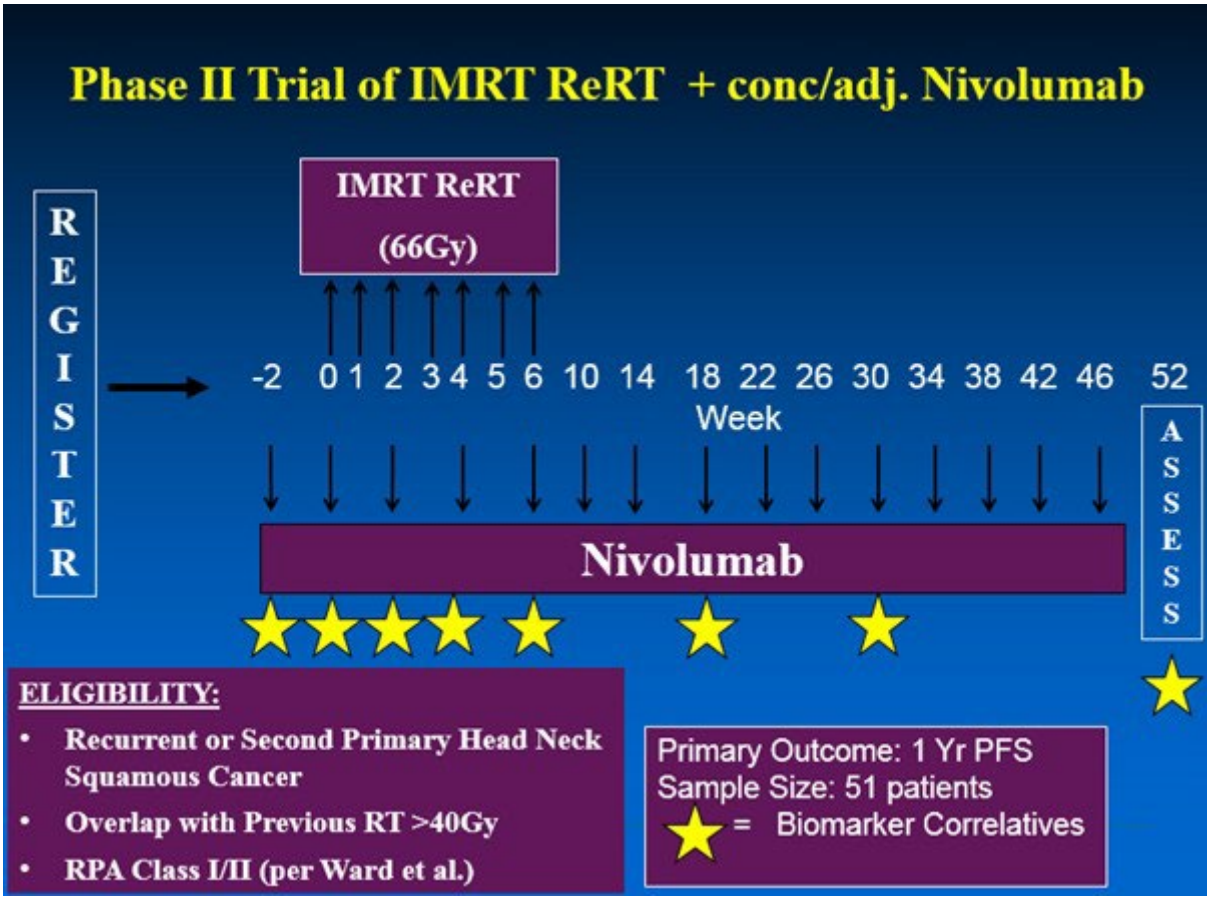
Research Investigators	1. Rafi Ahmed 2. Mohamed Abazeed 3. Georgia Chen 4. Andreas Wieland
Funding Organization	BMS
Study Sites	1. Emory University 2. Cleveland Clinic 3. Medical College of Wisconsin
Clinical Phase	Phase II
Objectives	**Primary Objectives:** 1- To assess the 1-year PFS for patients with RPA class I and II disease treated with nivolumab and IMRT re-irradiation **Secondary Objectives:** 1- Evaluate the OS of patients treated with re-irradiation and nivolumab 2- Evaluate patient QOL 3- Evaluate patterns of failure including rates of locoregional failure and distant failure 4- Identify and estimate the incidence rate of acute and late toxicities associated with combined re-irradiation and nivolumab followed by nivolumab **Exploratory Objectives:** • To identify potential biomarkers related to clinical benefit to concurrent nivolumab and re-irradiation in patients with recurrent HNSCC.

SAEStudy Design	This will be a phase II single arm study of IMRT re-irradiation in combination with nivolumab in the concurrent and maintenance setting. Patients with RPA class I and II based on the recursive partitioning analysis (RPA) classes reported by Ward et al (ASTRO 2016) will be enrolled. The allowable treatment approaches include IMRT. Based on this analysis, only patients with RPA classes I and II will be included; Class III patients will be excluded. RT will be given as 60-66Gy in once daily fractions (2 Gy per fraction). Nivolumab will be administered 2 weeks prior to the beginning of radiation therapy (1 dose at Week -2) and continue every 2 weeks during radiation (4 doses at Weeks 0, 2, 4, 6) for a total of 5 doses. Nivolumab will then be given every 4 weeks for 10 additional doses for a total of 15 doses of Nivolumab.
Number of Patients	From the MIRI study, the 1-year PFS rate for class I and II combined was 43.8% (95% CI: 38.6 - 49.7%). Assuming a one sided alpha of 0.05 and an 85% power to detect an improvement in 1-yr PFS from 40% to 55% we estimate 46 patients will need to be accrued in 2.5 years and followed for an additional 2 years (estimated maximum total of 51 patients). Accounting for a 20% drop out rate, 62 patients will need to be consented.
Inclusion Criteria	<u>Patient selection:</u> 1- Patients with recurrent squamous cell carcinoma or a second primary arising in a previously irradiated field 2- Patients must be ≥ 18 years of age. 3- Life expectancy of greater than 6 months. 4- Patients cannot have distant metastases and have to be candidates for curative re-irradiation 5- Patients with salivary gland tumors are excluded (patients with nasopharynx CA or sinonasal cancers can participate) 6- Patients with unresectable disease are eligible. 7- Patients who undergo surgical resection will be allowed regardless of HPV status provided they: have one of the following criteria: 1- Positive margins on pathology; 2- evidence of extracapsular spread on nodal pathology; 3- gross residual disease on postoperative or simulation imaging; 4 – N2/3 disease; 5 – T3/4 disease; 6 – multifocal perineural invasion and/or lymphovascular space invasion. 8- The majority of the anticipated target volume (>50%) must have been previously treated to ≥40Gy. Prior RT must have been completed >6 months prior to initiation of IMRT reirradiation. If previous RT records are unavailable, investigators can estimate the dose to previously treated tissues based on completion notes or other treatment history 9- An ECOG performance score 0-2 10- Granulocytes >1500/mm^3, platelets >100,000/mm^3, bilirubin <1.5 mg/dl, creatinine <1.5 mg/dl 11- No other concurrent invasive malignancies treated for the past year (localized prostate cancer or early stage skin cancer are not exclusion criteria)

	12- Patients with carotid artery involvement or encasement will be allowed provided they have no symptoms related to carotid involvement 13- No prior exposure to immunotherapy agents 14- Ability to understand and the willingness to sign a written informed consent document
Exclusion Criteria	1- Any known factors that would pose a contraindication to receiving nivolumab 2- RPA class III patients defined as those expected to begin reirradiation within 2 years of first course of radiation therapy AND are PEG dependent or have a tracheostomy (patients who have undergone total laryngectomy are not excluded) 3- Patients with metastases 4- Prior treatment with a PD-1/PD-L1 inhibitor. 5- Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to enrollment. 6- Patients with primary salivary gland cancers, or non squamous histology are excluded. 7- Patients who have had chemotherapy or biological therapy within 4 weeks of the study. 8- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, autoimmune disease requiring systemic steroids, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. 9- Patients who are pregnant or breast-feeding 10- Patients with known active HIV, Hep B, or Hep C infection 11- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.
Discontinuation Criteria	1- Patients with grade 3 or 4 infusion reaction must not receive further treatment with nivolumab. 2- If treatment is interrupted for >3 consecutive weeks, patient's protocol treatment will be discontinued. 3- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, the protocol treatment should be discontinued. 4- Patients who develop progressive disease will be discontinued from the protocol therapy. 5- Patients who develop unacceptable toxicity will be discontinued from the protocol therapy. 6- Patients may withdraw consent and withdraw from the study at any time for any reason.

SCHEMA


Phase II Trial of IMRT ReRT + conc/adj. Nivolumab
IMRT ReRT
(66Gy)
REGISTER
-2 0 1 2 3 4 5 6 10 14 18 22 26 30 34 38 42 46 52
Week
ASSESS
Nivolumab
ELIGIBILITY:
• Recurrent or Second Primary Head Neck Squamous Cancer
• Overlap with Previous RT >40Gy
• RPA Class I/II (per Ward et al.)
Primary Outcome: 1 Yr PFS
Sample Size: 51 patients
= Biomarker Correlatives

TREATMENT STUDY CALENDER

Test	Pre-therapy (Day -30 to -1 before Nivolumab)	Every 2 weeks during each Nivo cycle before and during radiation	Every 4 weeks during each Nivo cycle for maintenance phase[k]	Wk 18 and 30 disease assessment[a]	Wk 52 (1yr after start of radiation) or at the time of disease progression	Wk 104 (yr 2 after start of radiation) or at the time of disease progression
History and physical[b]	X	X[k]	X[k]	X[k]	X	X
Weight and ECOG PS	X	X[k]	X	X	X	X
Tumor measurement (if applicable)	X			X	X	X
CBC and diff[c]	X	X	X		X	X
Chemistries (Na, CL, CO2, K, BUN, Creatinine, Ca, Phos)	X	X[k]	X[k]		X	X
Liver function panel[d]	X	X	X		X	X
PT, PTT, INR	X				X	X
TSH	X		X		X	X
Tissue for research purposes - fresh biopsy (paraffin embedded if fresh tissue not available)[e, f]	X				X	
Blood for research purposes	X	X		X	X	X
Toxicity assessment[g]	X	X		X	X	X
QOL assessment	X	Wk 6 at completion of radiation		X	X	X
Radiology: 1. PET/CT or 2. CT- or MRI-neck AND CT-chest, CT-abdomen for tumor measurements[h]	X[i]			X	X	X

Serum B-HCG[j]	X					

[a.] Disease assessments may be done +/- 2 weeks of specified time in protocol to allow for scheduling and/or transportation needs of the patient

[b.] If Nivolumab or radiation has to be permanently discontinued due to side effects, H&P must be done 4 and 8 weeks after treatment discontinuation.

[c.] CBC and diff include WBC, ANC, HCT, HGB, PLT, % lymphocytes, % monocytes, % neutrophils.

[d.] Liver function panel includes Alk Phos, total bilirubin, SGOT (AST), SGPT (ALT), total protein.

[e.] Fresh biopsy will be obtained before the first treatment when feasible. If tissue is not obtained, it is not considered a protocol deviation.

[f]. Participating sites could have restricted number of research specimens (up to 6 draws per patient) depending on financial constraints;

[g.] Toxicity assessment: Common Toxicity Criteria (CTC) version 4.03 will be used. All toxicity grades (including grade 1) should be captured on the case report forms. All toxicities that occurred during treatment and until 100 days following completion of therapy should be followed until resolution.

[h] Tumor measurement: The scans may be performed within +/- 2 weeks of intended f/u times (wks 18, 30, 52, and 104). Additional scans should be obtained as clinically indicated if progression is suspected or symptoms warrant further investigation. No tumor measurements are required in the postoperative high risk setting where no gross disease is apparent.

[i.] For patients enrolled post salvage surgery, a CT of the Neck and Chest or a PET scan will be required as a baseline study prior to enrollment. The sites can use a simulation CT of the Neck and Chest for this purpose.

[j.] Pregnancy test should be done in woman of childbearing age who are sexually active and may potentially be pregnant. Prior to study enrollment, women of childbearing potential (WOCBP) must be advised of the importance of avoiding pregnancy during trial participation and the potential risk factors for an unintentional pregnancy. In addition, men enrolled on this study should understand the risks to any sexual partner of childbearing potential and should practice an effective method of birth control. All WOCBP MUST have a negative pregnancy test within 7 days prior to first receiving Nivolumab. If the pregnancy test is positive, the patient must not receive investigational product and must not be enrolled in the study. In addition, all WOCBP should be instructed to contact the Investigator immediately if they suspect they might be pregnant (e.g., missed or late menstrual period) at any time during study participation. The Investigator must immediately notify BMS in the event of a confirmed pregnancy in a patient participating in the study.

[k]. May allow a window of 7 days of delay for labs (CBC diff and Chemistries) and 7 days of delay for nivolumab infusion if nivolumab given every 4 weeks; may also allow a window of 3 days between History, PE and ECOG PS status and nivolumab infusion (regardless of the nivolumab schedule)

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1. INTRODUCTION

1.1. MEDICAL BACKGROUND

1.1.1. Treatment of Recurrent Locoregionally Advanced Head and Neck Squamous Cell Carcinoma

Head and neck squamous cell carcinoma (HNSCC) remains one of the most devastating cancers in the United States. The sites affected by HNSCC (oral cavity, oropharynx, hypopharynx and larynx) are critical to the complex and vital functions of speech and swallowing. Therefore, HNSCC is clinically challenging because the treatment frequently alters or destroys a patient's ability to have oral intake and to communicate verbally. Optimal treatment of HNSCC is based on the site and size of the tumor as well as clinical assessments of the presence or absence of cervical lymph node metastasis. Large tumors or tumors with regional metastases are typically treated with combined modality therapy, including surgery, radiation, and/or chemotherapy. Smaller tumors without cervical metastases can often be effectively controlled with either surgery or radiation therapy alone.

Approximately 30-40% of patients irradiated for HNSCC will recur with isolated locoregional disease and a substantial number will develop a second primary cancer (1, 2). Treatment of these non-metastatic patients with recurrent or second primary (RSP) cancers originating within a previously radiated field presents a challenging clinical scenario. Historically, systemic therapy alone produced median survival of only 8 months. Re-irradiation of RSP carcinoma was associated with significant acute and late morbidity with improved but still modest control rates. Attempts to improve outcomes with concurrent chemotherapy and hyper-fractionation provided only modest improvements. Overall, the risk benefit ratio of re-irradiation was questionable in many of these "curable" patients.

Therapeutic advances, such as the use of multi-modality therapies, have significantly improved survival of advanced-stage HNSCC patients over the past 10-15 years (3-5). However, still 30-40% of patients have recurrences (1, 2). There has been little improvement in survival for patients who have locoregional or metastatic recurrence. Chemotherapeutic agents employed in the management of locally recurrent and/or metastatic HNSCC have response rates in the range of 10-40% (6-11). Unfortunately, the duration of response is limited (2-4 months) and survival advantage has not been shown beyond the median survival of 6-10 months (12, 13).

Immunotherapy has recently become an attractive option in HNSCC. PD-1 is one of the clinically significant checkpoint molecules that have been shown to suppress T-cell function upon binding to its ligands, PD-L1 and PD-L2, which have been shown to be expressed in tumor cells from both preclinical models and clinical settings of cancer patients undergoing immunotherapy (14, 15). Tumor expression of PD-L1 was tightly correlated with clinical responsiveness to nivolumab in the early clinical trials, supporting the adaptive immune resistance hypothesis (16). Both human papilloma virus (HPV)-positive and HPV-negative HNSCC have been shown to express PD-L1 (17, 18). Nivolumab is a potent and highly selective humanized monoclonal antibody that binds PD-1 and blocks the interaction between PD-1 and its ligands, PD-L1 and PD-L2. A phase III clinical trial comparing nivolumab vs. investigator's choice (IC) chemotherapy (methotrexate, docetaxel, or cetuximab) in patients with recurrent and/or metastatic HNSCC showed an overall survival (OS) benefit with nivolumab (7.5 months median OS) vs IC chemotherapy (5.1 months) (HR 0.7, *P*=0.01) and minimal toxicities (19). Objective response rate was 13% with nivolumab versus 5.8% with IC. In a subset analysis, patients with PD-L1 expression had higher response rates compared to patients without PD-L1 expression, and HPV-positive patients showed longer OS compared to HPV-negative patients. Although these are encouraging results, the clinical benefit was seen in only a limited number of patients. Thus, identification of combination regimens is urgent in the management of HNSCC. With long term follow up (a median follow up of 11.4

months), nivolumab continued to significantly outperform chemotherapy with a significantly superior overall survival (p=0.0048) (ASCO 2017 (20)).

1.1.2. The Role of Reirradiation in HNSCC

With the advent of advanced radiation planning techniques (e.g. IMRT, VMAT), the feasibility and safety of re-irradiation has greatly improved, as has the therapeutic ratio. A recent multi-institutional collaborative study (named MIRI) of over 400 patients treated with IMRT based re-irradiation at 8 institutions, found that the overall acute grade 4-5 toxicity was only 5.6%, and grades ≥3 late toxicity was only 13% at two years. Overall, the 2-yr (40%) and 5-yr (22%) survival rates compared favorably to historical data (21). Most importantly, a recursive portioning analysis identified three distinct subgroups of patients with 2-yr OS of 62%, 40% and 17%, respectively, for classes I, II and III (21). This finding underscores the suboptimal outcomes in class III patients (e.g. <2 years between the first and planned second RT courses and in patients with pre-re-irradiation gastrostomy or tracheostomy tubes) for whom prolonged conventionally fractionated IMRT based re-irradiation may not be of benefit. On the other hand, IMRT based re-irradiation produces better results in patients with class I (e.g. >2 yrs between the first and planned second RT courses, and for patients managed with initial resection followed by post-op re-irradiation) and class II disease (e.g. all others), the associated 2 yr overall survival of 50% underscores the need for further improvements to this treatment paradigm in these patients. In a subset analysis of the MIRI collaborative study, the addition of systemic therapy (platinum or cetuximab based) did not appear to positively impact outcomes.

1.1.3. Immunotherapy in HNSCC

This study seeks to investigate the potential benefit of the addition of adjuvant immunotherapy to IMRT based re-irradiation in RPA Class I and II patients with RSP head and neck squamous cancer (21). Targeted immunotherapy has resulted in improved survival and durable objective responses in different solid tumors and offers a rationale for use in HNSCC (22). PD-L1 expression is observed in close to 68% of HNSCC patients regardless of HPV status (23, 24). Furthermore immune checkpoint inhibitors (CPIs) such as the PD-1 inhibitor nivolumab were recently noted to have a significant clinical activity in heavily pre-treated patients with HNSCC regardless of the HPV status (25). The results from Checkmate-141 a phase III trial randomizing patients with recurrent or metastatic platinum-refractory HNSCC to nivolumab versus investigator's choice (IC) of chemotherapy, have shown a doubling of the 1-year overall survival (OS) (36.0% versus 16.6%, p= 0.0101)(25, 26). The median OS was 7.5 vs. 5.1 months for nivolumab vs. IC (HR 0.70, p = 0.01). OS by PD-L1 status was 8.7 vs. 4.6 months for PD-L1+ > 1% versus PD-L1 < 1%. Longer-term follow-up data (presented at ASCO 2017 (20)) show that nivolumab continued to show a significant survival benefit and better tolerability vs IC in patients with platinum-refractory R/M HNSCC. At 11.4-months minimum follow-up, median OS (95% CI) was 7.7 months (5.7, 8.8) for nivolumab vs 5.1 months (4.0, 6.2) for IC; HR (95% CI) = 0.71 (0.55, 0.90); P = 0.0048. For nivolumab vs IC, the 18-mo OS rate was 21.5% vs 8.3% and ORR was 13.3% vs 5.8%. Nivolumab doubled the median duration of response vs IC (9.7 vs 4.0 months). Grade 3–4 treatment-related adverse event rates for nivolumab vs IC were 15.3% vs 36.0%.

Data reported at the ESMO 2016 meeting indicated that patients receiving nivolumab had a preservation of their quality of life measures compared to patients receiving chemotherapy. This supports the use of nivolumab in a heavily pre-treated patient population who are at high risk of recurrence and disease related mortality such as patients with re-irradiation.

Data from another a single arm study in recurrent/metastatic HNSCC treated with pembrolizumab (N=132) showed an ORR 18%; with 71% of responses lasting > 12 months and including both PD-L1 + and PD-L1- disease. The median progression free survival was 2 months (17% at 12 months) and median OS was 8 months (27). This led the FDA in August

of 2016 to approve pembrolizumab for treating recurrent or metastatic HNSCC that has progressed following platinum based therapy and further underscores the rationale for moving forward with this approach. Further data from a phase II expansion study using a fixed dose of pembrolizumab in patients who failed platinum and cetuximab revealed an overall response rate of close to 18% in this heavily pre-treated patient population (28).

Given these initial exciting results in patients with advanced HNSCC, there is strong rationale for the addition of PD-1 inhibition to an IMRT re-irradiation backbone. This study explores this combination therapy against the standard IMRT re-irradiation alone.

1.1.4. PD-1 and Nivolumab in HNSCC in the context of radiation therapy

Immunotherapy has now emerged as an alternative approach based on recent success in melanoma, lung and renal cell cancer. Checkpoint inhibitors and CTLA-4 inhibitors are being investigated in HNSCC in both the recurrent/metastatic setting with recently reported promising results (26, 28) and in the definitive setting with CTLA-4 inhibitors (ipilimumab). Pembrolizumab, a PD-1 blocker, was recently shown in a Phase I trial to have promising response outcomes in HPV+ recurrent HNSCC.

The effects of standard of care therapy on immune response (CD4(+), CD8(+) T cells, regulatory T cells (Treg) and myeloid-derived suppressor cells (MDSC)) in HNSCC suggest an immunosuppressive effect. Standard chemoradiotherapy and radiotherapy to both sites of gross and elective risk nodal regions in HNSCC have been found to reduce circulating T cell responses and upregulate MDSCs. PD-1 expression on CD4(+) T cells is upregulated by 2-fold after CRT. PD-1 blockade resulted in downregulation of MDSC, as well as TAM, CD47/SIRP pathway, and upregulated effector T cells and dendritic cells. Lower doses of radiotherapy without chemotherapy after surgery for HPV+ OPC may create an optimal microscopic tumor microenvironment that promotes neo-antigen expression and an abscopal effect without promoting a negative immunosuppressive environment. Combining this approach with PD-1 inhibition may lead to non-redundant immune response through several pathways that is additive and sustained.

PD-L1 and PD 1 expression may be virally mediated in HNSCC, and represent a potential biomarker to blockage with checkpoint inhibitors (29). PD-L1 expression however is variable and not clearly understood. HPV-SCC have also been shown in RNA sequencing TCGA data to express PD-L1. It remains unclear, as to the optimal method of PD-L1 measurement for patient stratification for future trials or whether PD-L1 expression predicts for response to checkpoint inhibitors. This has led to a search for other tumor biomarkers in addition to immune cell profiling to refine patient selection. Somatic gene alterations in HNSCC responsible for immune evasion, inflammation, and antigen presentation may play a role in response to checkpoint inhibition (30). Other investigations reported in metastatic solid tumors include possible association between checkpoint response and genomic instability due to mismatch repair deficiency leading to immune stimulation against epitopes (31), mutational burden and improved outcomes in melanoma and NSCLC with checkpoint inhibitors (32) and the possible correlation between neoantigen burden and response to immunotherapy. Neoantigen specific T-cell therapy that exposes epitopes derived from genetic aberrations has demonstrated promising results when combined with checkpoint inhibition (33-36).

Nivolumab is a fully human, IgG4 (kappa) isotype, mAb that binds to PD-1. Blockade of the PD-1 pathway by nivolumab was studied using the mixed lymphocyte reaction (MLR). PD-1 blockade resulted in a reproducible enhancement of both proliferation and IFN-γ release in the MLR.30. The effect of nivolumab on antigen-specific recall responses was investigated using a CMV-restimulation assay of human peripheral blood mononuclear cells (PBMCs) followed by ELISA-based detection of IFN-γ production. These data indicated that nivolumab, versus an isotype-matched control antibody, augmented IFN-γ secretion from CMV-specific memory T cells in a dose-dependent manner.

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

In CA209003, the clinical activity of nivolumab was demonstrated in a variety of tumor types, including melanoma, RCC, and NSCLC. Clinical activity was noted across a range of doses (0.1 mg/kg, 0.3 mg/kg, 1 mg/kg, 3 mg/kg, and 10 mg/kg). In CA209003, a total of 306 subjects with melanoma, RCC, and NSCLC have been evaluated for clinical activity. A response of either CR or PR, as determined by investigator assessed tumor evaluations based on RECIST 1.1 criteria108, has been reported at all dose levels.

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

Historically, ORR of 5% to 10% and median PFS (mPFS) of 2 to 3 months has been reported with docetaxel treatment in previously-treated NSCLC subjects. A complete response (CR) or partial response (PR) was reported in 31% (95% CI: 22% - 41%) of the 107 response-evaluable subjects with melanoma treated with nivolumab monotherapy Q2W at doses ranging from 0.1 to 10 mg/kg in CA209-003. Responses were durable with a PFSR at 24 weeks of 38% (95% CI: 28-47%) and OS at 24 months of 48% (95% CI: 38-57%).

In CA209017, a phase 3 trial in 272 patients with metastatic squamous NSCLC with progression on or after platinum-based chemotherapy, subjects were randomized to nivolumab 3 mg/kg IV q2 week (n=135) or docetaxel (n=137) at 75 mg/m2 every 3 weeks. Median OS was 9.2 months in the nivolumab group (95% CI: 7.3-13.3) vs 6.0 months in the docetaxel group (95% CI: 5.1-7.3) (HR of 0.59, P=0.00025).

Summary of Nivolumab Safety in the Metastatic Setting
In clinical trials, nivolumab has demonstrated an acceptable benefit-risk across multiple tumor types, including advanced melanoma, RCC, NSCLC, and some lymphomas. The two clinical trials that have contributed the most to the clinical experiences of nivolumab monotherapy are studies CA209003 and CA209037. Overall, the safety profile is quite similar between these two studies and is discussed further in the sections below. CA209003 is a completed Phase 1 open label, multiple dose escalation study in 306 subjects with select previously treated advanced solid tumors, including melanoma, RCC, NSCLC, colorectal cancer, and hormone-refractory prostate cancer. Subjects received nivolumab at doses of 0.1, 0.3, 1, 3, or 10 mg/kg intravenously every 2 weeks, up to a maximum of 2 years of total therapy. A total of 306 subjects were treated with nivolumab in the dose range of 0.1 - 10 mg/kg. No maximal tolerated dose was identified in CA209003.

The incidence, severity and relationship of AEs were generally similar across dose levels and tumor types. Nivolumab related AEs of any grade occurred in 75.2% of subjects. Of the 306 treated subjects, 303 (99.0%) subjects have at least 1 reported AE regardless of causality. The most frequently reported AEs were fatigue (54.9%), decreased appetite (35.0%), diarrhea (34.3%), nausea (30.1%), and cough (29.4%). Treatment-related AEs were reported in 230 (75.2%) of the 306 subjects. The most frequently reported treatment-related AEs were fatigue (28.1%), rash (14.7%), diarrhea (13.4%), and pruritus (10.5%). Most treatment-related AEs were low grade. Treatment-related high grade (Grade 3-4) AEs were reported in 52 (17.0%) of subjects. The most common treatment-related high grade AEs were fatigue (2.3%) and

diarrhea (1%). Drug-related SAEs occurred in 11.5% of subjects. Grade 3-4 drug-related SAEs reported in at least 2 subjects included: diarrhea (3 subjects, 1.0%), pneumonitis (3 subjects, 1.0%), pneumonia (2 subjects, 0.7%) and lipase increased (2 subjects, 0.7%). Select AE categories (events with a potential inflammatory mechanism requiring more frequent monitoring and/or unique intervention such as immune-suppressants and/or endocrine replacement therapy) include: GI AEs, pulmonary AEs, renal AEs, hepatic AEs, skin AEs, and endocrinopathies. In addition, select AEs include a category for infusion reactions Table 1). Each category is composed of a discrete set of preferred terms, including those of greatest clinical relevance. These select AEs are considered events of interest based on the mechanism of action and were previously referred to as immune-related AEs or immune-mediated AEs. Most high grade events resolved following the treatment guidelines for the treatment of pulmonary events, GI events, hepatic events, renal events, and endocrine events, respectively. Overall, the safety profile at 3 mg/kg (n = 54) was similar to safety profile across the dose ranges from 0.1 mg/kg to 10 mg/kg (n = 306).

Table 1: Treatment-related Select Adverse Events by Treatment - All CTC Grades Reported in at Least 10 Treated Subjects in CA209003

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

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

Treatment-related AEs leading to discontinuation were reported in 32 (10.5%) of the 306 nivolumab treated subjects on CA209003. The most frequent of these were pneumonitis (8 subjects; 2.6%) and colitis (3 subjects; 1.0%). There were 3 (1%) drug related deaths; each occurred after development of pneumonitis. CA209037 is an ongoing Phase 3, open-label

study of nivolumab (3 mg/kg administered by intravenous [IV] infusion every 2 weeks [Q2W]) vs investigator's choice therapy in subjects with previously-treated advanced melanoma. As of 30-Apr-2014, 268 subjects have been treated with 3 mg/kg IV nivolumab in CA209037 with safety results as outlined below (source document interim CSR, DCN930081508) 111 that are consistent with the Phase 1 experience of CA209003.

In CA209037, nivolumab related AEs of any grade occurred in 67.5% of subjects. Of the 268 subjects treated with nivolumab, 255 (95.1%) subjects had at least 1 reported AE regardless of causality. The most frequently reported treatment-related AEs were fatigue (25.0%), pruritus (16.0%), diarrhea (11.2%), and nausea (9.3%). Most treatment-related AEs were low grade.

Treatment-related high grade (Grade 3-4) AEs were reported in 24 (9.0%) of subjects. The most common treatment-related high grade AEs were fatigue (0.7 %), anemia (0.7%), diarrhea (0.4%), and vomiting (0.4%). Drug-related SAEs occurred in 4.5% of subjects. Grade 3-4 drug-related SAEs reported in at least 2 subjects included diarrhea (2 subjects, 0.7%). In addition, drug-related SAE of hyperglycemia occurred in 0.7%.

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

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

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

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

In addition, Nivolumab has been studied in the phase I portion of the RTOG 3504 trial in which it was seen to be safe to combine with head and neck radiotherapy and cisplatin based chemotherapy. Similarly, other PD-1 inhibitors are being actively investigated in a phase III setting with concurrent radiotherapy with or without other systemic therapies. As such, an adequate experience of a favorable safety profile supports the anticipated safety of this combination without other cytotoxic chemotherapy and no specific safety run-in is required.

2. RATIONALE, OBJECTIVES, AND BENEFIT-RISK ASSESSMENT

2.1. RATIONALE FOR PERFORMING THE TRIAL

This study seeks to investigate the potential benefit of the addition of adjuvant immunotherapy to IMRT based re-irradiation in RPA Class I and II patients with locoregional recurrent or second primary (RSP) head and neck squamous cancer. Our hypothesis is that nivolumab will lead to an improved disease control in this population at high risk of relapse which will translate into an improved 1 year progression-free survival (PFS) compared to the standard re-irradiation with IMRT. We also believe based on the recent PRO data presented at ESMO 2016, that nivolumab will preserve the quality of life in this heavily pre-treated patient population. Given these initial exciting results in patients with advanced head and neck squamous cancer, there is strong rationale for the addition of PD-1 inhibition to an IMRT re-irradiation backbone. This study explores this combination therapy against the standard IMRT re-irradiation with or without other systemic therapies used in the MIRI cohort.

2.2. TRIAL OBJECTIVES

2.2.1. Primary Objective

To assess the 1-year PFS for patients with recurrent or second primary head and neck squamous cancer treated with IMRT re-irradiation with concurrent and adjuvant nivolumab

2.2.3. Secondary Objectives

1- Evaluate the 1-yr OS of patients treated with re-irradiation and nivolumab
2- Evaluate patient QOL
3- Evaluate patterns of failure including local, regional and distant failure rates at 1yr
4- Identify and estimate the incidence rate of acute and late toxicities associated with combined re-irradiation and concurrent and adjuvant nivolumab

Exploratory Objectives:
To identify potential biomarkers related to clinical benefit to concurrent and adjuvant nivolumab and re-irradiation in patients with RSP HNSCC.

3. STUDY POPULATION

Number of Centers

Three sites will be involved.

Number of Participants

A total of 46 patients will need to be accrued in 2.5 years and followed for an additional 2 years (estimated maximum total of 51 patients). Accounting for a 20% drop out rate, 62 patients will need to be consented.

3.1. SELECTION OF STUDY POPULATION

Main Diagnosis for Study Entry

All patients included in this trial must be candidates for re-irradiation with IMRT

3.1.1. Inclusion Criteria

1- Patients with recurrent squamous cell carcinoma or a second primary arising in a previously irradiated field

2- Patients must be ≥ 18 years of age.
3- Life expectancy of greater than 6 months.
4- Patients cannot have distant metastases and have to be candidates for curative re-irradiation
5- Patients with salivary gland tumors are excluded (patients with nasopharynx CA or sinonasal cancers can participate)
6- Patients with unresectable disease are eligible.
7- Patients who undergo surgical resection will be allowed regardless of HPV status provided they: have one of the following criteria: 1- Positive margins on pathology; 2- evidence of extracapsular spread on nodal pathology; 3- gross residual disease on postoperative or simulation imaging; 4 – N2/3 disease; 5 – T3/4 disease; 6 – multifocal perineural invasion and/or lymphovascular space invasion.
8- The majority of the anticipated target volume (> 50%) must have been previously treated to ≥40Gy; Prior RT must have been completed >6 months prior to initiation of IMRT reirradiation. If previous RT records are unavailable, investigators can estimate the dose to previously treated tissues based on completion notes or other treatment history.
9- An ECOG performance score 0-2 (see Appendix 1)
10- Granulocytes >1500/mm^3, platelets >100,000/mm^3, bilirubin <1.5 mg/dl, creatinine <1.5 mg/dl
11- No other concurrent invasive malignancies treated for the past year (localized prostate cancer or early stage skin cancer are not exclusion criteria);
12- Patients with carotid artery involvement or encasement will be allowed provided they have no symptoms related to carotid involvement;
13- No prior exposure to immunotherapy agents
14- Ability to understand and the willingness to sign a written informed consent document

3.1.2. Exclusion criteria:

1- Any known factors that would pose a contraindication to receiving nivolumab
2- RPA class III patients defined as those expected to begin reirradiation within 2 years of first course of radiation therapy AND are PEG dependent or have a tracheostomy (patients who have undergone total laryngectomy are not excluded)
3- Patients with metastases
4- Prior treatment with a PD-1/PD-L1 inhibitor.
5- Female patients of childbearing potential must have a negative serum pregnancy test within 7 days prior to enrollment.
6- Patients with primary salivary gland cancers are excluded.
7- Patients who have had chemotherapy or biological therapy within 4 weeks of registration.
8- Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, autoimmune disease requiring systemic steroids, symptomatic congestive heart failure, unstable angina pectoris, cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements.
9- Patients who are pregnant or breast-feeding
10- Patients with known active HIV, Hep B, or Hep C infection
11- Subjects with a condition requiring systemic treatment with either corticosteroids (> 10 mg daily prednisone equivalents) or other immunosuppressive medications within 14 days of study drug administration. Inhaled or topical steroids and adrenal replacement doses > 10 mg daily prednisone equivalents are permitted in the absence of active autoimmune disease.

3.1.3. Discontinuation Criteria

Patients will be removed from study when any of the following criteria applies:

- Patients with grade 3 or 4 infusion reaction must not receive further treatment with nivolumab

- If radiotherapy is interrupted for > 3 consecutive weeks, patient's protocol treatment will be discontinued.
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, the protocol treatment should be discontinued.
- Patients who develop progressive disease will be discontinued from the protocol therapy.
- Patients who develop unacceptable toxicity will be discontinued from the protocol therapy.
- Patients may withdraw consent and withdraw from the study at any time for any reason.

3.1.4. Premature Discontinuation of Patients from the Study

Those who discontinue protocol therapy early will be followed for response until progression and for survival for 2 years from the date of initiation of radiation. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

4. STUDY DESIGN AND TREATMENT

4.1 OVERALL TRIAL DESIGN AND PLAN

This will be a phase II single arm study of IMRT re-irradiation in combination with nivolumab in the concurrent and maintenance setting. IMRT based reirradiation must be used. VMAT and Cyberknife technologies will be allowed.

Treatment plan:

RT will be given as 60-66Gy in 30-33 once daily fractions. Nivolumab will be given 2 weeks prior to the initiation of IMRT (week -2), and every 2 weeks for 4 more doses during radiation (weeks 0, 2, 4, 6) (240 mg over 30-60 minutes IV each dose, for a total of 5 doses). After the completion of IMRT, nivolumab will be given on a q4wk schedule for an additional 10 treatments (480 mg over 30-60 minutes IV each dose4.2 RADIATION THERAPY

4.2.1. IMRT reirradiation

IMRT reirradiation will be delivered in 60-66Gy in 30-33 once daily fractions over 6-6.5 weeks. Missed treatments due to holidays or logistic reasons can be compensated for by delivering an additional BID treatment during the week, OR treating on the Saturday or Sunday of that week, OR adding to the end of treatment.

4.2.2. Immobilization and Simulation

Patients must have an immobilization device (e.g. Aquaplast mask) made prior to treatment planning CT scan. Use of an immobilizing mouthpiece is optional as clinically indicated but preferred for any target of the oropharynx, or the hard palate/paranasal region. It is preferable to perform treatment planning CT scan with IV contrast if there are no medical contraindications to the use of contrast. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be 0.3 cm or thinner.

4.2.3. Target Delineation

In setting of gross disease: In the setting of gross disease, the gross tumor volume (GTV) is defined as any tumor visible on imaging and/or physical exam. The Clinical Target Volume (CTV_66) is defined as the GTV plus an additional 3-5mm expansion that includes adjacent tissue at risk but respects normal tissue boundaries to tumor spread (e.g. bone, uninvolved muscle, etc). Generally an elective nodal volume will not be targeted. However, there are

several instances where an optional CTV_56.1 can be used to target initially uninvolved adjacent tissue for select patients with high risk of microscopic disease extent. Examples may include gross multifocal nodal disease, in which a CTV_56.1 can target an adjacent uninvolved nodal echelon to provide margin on the involved nodes, or disease that is grossly involving a cranial nerve for which a CTV_56.1 can be used to target the pathway of the nerve to the skull base. The Planning Target Volume (PTV_66) should be a 3mm isotropic expansion around CTV_66. If a CTV_56.1 is used, then a 3mm isotropic expansion around it will be generated to create the PTV_56.1. This volume should be given in 33 fractions.

In high risk postoperative setting
There is no gross tumor volume in the postoperative patient. However, the tumor/involved nodal bed should be included in the CTV_60Gy. Areas that are surgically dissected but uninvolved with tumor (e.g. elective neck dissection that is negative for disease) should generally not be targeted. However, there are several instances where an optional CTV_54 can be used to target adjacent tissue for select patients with high risk of microscopic disease extent. Examples may include pathologically proven multifocal nodal disease, in which a CTV_54 can target an adjacent uninvolved nodal echelon to provide margin on the involved nodes, or disease that is grossly involving a cranial nerve for which a CTV_54 can be used to target the pathway of the nerve to the skull base. The Planning Target Volume (PTV_60) should be a 3mm isotropic expansion around CTV_60. If a CTV_54 is used, then a 3mm isotropic expansion around it will be generated to create the PTV_54. This volume should be given in 30 fractions.

4.2.4. Critical Normal Structures

The normal tissue volume to be contoured will depend on the site of origin of the cancer. For all patients, they will include the brainstem, spinal cord, cochlea, mandible, constrictors, esophagus, trachea, oral cavity, glottis/supraglottic larynx, supraglottis, lips and parotid and submandibular salivary glands. Any of these structures surgically removed or absent can be ignored. The carotid artery should also be contoured. For tumors near the low neck, the brachial plexus must be contoured. For tumors near the skull base, the following should also be included: eyes, lenses, optic nerves, optic chiasm, and pituitary.

4.2.5. Treatment Planning and Delivery

Megavoltage energy photon beam irradiation is required. Inverse planning using intensity modulated RT or Cyberknife is mandatory. Static beam intensity modulation or volumetric arc based planning are acceptable for planning. Proton therapy is not allowed.

4.2.6. Image Guidance for IGRT

IGRT with daily conebeam CT is required. If a cone beam CT is not available, portal images or other on board imaging should be used daily. Region-of-Interest (ROI) or “clip box” for fusion should be set to encompass the PTV and adjacent spinal cord. When the skull base is targeted, the globes and optic nerves should routinely be included, if possible, for alignment purposes. 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 10 mm (this typically corresponds to one half of the usual PRV margin), the treatment can proceed with appropriate corrections; however, re-imaging is not mandatory. If one or more of the corrections are larger than 10 mm, the imaging must be repeated in addition to performing table/positioning adjustments. However, the use of numerous repeat IGRT studies should be avoided (see next section).

4.2.7. Definition of Normal Tissues/Organs at Risk (OARs)

NOTE: Only the parts of the normal tissues/organs at risk outside the PTVs will be considered for dose optimization purposes, except for the spinal cord and brainstem. Only those OAR that are in proximity to the treatment volume must be contoured. Contouring OAR that are far from the treated area and will receive negligible doses is unnecessary.

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 inferior border of the spinal cord volume will be defined at approximately T3-4 (ie, just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined as: SpinalCord_05 = cord + 5 mm in all directions.

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 all directions.

Globe of the eye: Self-explanatory

Optic Nerve: Self-explanatory

Optic Chiasm: Self-explanatory

Cochlea: Self-explanatory

Carotid Artery: This will include the carotid artery at the same level of the PTV plus an additional 2cm cranial and caudal to the level of the PTV. When the PTV is located above the carotid bifurcation, only the internal carotid artery (not the external branch) should be contoured.

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 1/2 to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and superiorly the palate, and inferiorly to the plane containing the tip of the mandible.

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 or superior (S) esophagus, a tubular structure that starts at the bottom of pharynx (cricopharyngeal inlet) and extends to the thoracic inlet.

Glottic/Supraglottic Larynx: This will be defined as the glottic and supraglottic larynx, including the tip of the epiglottis, 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.

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

Brachial Plexus: The defined ipsilateral brachial plexus originates from the spinal nerves exiting the neuroforamine on the involved side from around C5 to T2. However, for the purposes of this protocol, only the major trunks of the brachial plexus will be contoured using the subclavian and axillary vessels as a surrogate for identifying the location of the brachial plexus. This neurovascular complex will be contoured starting proximally at the bifurcation of the brachiocephalic trunk into the jugular/subclavian veins (or carotid/subclavian arteries) and following along the route of the subclavian vein to the axillary vein ending after the neurovascular structures cross the second rib.

Unspecified Tissue Outside the Targets (E-PTV): 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.

Skin: This will be defined as an inner ring of tissue comprising the external skin and the tissue 3mm underneath it.

4.2.8. Dose Prescription

Doses to PTVs

All plans must be normalized such that 95% of the volume of the prescription PTV (PTV_66 for gross disease; PTV_60 for postoperative cases) is covered with the prescription dose (66Gy or 60Gy respectively). At 1 cc PTV_66 volume or PTV_60 volume on the DVH curve, the dose should not be > 110% of the prescribed dose. Ideally, less than 10% of PTV_66 or PTV_60 should receive 105% of the prescription dose (69.3Gy or 63.5Gy respectively). However, up to 20% of PTV_66 or PTV_60 can receive 105% of the prescription dose (69.3Gy or 63.5Gy) to allow for meeting dose constraints. For any volume of tissue outside the PTV(s) that has a size of 1 cc or more, the dose should not be > 66 Gy for definitive cases and >60Gy for postoperative cases.

Doses to Normal Structures

Spinal Cord: The cumulatibe dose to the spinal cord should not exceed 52Gy. In the event that the old plan is not available for review, the dose to the spinal cord should not exceed 10Gy and preferably be less than 8Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm).
In treatment planning, the spinal cord should be given the highest priority.
Spinal Cord PRV: The cumulative dose to the spinal cord PRV should not exceed 55Gy. In the event that the old plan is not available for review, the dose to the spinal cord should not exceed. The Spinal Cord PRV should not exceed 16Gy and ideally less than 14Gy.
Brainstem: The cumulative dose to the brainstem should ideally be limited to 0.03cc to 60Gy. However, if disease is in close proximity to brainstem and requires higher doses, especially if the original RT course exceeded this dose, this is acceptable. Ideally the max dose per fraction to the brainstem should be <1Gy per fraction. If the disease mandates exceeding this constraint, the patient should be informed of the risks of severe or life threatening toxicity. In the event that the old plan is not available for review the brainstem should not exceed 12Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm) and preferably should be less than 10Gy and the PRVbrainstem (brainstem +3mm) should be limited to 16Gy. However, if disease is in extremely close proximity to the brainstem, this may need to be exceeded. In this case, Ideally the max dose per fraction to the brainstem should be <1Gy

per fraction.
Coverage can be compromised to meet spinal cord and brainstem constraints as clinically indicated at the discretion of the treating radiation oncologist.
Optic Nerves and Chiasm: The cumulative dose to the optic structures should not exceed 55 Gy. In the event the that old plan is not available for review, the dose to the optic structures should not exceed a max dose of 10Gy to any volume greater than 0/03cc. In the rare event that a single optic nerve is involved with tumor, these constraints can be violated to achieve coverage of thetuor. However this would not apply to the optic chiasm or bilateral optic nerves.
Orbits: Should be limited to a cumulative max dose of 50Gy including previous radiation.
Lips: Reduce the dose as much as possible. The mean dose should be < 20 Gy when possible.
Oral Cavity: Reduce the dose as much as possible. The mean dose should be < 30 Gy when possible.
Parotid Glands (not targeted): 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.
Submandibular gland (not targeted): If level Ib is not a target, aim to reduce mean contralateral submandibular gland to < 39 Gy.
OARpharynx/constrictors: Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the OARpharynx exceeds 50Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the OARpharynx exceeds 60 Gy.
Cervical Esophagus: Reduce the dose as much as possible. Some recommended (but treatment goals include: Mean dose < 30 Gy.
Glottic and Supraglottic larynx (GSL): Reduce the dose as much as possible. The glottic larynx mean dose is recommended to be <25 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 < 66 Gy, except in areas overlapping PTV.
Unspecified Tissue Outside the Targets: No more than 1cc of unspecified tissue outside the targets can receive 66 Gy or more
Brachial Plexus: The dose to the plexus should be limited as much as possible. The plexus can never exceed 66Gy unless it is clinically involved with tumor. If it is uninvolved, it should be limited to <30Gy whenever possible.

4.2.9. Radiation Therapy Treatment Interruptions

Treatment interruptions are strongly discouraged. Treatment breaks must be clearly indicated in the treatment record when they occur. Patients who have treatment interruptions in radiation for >3 weeks will be taken off study. The interruption of radiation therapy for grade 4 mucositis / dermatitis / dysphagia is at the discretion of the treating radiation oncologist. Treatment breaks, if necessary, ideally should not exceed five treatment days at a time and ten 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.

4.3. NIVOLUMAB ADMINISTRATION:

4.3.1. Administration of Nivolumab

4.3.1. Administration of Nivolumab

Nivolumab will be administered at a fixed dose of 240 mg over 30-60 minutes IV two weeks prior to the beginning of RT and every 2 weeks during radiotherapy for a total of 5 doses. Then Nivolumab will be given at 480 mg over 30-60 minutes IV every 4 weeks for 10 additional doses after radiotherapy. . The first dose will be given two weeks prior to the first fraction of radiation (+/- 5 days), and continued every 2 weeks (+/- 3 days). Nivolumab will thus be given in at -2 weeks, then week 0, 2, 4 and 6. Adjuvant nivolumab will then be given for a total of 10 additional doses after the completion of radiotherapy every 4 weeks (+/- 7 days).

There are no premedications for nivolumab recommended.

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

4.3.2. Dose delay criteria apply for all drug-related AEs

Treatment delay up to 6 weeks for nivolumab from the last dose are allowable (any dose delays greater than these will require approval from the local principal investigator).

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

Nivolumab should be delayed for the following:

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

4.3.3. Nivolumab Dose Discontinuation Due to Drug-Related AE(s)

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

- Any Grade 2 drug-related uveitis or eye pain or blurred vision that does not respond to topical therapy and does not improve to Grade 1 severity within the re-treatment period OR requires systemic treatment
- Any Grade 3 drug-related bronchospasm, hypersensitivity reaction, or infusion reaction, regardless of duration
- Any Grade 3 non-skin, drug-related adverse event lasting > 7 days, with the following exceptions for uveitis, pneumonitis, bronchospasm, diarrhea, colitis, neurologic toxicity, hypersensitivity reaction, or infusion reaction of any duration requires discontinuation.
- Any Grade 3 neurologic toxicity including encephalitis required discontinuation of Nivolumab.
- Any Grade 3 drug-related endocrinopathies adequately controlled with only physiologic hormone replacement do not require discontinuation.

- Any Grade 3 drug-related laboratory abnormalities do not require treatment discontinuation except:
    - Grade 3 drug-related thrombocytopenia > 7 days or associated with bleeding requires discontinuation.
    - Any drug-related liver function test (LFT) abnormality that meets the following criteria require discontinuation
        - AST or ALT > 5 -10x ULN for > 2 weeks
        - AST or ALT > 10x ULN
        - Total bilirubin > 5 x ULN
        - Concurrent AST or ALT > 3 x ULN and total bilirubin > 2 x ULN
- Any Grade 4 drug-related adverse event or laboratory abnormality, except for the following events, which do not require discontinuation:
    - Grade 4 neutropenia ≤ 7 days
    - Grade 4 lymphopenia or leukopenia
    - Isolated Grade 4 amylase or lipase abnormalities that are not associated with symptoms or clinical manifestations of pancreatitis and decrease to < Grade 4 within 1 week of onset. The local principal investigator 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
- Any adverse event, laboratory abnormality, or intercurrent illness which, in the judgment of the Investigator, presents a substantial clinical risk to the subject with continued nivolumab dosing.

4.3.4. Criteria to Resume Nivolumab Dosing

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

- Subjects may resume treatment in the presence of Grade 2 fatigue.
- Subjects who have not experienced a Grade 3 drug-related skin AE may resume treatment in the presence of Grade 2 skin toxicity.
- Subjects with combined Grade 2 AST/ALT and total bilirubin values meeting discontinuation parameters should have treatment permanently discontinued.
- Drug-related pulmonary toxicity, diarrhea, or colitis must have resolved to baseline before treatment is resumed. Subjects with persistent Grade 1 pneumonitis after completion of a steroid taper over at least 1 month may be eligible for retreatment if discussed with and approved by the local principal investigator.
    - Subjects who received systemic corticosteroids for management of any drug-related toxicity must be off corticosteroids or have tapered down to an equivalent dose of prednisone ≤ 10 mg/day.
- Drug-related endocrinopathies adequately controlled with only physiologic hormone replacement may resume treatment.
- Dose delay of nivolumab which results in treatment interruption of > 6 weeks requires treatment discontinuation, with exceptions as noted above.

4.3.5. Nivolumab Infusion Reactions

Since nivolumab contains only human immunoglobulin protein sequences, is unlikely to be immunogenic and induce infusion or hypersensitivity reactions. However, if such a reaction were to occur, it might manifest with fever, chills, rigors, headache, rash, pruritus, arthralgias, hypo- or hypertension, bronchospasm, or other symptoms. All Grade 3 or 4 infusion reactions should be reported within 24 hours as an SAE if criteria are met. Infusion reactions should be graded according to National Institute of cancer (NCI) common terminology criteria for adverse event (CTCAE, Version 4.03) 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 325 to 1000 mg at least 30 minutes before additional nivolumab administrations.

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

- Stop the nivolumab infusion, begin an IV infusion of normal saline, and treat the subject with diphenhydramine 50 mg IV (or equivalent) and/or acetaminophen 325 to 1000 mg; remain at bedside and monitor subject until resolution of symptoms. Corticosteroid and/or bronchodilator therapy may also be administered as appropriate. If the infusion is interrupted, then restart the infusion at 50% of the original infusion rate when symptoms resolve; if no further complications ensue after 30 minutes, the rate may be increased to 100% of the original infusion rate. Monitor subject closely. If symptoms recur, then no further nivolumab will be administered at that visit. Administer diphenhydramine 50 mg IV, and remain at bedside and monitor the subject until resolution of symptoms. The amount of study drug infused must be recorded on the electronic case report form (eCRF).
- For future infusions, the following prophylactic premedications are recommended: diphenhydramine 50 mg (or equivalent) and/or acetaminophen 325-1000 mg should be administered >30 minutes before nivolumab infusion. If necessary, corticosteroids (up to 25 mg of SoluCortef or equivalent) may be used.

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

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

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

4.3.6. Duration of Nivolumab

Nivolumab will be given for a total of 15 doses (1 before RT, 4 during radiation therapy and 10 following completion of radiation), or until progressive disease, unacceptable toxicity, withdrawal of consent, or the study ends, whichever occurs first. For all subjects, global

deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time is allowed, if necessary.

4.3.7. Patient Reported Outcomes (PROs)

The FACT-HN and FACT-G (Appendix 2) Quality of Life (QOL) assessments will be performed at baseline, end of IMRT, and weeks 18, 30, 52, and 104. Patients who do not have QOL collected or refuse QOL completion will not be considered a protocol deviation. Paper or electronic questionnaires may be completed by the patient. A copy of the responses needs to be kept in the study subject's research binder.

4.3.8. Nivolumab Dose Levels

There will be no dose reductions allowed for nivolumab; delays will be allowed as detailed in the section describing nivolumab administration.

4.3.9. Nivolumab Packaging, Labelling, and Storage

Please refer to the Investigators Brochure for detailed information. Medication numbers will be unique to each bottle and will be used for tracking purposes only.

Supply

Nivolumab is supplied in a 100 mg/ 100 ml solution in a single use vial.

Storage Conditions

Nivolumab must be stored in accordance with the instructions on the label (Refer to investigator brochure. Supplies must be kept refrigerated (2 – 8 deg C). Do not freeze and protect from light).

Drug Accountability

Investigational supply of Nivolumab is obtained from Bristol Myers Squibb. Drug supplies, will be kept in a secure, limited access storage area under the storage conditions. Where necessary, a temperature log must be maintained to make certain that the drug supplies are stored at the correct temperature.

The responsible person must maintain records of the product's delivery to the study site, the inventory at the site and the use by each patient. The Principal Investigator (and participating site investigators) are responsible for all destructions/disposals of partially used and unused supplies. Supplies are not to be shipped back to BMS. BMS only needs to be notified of dtestructions/disposals of partially used samples. A copy of the drug destruction certificate must be maintained for provision to BMS at the end of the study.

These records will include dates, quantities, batch/serial numbers, expiry ("use by") dates, and the unique code numbers assigned to the investigational product(s) and study patients. The responsible person will maintain records that document adequately that the patients were provided the doses specified by the CSP and reconcile all investigational product(s) received from BMS. The responsible person must verify that all unused or partially used drug supplies have been returned by the clinical study patient.

4.4. MANAGEMENT OF SIDE EFFECTS FOLLOWING TREATMENT WITH NIVOLUMAB

4.4.1. Management of immunological toxicities following treatment with nivolumab

A proactive and early approach to management of immunological toxicities is crucial. The toxicities can be managed by a variety of treatment options to relieve symptoms and to reduce the risk of worsening symptoms.

4.4.2. Management of non-immunological toxicities following treatment with nivolumab

A proactive and early approach to management of immunological toxicities is crucial. The toxicities can be managed by a variety of treatment options to relieve symptoms and to reduce the risk of worsening symptoms.

4.4.4. Treatment Compliance

Records of study medication used, dosages administered and intervals between visits will be recorded by study personnel.

4.5. ENDPOINTS OF SAFETY

Safety of nivolumab will be evaluated as indicated by intensity and incidence of adverse events, graded according to US NCI CTCAE Version 4.03. Safety endpoints include:

- Events leading to dose holding
- Events leading to permanent treatment discontinuation
- The overall incidence and CTC criteria grade of adverse events, as well as relatedness of adverse events to treatment
- Causes of death

5. ADVERSE EVENTS DEFINITIONS AND REPORTING

5.1. ADVERSE EVENT DEFINITION

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.

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.)

5.2. SERIOUS ADVERSE EVENT DEFINITION

A **S*erious 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).

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)

5.3. INTENSITY OF ADVERSE EVENT

The intensity of adverse events should be classified and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.03 in the CRF.

5.4. CAUSAL RELATIONSHIP OF ADVERSE EVENT

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.

5.5. ADVERSE EVENT AND SERIOUS ADVERSE EVENT REPORTING

- All Serious Adverse Events (SAEs) that occur following the subject's written consent to participate in the study through 100 days of discontinuation of dosing must be reported to BMS Worldwide Safety, whether related or not related to study drug. If applicable, SAEs must be collected that relate to any later protocol-specified procedure (eg, a follow-up skin biopsy).
- Following the subject's written consent to participate in the study, all SAEs, whether related or not related to study drug, are collected, including those thought to be associated with protocol-specified procedures. The investigator should report any SAE occurring after these aforementioned time periods, which is believed to be related to study drug or protocol-specified procedure.
- An SAE report should be completed for any event where doubt exists regarding its seriousness;
- If the investigator believes that an SAE is not related to study drug, but is potentially related to the conditions of the study (such as withdrawal of previous therapy or a complication of a study procedure), the relationship should be specified in the narrative section of the SAE Report Form.
- If the BMS safety address is not included in the protocol document (eg, multicenter studies where events are reported centrally), the procedure for safety reporting must be reviewed/approved by the BMS Protocol Manager. Procedures for such reporting must be reviewed and approved by BMS prior to study activation.
- An appropriate SAE form (e.g. ex-US = CIOMS form or USA = Medwatch form) should be used to report SAEs to BMS . The BMS protocol ID number must be included on whatever form is submitted by the Sponsor/Investigator.
    - The CIOMS form is available at: http://www.cioms.ch/index.php/cioms-form-i
    - The MedWatch form is available at: https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048334.pdf
-
-
- 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). 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 a SUSAR Report and provided in the FastTrack portal system.
    - Other important findings which may be reported by BMS as an Expedited Safety Report (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, important safety recommendations from a study data monitoring committee, or Principal Investigator 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 investigator will submit the ESR to the appropriate IRB/IEC. The investigator and IRB/IEC will determine if the informed consent requires revision. The investigator should also comply with the IRB/IEC procedures for reporting any other safety information.
    - In addition to the Principal Investigator's responsibility to report events to their local HA, 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 either CIOMS or MedWatch form & pregnancies must be reported on a Pregnancy Surveillance Form or can be submitted on the aforementioned SAE form to BMS.

SAE Email Address: Worldwide.Safety@BMS.com

SAE Facsimile Number: +1 609-818-3804

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

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

All SAEs should be followed to resolution or stabilization.

The Sponsor will reconcile the clinical database SAE cases (case level only) transmitted to BMS Global Pharamacovigilance (WoldwideWorldwide.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.

5.6. OTHER REPORTING

Non-serious Adverse Event

- Non-serious Adverse Events (AE) are to be provided to BMS in aggregate via interim or final study reports as specified in the agreement or, if a regulatory requirement [eg, IND US trial] as part of an annual reporting requirement.
- Non-serious 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 ***non-serious adverse event*** is an AE not classified as serious.

Non-serious Adverse Event Collection and Reporting

The collection of non-serious AE information should begin at initiation of study drug. All non-serious 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.

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

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 to BMS 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).

Potential Drug Induced Liver Injury (DILI)

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.

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 either the CIOMS, MedWatch or appropriate 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 CIOMS, MedWatch or appropriate Pregnancy Surveillance Form. A BMS Pregnancy Surveillance Form may be provided upon request.

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 Principal Investigator 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.

For this reason, female participants in t he study will need to use appropriate methods of birth control on study through 5 months post discontinuation of nivolumab. For male participants that have female partners of child bearing potential, they will need to use appropriate methods of birth control on study thorugh 7 months post discontinuation of nivolumab.

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.

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 non-serious or serious AE, as appropriate, and reported accordingly.

6. BIOMARKER(S) AND CORRELATIVE STUDIES

Baseline PDL1 status will be required for analysis; collection of the diagnostic biopsy specimen upon recurrence or disease persistence will be required for enrollment; a new biopsy will not be mandated upon study entry; collection of diagnostic tissue biopsy at presentation will be required for additional correlative studies; P16 status will be required and performed at local institutions;

6.1. CORRELATIVE TISSUE RESEARCH

Tissue/Specimen Submission

Tumor tissue samples will be collected at pre-treatment and at the time of disease progression if clinically feasible. Tumor tissue collected at the time of pre-treatment may represent frozen samples if collected using a previously established repository or, most likely, formalin-fixed paraffin-embedded (FFPE) blocks. If the former, a section of the tissue will be submitted to the respective lab(s). For the latter, an FFPE tumor block will be submitted to the respective lab(s) (see below for more details). A biopsy at the time of progression is strongly encouraged but if not obtained, does not constitute a protocol violation. If a biopsy is obtained, extra cores may be obtained to allow for biomolecular evaluation. For cases treated at Emory University, tumor tissue samples will be submitted to Rafi Ahmed's laboratory and will be banked in the department of pathology at Emory University. For cases treated at the Cleveland Clinic, tumor tissue samples will be submitted to Mohamed Abazeed's laboratory and will be banked in his laboratory. The respective labs may exchange samples at will. Genomic profiling of tissue samples will be mainly conducted at the Cleveland Clinic. Note that all tissue obtained for correlative reseach is supernumerary to the needs of establishing a clinical diagnosis of recurrence.

<u>FFPE tumor samples (Mandatory)</u>

A FFPE tumor block should be submitted with the submission form. A Pathology Report and one H&E stained slide documenting that the submitted block or slides contain tumor should also be submitted with the tissue. The report and H&E stained slide must include the protocol

number and patient's case number. The patient's name and/or other identifying information should be removed from the report. The surgical pathology numbers and information must NOT be removed from the report.

The pre- and post-progression tumor biopsies can be obtained from the primary tumor or lymph node metastasis as a punch biopsy or a core needle biopsy: a punch or core in formalin and secondary 1-2 punches or cores in liquid nitrogen (or dry ice/ethanol slurry). The biopsy samples should be prepared as: 1) formalin-fixed paraffin-embedded tumor blocks and shipped to the designated laboratories in ambient temperature, and 2) flash frozen samples in liquid nitrogen (or dry ice/ethanol slurry) and shipped on dry ice. The frozen specimens can be stored at -80 degree C (-70 degree C to -90 degree C) until ready to ship. If a -80 degree C freezer is not available, samples can be stored short term in a -20 degree C freezer (non-frost-free refrigerator preferred) for up to 7 calendar days (please ship out Monday-Wednesday only).

6.2. CORRELATIVES WITH BLOOD

Blood samples must be submitted with the submission form documenting the date of collection of the sample. Blood samples will be obtained at baseline and prior to each nivolumab infusion during radiation therapy; subsequently blood will be obtained at weeks 18, 30 52, and 104 as outlined in study calendar above. Peripheral blood mononuclear cells (PBMCs) and plasma will be isolated from collected CPTs and cryopreserved as outlined in the blood processing Appendix 3.

Specimen collection summary for correlative studies (Samples can be batched and sent in one shipment)

Specimens for Correlative Studies			
Specimens taken from patient:	**Collected when:**	**Submitted as:**	**Shipped:**
A paraffin-embedded tissue of the primary tumor taken before initiation of treatment	Pre-treatment	Paraffin-embedded tissue block	Block shipped ambient
Fresh frozen tissue of the primary or metastatic tumor taken before initiation of treatment (for research purposes only: OPTIONAL)	Pre-treatment	Frozen tumor in a 2 mL cryovial	Tumor sent frozen on dry ice via overnight carrier
A paraffin-embedded tissue of the primary or metastatic tumor (for research purposes only: OPTIONAL)	At the time of disease progression	Paraffin-embedded tissue block	Block shipped ambient
Fresh frozen tissue of the primary or metastatic tumor (for research purposes only: OPTIONAL)	At the time of disease progression	Frozen tumor in a 2 mL cryovial	Tumor sent frozen on dry ice via overnight carrier
PBMCs and PLASMA: 4 CPTs (8 mL each) of whole blood for	Pre-treatment and prior to each Nivolumab infusion during radiation	Frozen plasma samples containing 2 mL per aliquot in 2 mL cryovials:	Plasma sent frozen on dry ice or liquid nitrogen via overnight carrier

collection of plasma and PBMCs	therapy ; subsequently at wk 18, 30, 52 and 104.	Cryopreserved PBMCs containing 10^7 PBMCs per aliquot in 2 mL cryovials	

Submit materials for translational research as following:

U. S. Postal Service Mailing Address:
Ahmed Lab
Department of Microbiology & Immunology
Emory University
1462 Clifton Road NE, Room 412
Atlanta, GA 30322

Or
Abazeed Laboratory
Cleveland Clinic Foundation
Department of Translational Hematology Oncology Research
2111 E 96th Street
Lerner Res Stockroom
NE6-258 Abazeed Lab
Cleveland, OH 44106

For Non-urgent, Non-frozen Specimens Only
Courier Address (FedEx, UPS):
Ahmed Lab
Department of Microbiology & Immunology
Emory University
1462 Clifton Road NE, Room 412
Atlanta, GA 30322

Or
Abazeed Laboratory
Cleveland Clinic Foundation
Department of Translational Hematology Oncology Research
2111 E 96th Street
Lerner Res Stockroom
NE6-258 Abazeed Lab
Cleveland, OH 44106

For Frozen Specimens and Urgent FFPE Samples
Ahmed Lab
Department of Microbiology & Immunology
Emory University
1462 Clifton Road NE, Room 412
Atlanta, GA 30322

Or
Abazeed Laboratory
Cleveland Clinic Foundation
Department of Translational Hematology Oncology Research
2111 E 96th Street
Lerner Res Stockroom
NE6-258 Abazeed Lab
Cleveland, OH 44106

6.3. PROPOSED BIOMARKER EVALUATIONS

A. Despite the unprecedented success of PD-1 targeted therapies a significant number of patients still fail to respond due to mainly unknown reasons. A deeper understanding of the mechanisms underlying responsiveness to blockade of the PD-1 pathway and the identification of predictive biomarkers are thus essential to optimize current treatments and to develop novel treatment approaches in order to improve response rates. Two recent studies analyzing the CD8 T cell response in the peripheral blood of non-small lung cancer and melanoma patients undergoing PD-1 targeted therapies observed an increase in activated and proliferating PD-1+ CD8 T cells in a subset of patients which in combination with tumor burden correlated with clinical outcome (37, 38). We will therefore monitor T cell activation and proliferation in the peripheral blood by multi-parameter flow cytometry of isolated PBMCs including but not limited to the following markers: CD3, CD4, CD8, CD45RA, CCR7, CD27, CD28, CD38, HLA-DR, Ki-67, PD-1. Activated CD38+ HLA-DR+ CD8 T cells at the peak of activation/proliferation will be isolated by flow cytometric sorting followed by DNA and RNA isolation. RNA will be used to transcriptionally profile CD8 T cells responding to therapy using RNAseq. Furthermore, we will use DNA isolated from activated CD8 T cells in the peripheral blood and from frozen tumor tissue to analyze and compare the T cell receptor repertoire of activated/proliferating CD8 T cells in the blood and tumor-infiltrating lymphocytes in the obtained biopsy. It has recently been shown that a particular subset of PD-1+ CD8 T cells expressing the transcription factor TCF-1 possesses stem cell-like feature and is responsible for the proliferative burst of antigen-specific CD8 T cells following PD-1 pathway in a mouse model of persistent viral infection (39). Two recent studies also demonstrated that costimulatory signaling through CD28 is required for CD8 T cell proliferation following PD-1 pathway blockade (40, 41). We hypothesize that increased numbers of CD28+ and/or TCF-1+ among PD-1+ CD8 T cells will be predictive of response to PD-1 pathway blockade. To test this hypothesis, we will characterize tumor-infiltrating lymphocytes by immunofluorescent staining of FFPE sections using antibodies directed against CD4, CD8, PD-1, CD28, TCF-1 as well as additional markers, and correlate with the observed CD8 T cell responses in the blood as well as with clinical outcome.

B. We expect that recurrent cancers will have a substantially higher alteration frequency and a distinct composition of genetic lesions compared to matched treatment naïve tumors. The extent of genetic alterations has been previously associated with response to checkpoint blockade. Therefore, we posit that the extent of non-synonymous mutational load will be predictive of the presence of neo-antigens and therefore predictive of response to nivolumab in patients with recurrent head and neck cancer. We will assess mutational and neoantigen load using whole exome sequencing. We will assess transcriptomic states using RNAseq. We will correlate clinical outcomes with the extent and composition of mutations and identify transcriptomic states (or gene signatures) that could predict improved clinical outcomes (see Appendix 4 for instructions on processing frozen tumor samples for DNA/RNA extraction).

C. Submit materials for translational research as following:

For FFPE tissue samples
Cancer Genetics (CGI)
CGI will provide shipping supplies to each site

7. INVESTIGATIONAL PLAN

7.1. VISIT SCHEDULE

Details of study procedures are in Study Calendar.

7.2 SCREENING PERIOD

Therapeutic Parameters

Pre-study scans used to assess all measurable or non-measurable sites of disease must be done within 30 days prior to registration.

Pre-study CBC (with differential and platelet count) should be done ≤ 30 days before registration. All required pre-study chemistries, should be done ≤ 30 days before registration.

7.3 END OF STUDY TREATMENT AND FOLLOW-UP PERIOD

Patients will be followed for 2 years from the initiation of treatment. The imaging studies will be performed at baseline and at week 18, 30, 52, and 104. Patients will continue to be followed thereafter by their treating physicians as per standard of care.

7.4 DURATION OF THERAPY

Patients will receive radiation in concurrence with nivolumab and post radiation maintenance nivolumab for 10 cycles unless:

- Radiation is interrupted for > 3 consecutive weeks, in which case they will be removed from the protocol.
- Extraordinary Medical Circumstances: If at any time the constraints of this protocol are detrimental to the patient's health, protocol treatment should be discontinued.
- Patient develops progressive disease; then the patient will discontinue protocol therapy.
- Patient develops unacceptable toxicity; then the patient will discontinue protocol therapy.
- Patients may withdraw consent and withdraw from the study at any time for any reason.

7.5 DURATION OF FOLLOW-UP

For this protocol, all patients, including those who discontinue protocol therapy early, will be followed for response until progression and for survival for 2 years from the start of radiation. All patients must also be followed through completion of all protocol therapy. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

8. STATISTICAL METHODS

Power Caclulation: From the MIRI study, the 1-year PFS rate for class I and II combined was 43.8% (95% CI: 38.6 - 49.7%) Assuming a one sided alpha of 0.05 and an 85% power to detect an improvement in 1-yr PFS from 40% to 55% we estimate 46 patients will need to be accrued in 2.5 years and followed for an additional 2 years (estimated maximum total of 51 patients). Accounting for a 20% drop out rate, 62 patients will need to be consented. The sample size calculation was based on assumptions of exponentially distributed death times and use of the exponential MLE test (42). Definition of clinical outcomes: PFS is defined as months from treatment started to evidenced progression or death and censored at last follow up without progression, and OS is defined as months from treatement started to death or censored at last follow up if alive.

Analysis plan: For primary objective, the 1-yr PFS and its 95% confidence interval will be estimated by Kaplan-Meier method for all patients, as well as in each stratum defined by p16 and RPA status, but this study is not powered at the level of subgroups. For the secondary objectives, Kaplan-Meier method will be used to assess 1-yr OS, PFS, or pattern of failure, and the incidence rate of acuate and late toxicities will be described as frequency and percentage. QOL will be summerized by mean and standard deviation. For exploratory objectives, the predictability of related biomarkers (baseline PDL1 status, T-cell activation biomarkers, CD28 and TCF1 positivity on T lymphocytes and other biomarkers) to clinical

outcomes (OS and PFS) will be explored using both univariate and multivariable Cox proportional hazards model controlling for potential confounders.

9. ADMINISTRATION, HANDLING OF DATA AND SAFETY MONITORING

9.1. PROTOCOL AMENDMENTS

Any changes to the protocol will be made in the form of an amendment and must be approved by the coordinating site IRB before implementation. Any modifications made to the protocol or informed consent document according to local requirements or any other reason may also require approval from sponsoring agencies.

9.2. INFORMED CONSENT

An investigator will explain to each subject the nature of the study, its purpose, procedures involved, expected duration, potential risks and benefits. Each subject will be informed that participation in the study is voluntary and that she may withdraw from the study at any time, and that withdrawal of consent will not affect her subsequent medical treatment. This informed consent will be given by means of a standard written statement and will be submitted for IRB approval prior to use. No patient will enter the study before her informed consent has been obtained. In accordance with the Health Information Portability and Accountability Act (HIPAA), the written informed consent document (or a separate document to be given in conjunction with the consent document) will include a subject authorization to release medical information to the Principal Investigator and supporting agencies and/or allow these bodies, a regulatory authority, or Institutional Review Board access to subjects' medical information that includes all hospital records relevant to the study, including subjects' medical history.

9.3. ETHICS AND GOOD CLINICAL PRACTICE

This study must be carried out in compliance with the protocol and Good Clinical Practice, as described in:

1. ICH Harmonized Tripartite Guidelines for Good Clinical Practice 1996.
2. US 21 Code of Federal Regulations dealing with clinical studies (including parts 50 and 56 concerning informed consent and IRB regulations).
3. Declaration of Helsinki, concerning medical research in humans (Recommendations Guiding Physicians in Biomedical Research Involving Human Subjects, Helsinki 1964, amended Tokyo 1975, Venice 1983, Hong Kong 1989, Somerset West 1996).

The investigator agrees to adhere to the instructions and procedures described in it and thereby to adhere to the principles of Good Clinical Practice that it conforms to.

9.4. REGULATORY AUTHORITIES

Institutional Review Board

Information regarding study conduct and progress will be reported to the Institutional Review Board (IRB) per the current institutional standards of each participating center.

9.5. DATA QUALITY ASSURANCE

9.5.1 Data Management

All information will be collected on study-specific case report forms by the study staff at each institution. The necessary forms will be provided to each site by the Coordinating Center.

The completed forms will be forwarded to the Coordinating Center for central review and inclusion in the study dataset with relevant source documentation as outlined in the case report forms. The data submission schedule is as follows:

At the time of registration:

- Registration Form
- Informed Consent Form (signed by the subject)
- Eligibility Checklist
- Source documents related to eligibility.

Within 2 weeks after registration:

- Baseline study case report forms
- Pertinent source documents

Within 2 weeks after 30 day follow-up:

- On study case report forms
- Pertinent source documents

All study data will be reviewed for completeness and accuracy by the Protocol Chair. The Principal Investigator (or his/her designee) at each respective institution is responsible for review, and ensuring the completeness and accuracy, of the data generated by his/her institution. The study data will also be periodically reviewed by the Emory Winship Cancer Institute Clinical Research Office.

9.5.2. Meetings and Conference Calls

Scheduled meetings and conference calls will take place as needed with the PI and co-investigators and study personnel involved at coordinating center and participating site. In addition, separate meetings will be scheduled and include the protocol principal investigator, study coordinator(s), data manager(s). During these meetings matters related to the following will be discussed: safety of protocol participants, validity and integrity of the data, enrollment rate relative to expectation, characteristics of participants, retention of participants, adherence to protocol (potential or real protocol violations), data completeness, and progress of data for objectives.

9.5.3. Monitoring and Auditing

The Emory Winship Cancer Institute (Winship) clinical trials office will serve as the coordinating center for the Emory patients. The coordinating center will review responses and toxicity and report these to the regularly scheduled meetings of the DSMC of the Emory Winship Cancer Institute. Each participating site is expected to have its own data monitoring and safety plan (DMSP) with regard to forwarding information to their IRBs. If the data reveals a change in the risk/benefit ratio, the investigator will notify the IRB and the PI.

The PI and co-investigators will review the data and forward any changes or protocol amendments to the IRBs. All serious adverse events will be reported immediately to the IRB. All study participant information will be kept in a confidential manner by the assigning of a random number to each study participant. All data will be kept confidential as per institutional guidelines and policies. Any breach of confidentiality is a serious matter and conflicts with institutional policies and will be reported to the IRB. A cumulative summary of all adverse events occurring on this study and a report of the data safety and monitoring plan will be submitted to the IRBs with the annual renewal reports.

The Data and Safety Monitoring Committee (DSMC) of the Winship Cancer Institute will provide oversight for the conduct of this study. The DSMC functions independently within Winship Cancer Institute to conduct internal monitoring functions to ensure that research being conducted by Winship Cancer Institute Investigators produces high-quality scientific data in a manner consistent with good clinical practice (GCP) and appropriate regulations that govern clinical research. Depending on the risk level of the protocol, the DSMC review may occur every 6 months or annually. For studies deemed High Risk, initial study monitoring will occur within 6 months from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. For studies deemed Moderate Risk, initial study monitoring will occur within 1 year from the date of the first subject accrued, with 2 of the first 5 subjects being reviewed. Subsequent monitoring will occur in routine intervals per the Winship Data and Safety Monitoring Plan (DSMP).

The DSMC will review pertinent aspects of the study to assess subject safety, compliance with the protocol, data collection, and risk-benefit ratio. Specifically, the Winship Cancer Institute Internal Monitors assigned to the DSMC may verify informed consent, eligibility, data entry, accuracy and availability of source documents, AEs/SAEs, and essential regulatory documents. Following the monitoring review, monitors will provide a preliminary report of monitoring findings to the PI and other pertinent individuals involved in the conduct of the study. The PI is required to address and respond to all the deficiencies noted in the preliminary report. Prior to the completion of the final summary report, monitors will discuss the preliminary report responses with the PI and other team members (when appropriate). A final monitoring summary report will then be prepared by the monitor. Final DSMC review will include the final monitoring summary report with corresponding PI response, submitted CAPA (when applicable), PI Summary statement, and available aggregate toxicity and safety data.

The DSMC will render a recommendation and rating based on the overall trial conduct. The PI is responsible for ensuring that instances of egregious data insufficiencies are reported to the IRB. Continuing Review submissions will include the DSMC recommendation letter. Should any revisions be made to the protocol-specific monitoring plan after initial DSMC approval, the PI will be responsible for notifying the DSMC of such changes. The Committee reserves the right to conduct additional audits if necessary.

The trial be monitored at each other site by having sites participate in the Emory working group meetings occurring every Thursday morning at 745 AM (EST); the sites will be providing information and updates on their enrolled patients to the Emory HNCA working group; this will be a weekly meeting;

The following applies for monitoring of Sub-sites:

At the time of study initiation at a non-Emory site, the Emory Principal Investigator, Winship regulatory specialist, and Winship research coordinators will perform a site initiation teleconference. During this teleconference, the Emory team will review the study, enrollment, reporting, and regulatory compliance. The participating site will have internal monitoring meetings. These meetings which will include the participating site investigator, the clinical research coordinator and the regulatory affairs coordinator, will meet at least on a monthly basis to review and discuss study data to ensure subject safety. The research coordinators will maintain a spread sheet which will be de-identified and will summarize all the patient data for subjects actively being treated on the trial as well as a roadmap detailing pending tests/treatments for each individual subject. The spread sheet will be shared with the Emory PI via e-mail monthly. Teleconferences will be conducted weekly between the PI at Emory and the research team at the participating site(s). The purpose of the meetings is to discuss the enrollment, regulatory updates, monitor toxicities, and evaluate the progress of the trial. A record of the teleconferences will be kept in the regulatory binder. Scheduled teleconferences may stop after all patients have completed assigned protocol therapy and the PI at Emory will

communicate with participating sites via email as needed. This communication will also be maintained in the regulatory binder. Chart reviews will be performed on selected cases by the participating site staff to confirm that the data collection is accurate.

Winship's MSC will perform an on-site or remote monitoring visit within the first three months of enrollment of the first subject. Quarterly monitoring visits will occur (annually once onsite and three times remotely) until subject follow-up is terminated. Monthly reviews of data in OnCore will be conducted to ensure compliance or identify discrepancies.

10. COORDINATING CENTER & SITE RESPONSIBILITIES

10.1. PROTOCOL CHAIR

The Protocol Chair is responsible for performing the following tasks:

- Coordinating, developing, submitting, and obtaining approval for the protocol as well as its subsequent amendments.
- Assuring that all participating institutions are using the correct version of the protocol.
- Taking responsibility for the overall conduct of the study at all participating institutions and for monitoring the progress of the study.
- Reviewing and ensuring reporting of Serious Adverse Events (SAE).
- Reviewing data from all sites.

10.2. COORDINATING CENTER

The Coordinating Center is responsible for performing the following tasks:

- Ensuring that IRB approval has been obtained at each participating site prior to the first patient registration at that site, and maintaining copies of IRB approvals from each site.
- Managing central patient registration.
- Collecting and compiling data from each site.
- Establishing procedures for documentation, reporting, and submitting of AE's and SAE's to the Protocol Chair, and all applicable parties.
- Facilitating audits by securing selected source documents and research records from participating sites for audit, or by auditing at participating sites.

10.3. PARTICIPATING SITES

Participating sites are responsible for performing the following tasks:

- Following the protocol as written, and the guidelines of Good Clinical Practice (GCP).
- Submitting data to the Coordinating Center.
- Registering all patients with the Coordinating Center by submitting patient registration form, and signed informed consent promptly.
- Providing sufficient experienced clinical and administrative staff and adequate facilities and equipment to conduct a collaborative trial according to the protocol.
- Maintaining regulatory binders on site and providing copies of all required documents to the Coordinating Center.
- Collecting and submitting data according to the schedule specified by the protocol.

Additional information for participating sites:

10.3.1 Staffing

The participating sites will provide experienced staff, and adequate equipment and facilities to support this clinical trial. The participating sites will also be responsible for research staff training, human subjects research, and HIPAA compliance, as well as the continuing education in these areas as required by local institutional standards.

10.3.2. Documentation

Each participating site is responsible for submitting copies of all relevant regulatory documentation to the Coordinating Center. The required documents include, but are not limited to the following: local IRB approvals (i.e., protocol, consent form, amendments, patient brochures and recruitment material, etc.), IRB membership rosters, summary of unanticipated problems or protocol deviations, and documentation of expertise of the investigators. The Coordinating Center will provide each participating site with a comprehensive list of the necessary documents. It is the responsibility of the participating sites to maintain copies of all documentation submitted to the Coordinating Center.

The requirements for data management, submissions, and monitoring are outlined below.

10.3.3. Confidentiality

All unpublished information that the Coordinating Center gives to the investigator shall be kept confidential and shall not be published or disclosed to a third party without the prior written consent of the Protocol Chair (or her designee).

10.3.4. Record Retention

Following closure of the study, each participating center will maintain a copy of all site study records in a safe and secure location. The Coordinating Center will inform the investigator at each site at such time that the records may be destroyed. This will also follow each institution guidelines.

10.3.5. Publication

It is understood that any manuscript or releases resulting from the collaborative research will be circulated to all participating sites prior to submission for publication or presentation. The Protocol Chair will be the final arbiter of the manuscript content.

10.3.6. Additional Information

Each participating site is responsible for submitting additional information as requested by the Protocol Chair (or her designee).

10.4. RECORDS

Case Report Forms (CRFs) for individual patients will be provided by the Principal Investigator.

10.4.1. Source Documents

Source documents provide evidence for the existence of the patient and substantiate the integrity of the data collected. Source documents are filed at the investigator's site.

Data entered in the CRFs that are transcribed from source documents must be consistent with the source documents or the discrepancies must be explained. The investigator may need to request previous medical records or transfer records, depending on the study; also current medical records must be available.

For CRFs all data must be derived from source documents.

10.4.2. Direct Access to Source Data and Documents

The investigator/institution will permit study-related monitoring, audits, IRB review and regulatory inspection, providing direct access to all related source data/documents. CRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the clinical study monitor, auditor and inspection by health authorities (e.g. FDA). The Clinical Research Associate (CRA) / on site monitor and auditor may review all CRFs, and written informed consents.

10.5. STATEMENT OF CONFIDENTIALITY

Individual patient medical information obtained as a result of this study is considered confidential and disclosure to third parties is prohibited with the exceptions noted below.

Patient confidentiality will be ensured by using patient identification code numbers.

Treatment data may be given to the patient's personal physician or to other appropriate medical personnel responsible for the patient's welfare. Data generated as a result of the study need to be available for inspection on request by the participating physicians or the Grantor's representatives, by the IRB and the regulatory authorities.

10.6. COMPLETION OF STUDY

The IRB/competent authority needs to be notified about the end of the trial (last patient/patient out, unless specified differently in the CSP) or early termination of the trial.

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12. APPENDICES

APPENDIX 1 - PERFORMANCE SCALES

ECOG Performance Status Scale		Karnofsky Performance Scale	
Grade	Descriptions	Percent	Description
0	Normal activity. Fully active, able to carry on all pre-disease performance without restriction.	100	Normal, no complaints, no evidence of disease
		90	Able to carry on normal activity; minor signs or symptoms of disease.
1	Symptoms, but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (e.g., light housework, office work).	80	Normal activity with effort; some signs or symptoms of disease.
		70	Cares for self, unable to carry on normal activity or to do active work
2	In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours.	60	Requires occasional assistance, but is able to care for most of his/her needs.
		50	Requires considerable assistance and frequent medical care
3	In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours	40	Disabled, requires special care and assistance.
		30	Severely disabled, hospitalization indicated. Death not imminent
4	100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair	20	Very sick, hospitalization indicated. Death not imminent.
		10	Moribund, fatal processes progressing rapidly
5	Dead	0	Dead

APPENDIX 2: FACT-G AND FACT-HN QUESTIONNAIRES

FACT-G (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-G (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I feel sad	0	1	2	3	4
GP2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GP3	I am losing hope in the fight against my illness	0	1	2	3	4
GP4	I feel nervous	0	1	2	3	4
GP5	I worry about dying	0	1	2	3	4
GP6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-H&N (Version 4)

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GS1	I feel sad	0	1	2	3	4
GS2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GS3	I am losing hope in the fight against my illness	0	1	2	3	4
GS4	I feel nervous	0	1	2	3	4
GS5	I worry about dying	0	1	2	3	4
GS6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

FACT-H&N (Version 4)

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
HANN1	I am able to eat the foods that I like	0	1	2	3	4
HANN2	My mouth is dry	0	1	2	3	4
HANN3	I have trouble breathing	0	1	2	3	4
HANN4	My voice has its usual quality and strength	0	1	2	3	4
HANN5	I am able to eat as much food as I want	0	1	2	3	4
HANN6	I am unhappy with how my face and neck look	0	1	2	3	4
HANN7	I can swallow naturally and easily	0	1	2	3	4
HANN8	I smoke cigarettes or other tobacco products	0	1	2	3	4
HANN9	I drink alcohol (e.g. beer, wine, etc.)	0	1	2	3	4
HAN 10	I am able to communicate with others	0	1	2	3	4
HAN 11	I can eat solid foods	0	1	2	3	4
HAN 12	I have pain in my mouth, throat or neck	0	1	2	3	4

APPENDIX 3 - PROTOCOL FOR PROCESSING PBMC FROM CPT SODIUM CITRATE

1. CPT tubes should be at stored at Room Temperature. Following blood collection, CPT tubes should be inverted approximately 10 times.
2. CPT tubes must be kept at Room Temperature following blood collection. CPT tubes should be processed within 2-3 hours of blood draw. Leave rocking until processing.
3. Spin CPT tubes at 2820rpm (1600g), 25minutes, 22°C (acceleration: 9, brake:3). Be careful on the position of the tubes (tubes are tall and need to be centered).
4. Carefully remove top layer (plasma) without disturbing the PBMC layer. Save 2 ml of plasma and freeze in a 2 mL cryovial. Store at -20ºC.
5. Collect PBMCs without touching the separation gel and transfer cells to collection tube (15mL falcon tube if 1 or 2 CPTs, 50 mL falcon tube if more CPTs are processed).
6. Rinse each CPT tube with 3 mL PBS+2% FBS (P2) once. Carefully pipette up and down to re-suspend cells sitting directly on the separation gel. Transfer to collection tube.
7. Add P-2 to cells in collection tube to bring volume up to maximum.
8. Centrifuge at 1200 rpm for 10 minutes.
9. Decant and re-suspend pellet; add 5mL of sterile ACK Lysing Buffer, let stand for 3-5 minutes
10. Add P-2 to bring volume up to maximum to stop lysis.
11. Centrifuge at 1500 rpm for 8 minutes.
12. Decant and re-suspend pellet in full tube volume of P2
13. Centrifuge at 1500 rpm for 8 minutes
14. Decant and re-suspend pellet in P2 (as a rough guideline: 1ml P2 per processed CPT tube)
    aliquot 10 uL cell mixture into 90 uL of trypan blue for counting
15. Fill tube volume with P2, spin at 1500 rpm for 8 min.
16. Decant and re-suspend pellet in FBS at a concentration of $2x10^7$/mL, pipette up and down.
17. Add equal volume of FBS+20%DMSO drop by drop while swirling tube containing PBMCs.
    (Final concentration is $10x10^6$ cells/ml, 5-10 M cells/vial, when possible freeze more than 1 vial)
18. Divide into sterile cryovials (labeled with special sticker and also labeled in the top).
19. Transfer vials into room temperature temp cryovial freezing chamber (Mr. Frosty) and place in -80°C. Remember to mark how many times the freezing chamber was used! If used 5 times, you need to exchange the Isopropanol.
20. Transfer frozen aliquots to liquid nitrogen the following day

APPENDIX 4 - PROTOCOL FOR PROCESSING FROZEN TISSUE/BIOPSIES FOR DNA/RNA EXTRACTION

1. The frozen sample is thawed on ice. The tissue is placed in a suitably sized vessel and the appropriate volume of Buffer RLT is added.
2. A hand-held homogenizer is used to disrupt the tissue sample. Core and FNA biopsy sample are vigorously triturated with an appropriately sized pipette tip.
3. Pipet the lysate directly into a QIAshredder spin column placed in a 2 ml collection tube, and centrifuge for 2 min at full speed.
4. Centrifuge the lysate for 3 min at full speed. Carefully remove the supernatant by pipetting, and transfer it to an AllPrep DNA spin column placed in a 2 ml collection tube. Close the lid gently, and centrifuge for 30 s at >8000 x *g*.
5. Place the AllPrep DNA spin column in a new 2 ml collection tube and store at room temperature or at 4° C for later DNA purification per the AllPrep DNA purification instructions.
6. Use the flow-through for RNA purification per the AllPrep RNA purification instructions.

APPENDIX 5- RECURSIVE PARTITIONING ANALYSIS FOR OVERALL SURVIVAL IN PATIENTS TREATED WITH REIRRADIATION IN A MULTIINSTITUTIONAL ANALYSIS (WARD, ET AL. IJROBP 2017)

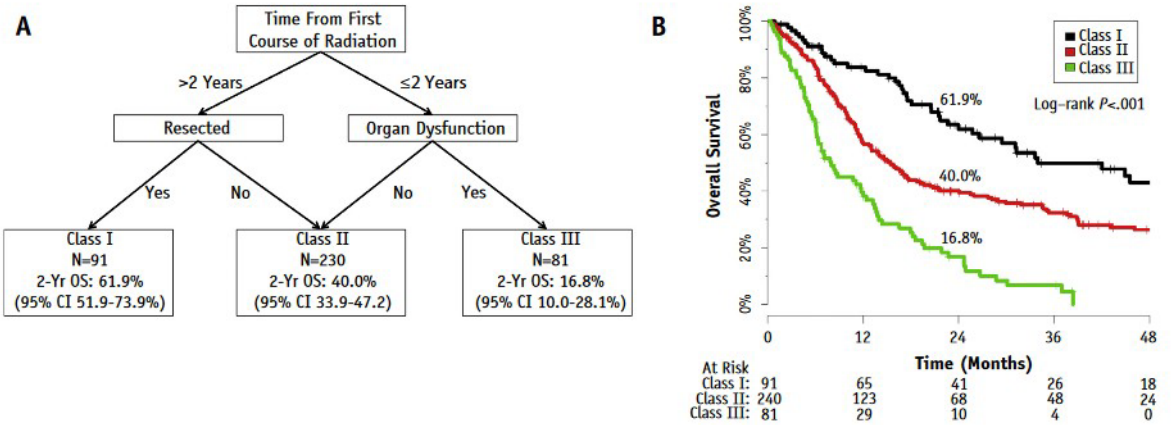

Fig. 3. (A) Recursive partitioning analysis (RPA) for overall survival. *Abbreviations:* OS = overall survival; CI = confidence interval. Organ dysfunction defined as pretreatment dependence on a feeding tube or tracheostomy. (B) Kaplan-Meier curves for overall survival separated by RPA class.

NOTE: RPA class III patients are defined as those expected to begin reirradiation within 2 years of first course of radiation therapy AND are PEG dependent or have a tracheostomy (patients who have undergone total laryngectomy and have a stoma are not included in this category of organ dysfunction)