**RTOG Foundation Collaboration with Merck**

**RTOG 3507**

**A Limited Participation Study**

# KEYSTROKE: A RANDOMIZED PHASE II STUDY OF PEMBROLIZUMAB (KEYTRUDA®) PLUS STEREOTACTIC RE-IRRADIATION VERSUS SBRT ALONE FOR LOCOREGIONALLY RECURRENT OR SECOND PRIMARY HEAD AND NECK CARCINOMA

Protocol Version Date: March 11, 2019

Sponsor: RTOG Foundation

| | |
|---|---|
| **Principal Investigator**/ Medical Oncology | Stuart J. Wong, MD |
| Study Co-Chairs | |
| Radiation Oncology | Shlomo A. Koyfman, MD |
| Radiation Oncology | Quynh-Thu Le, MD |
| Surgical Oncology | John A. Ridge, MD, PhD |
| Translational Science | Christine H. Chung, MD |
| Medical Physics | Si Young Jang, PhD |
| Medical Physics | M. Saiful Huq, PhD, FAAPM, FInstP |
| Pathology | Richard Jordan, DDS, PhD |
| Senior Statistician | Pedro Torres-Saavedra, PhD |

Protocol Acceptance
On behalf of the RTOG Foundation, Inc.

March 11, 2019

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

Date

**RTOG 3507**
***(ClinicalTrials.gov NCT #03546582)***

**A Limited Participation Study**

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**Study Team** (11-MAR-2019)


**Principal Investigator/Medical Oncology**
Stuart J. Wong, MD
Medical College of Wisconsin
9200 W. Wisconsin Ave
Milwaukee, WI 53226
414-805-4621/FAX 414-805-4606
swong@mcw.edu

**Translational Science Co-Chair**
Christine H. Chung, MD
Moffitt Cancer Center
12902 Magnolia Dr.
Tampa, FL 33612
813-745-5431/FAX 813-745-7229
christine.chung@moffitt.org

**Radiation Oncology Co-Chair**
Shlomo A. Koyfman, MD
Cleveland Clinic
9500 Euclid Ave - Desk T28
Cleveland, OH 44195
216-444-7552 / FAX 216-445-1068
KOYFMAS@ccf.org

**Medical Physics Co-Chair**
Si Young Jang, PhD
University of Pittsburgh Medical Center
5230 Centre Avenue
Pittsburgh PA 15232
412-623-0345/FAX 412-623-1475
jangs@upmc.edu

**Radiation Oncology Co-Chair**
Quynh-Thu Le, MD
Stanford University
875 Blake Wilbur Drive, MC 5847
Stanford, CA 94305
650-498-5032/FAX 650-725-8231
qle@stanford.edu

**Medical Physics Co-Chair**
M. Saiful Huq, PhD, FAAPM, FInstP
University of Pittsburgh Cancer Institute and UPMC Cancer Center
UPMC Cancer Pavilion
Fifth Floor, Suite 542
5150 Centre Avenue
Pittsburgh, PA 15232
412-647-1813/FAX 412-647-1161
huqs@upmc.edu

**Surgical Oncology Co-Chair**
John A. Ridge, MD, PhD
Fox Chase Cancer Center
333 Cottman Avenue
Philadelphia, PA 19111
215-728-3517/FAX 215-214-4222
drew.ridge@fccc.edu


**Continued on next page**

**RTOG FOUNDATION STUDY 3507**

**KEYSTROKE: A RANDOMIZED PHASE II STUDY OF PEMBROLIZUMAB (KEYTRUDA®) PLUS STEREOTACTIC RE-IRRADIATION VERSUS SBRT ALONE FOR LOCOREGIONALLY RECURRENT OR SECOND PRIMARY HEAD AND NECK CARCINOMA**

**Study Team (continued from previous page)**


**Pathology Co-Chair**
Richard Jordan, DDS, PhD
Biospecimen Bank at UCSF
2340 Sutter Street, Rm S341
San Francisco, CA 94115
415-476-7864/FAX 415-476-5271
Richard.Jordan@ucsf.edu

**Senior Statistician**
Pedro Torres-Saavedra, PhD
RTOG Foundation
1818 Market Street, Suite 1720
Philadelphia, PA 19103
215-717-0851/FAX 215-928-0153
ptorres@acr.org


| RTOG Foundation Headquarters Contact Information | |
|---|---|
| **Data Managers**: For questions concerning eligibility or data submission | Vanita Patel, 215-574-3170, vpatel@acr.org<br>Janelle Robinson, 215-717-0837, jrobinson@acr.org |
| **RTQA**: For questions concerning RT data submission | Nancy Linnemann, 215-717-0853, nlinnemann@acr.org<br>Marsha Radden, 215-717-2757, mradden@acr.org |
| **RTQA**: For questions concerning data submission to TRIAD | Triad-Support@acr.org |
| **Serious Adverse Event Coordinator** For questions concerning serious adverse event reporting procedures, timelines, and queries | Sara McCartney, 267-940-9404, smccartney@acr.org |
| **Protocol Administrator**: For questions concerning protocol versions & amendments | Kathryn Okrent, 215-717-0856, kokrent@acr.org |
| **Project Manager**: For questions concerning regulatory documentation, investigational drug supply and/or shipment issues. | Treena Davis-Trotman, 215-574-3205, ttrotman@acr.org |
| **Membership**: For questions concerning contracts and reimbursement | RTOG-Membership@acr.org |

**Protocol Agent**

| Agent | Supply | IND # | IND Sponsor |
|---|---|---|---|
| Pembrolizumab (MK-3475) | Merck, clinical supply | 135196 | RTOG Foundation, Inc. |

**RTOG FOUNDATION STUDY 3507**

# KEYSTROKE: A RANDOMIZED PHASE II STUDY OF PEMBROLIZUMAB (KEYTRUDA®) PLUS STEREOTACTIC RE-IRRADIATION VERSUS SBRT ALONE FOR LOCOREGIONALLY RECURRENT OR SECOND PRIMARY HEAD AND NECK CARCINOMA

**Document History**

| | **Version Date** |
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| Amendment 2 | **March 11, 2019** |
| Amendment 1 | April 11, 2018 |
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**A RANDOMIZED PHASE II STUDY OF RE-IRRADIATION OF SBRT PLUS ANTI-PD-1 ANTIBODY PEMBROLIZUMAB (KEYTRUDA®) VERSUS SBRT ALONE FOR LOCOREGIONALLY RECURRENT OR SECOND PRIMARY HEAD AND NECK CARCINOMA**

**RTOG 3507**

**SCHEMA**

**SAFETY RUN-IN COMPONENT**

**REGISTER**

**Re-Irradiation**: SBRT, 8 Gy x 5 fractions over 2 weeks, for a total dose of 40 Gy

**Systemic Therapy**: Pembrolizumab, 200 mg IV, q3 weeks for up to 2 years

**Note**: Accrual will be suspended after 8 patients have been accrued to safety run-in component. The study will remain closed until a safety analysis on the first 6 analyzable patients is performed. See Section 14.3.2 for further details.

**RANDOMIZED PHASE II COMPONENT**

| **STRATIFY** | **RANDOMIZE** |
|---|---|
| Oropharyngeal with p16 positive, oropharyngeal with p16 negative, vs. non-oropharyngeal* | **Arm 1**: Re-Irradiation: SBRT, 8 Gy x 5 fractions over 2 weeks, for a total dose of 40 Gy + Pembrolizumab**, 200 mg IV, q3 weeks for up to 2 years<br>**Arm 2:** Re-Irradiation: SBRT, 8 Gy x 5 fractions over 2 weeks, for a total dose of 40 Gy |

*See Appendix III for the allocation table
**Starting 14 days prior to initiation of radiation therapy

## 1. OBJECTIVES

### 1.1 Primary Objective for Run-In Component

To evaluate the safety of the addition of pembrolizumab (anti PD-1 immunotherapy) to re-irradiation with SBRT for patients with recurrent or new second primary head and neck squamous cell carcinoma

### 1.2 Primary Objective for Phase II Trial

To compare progression-free survival (PFS) for patients with recurrent or new second primary head and neck squamous cell carcinoma with SBRT re-irradiation with or without pembrolizumab

### 1.3 Secondary Objectives for Phase II Trial (11-MAR-2019)

- To compare overall survival (OS) for patients with recurrent or new second primary head and neck squamous cell carcinoma with SBRT re-irradiation with or without pembrolizumab;
- To compare safety and toxicity in patients treated with SBRT re-irradiation with or without pembrolizumab;
- To determine the radiographic response rate, PFS and OS in patients who receive cross-over treatment to pembrolizumab following disease progression on SBRT alone;
- Correlative: Tumor biopsy specimens will be used to examine:
  1) the presence of high density of tumor infiltrating immune cells defined by the multiplex immunohistochemical staining;
  2) the presence of "T cell-inflamed phenotype" defined by the 12-gene cytokine signature;
  3) the presence of a genetic alteration profile that associates with PD-1 inhibitor sensitivity.

  These correlative study data will be associated with clinical outcome measures.

## 2. BACKGROUND

### 2.1 Rationale for Selected Approach and Trial Design (11-MAR-2019)

Over 40,000 new cases of HNSCC are diagnosed each year in the U.S. with the majority of cases requiring combinations of treatment modalities, including radiation. Unfortunately for patients who experience recurrence after definitive therapy, curative treatment options are limited. While surgical rescue is optimal, it is not feasible for many patients due to the location or extent of disease. The prognosis for these patients is very poor. Systemic chemotherapy is a treatment option for many patients but is considered palliative as it is associated with very low rates of long-term survivorship. A repeat course of radiation is a treatment option for some patients depending upon many factors including the extent of overlap with the previous radiation field. Relative to chemotherapy alone however, a repeat course of radiation has demonstrated improved disease control and long-term survival (Langer 2007).

RTOG pioneered the study of many new radiation therapy technologies over its 40-year history including re-irradiation for recurrent HNSCC. The results of RTOG 99-11 (Langer 2007) demonstrated a step-wise improvement over the predecessor trial, RTOG

96-10 (Spencer 2008). While both studies firmly established a potentially curative outcome for a subgroup of patients with recurrent HNSCC, they also highlight the need for more effective treatment approaches incorporating new radiation techniques and effective systemic therapy. Combining SBRT with an active systemic agent carries the potential benefit of not only enhancing the effects of radiation but possibly inducing out-of-field anti-cancer effects.

Stereotactic Body Radiation Therapy (SBRT) may have advantages over conventional radiation therapy for retreatment of the head and neck by virtue of achieving high doses to target volumes given over a shorter period. Studies have demonstrated the safety and potential efficacy of SBRT in this setting (Heron 2011, Unger 2010, Lartigau 2013). The abbreviated course of SBRT allows the patients to continue with their routine functions during the course of radiotherapy, which is desirable to both the patients and their families.

As a single modality, radiation therapy is curative for early stage HNSCC. However, a recognized limitation of radiation is triggered by alteration of the inflammatory tumor microenvironment — a phenomenon that is a consequence of stimulation of inhibitory immune cells such as Tregs, alternatively activated macrophages, and myeloid-derived suppression cells that in turn suppress T cell activation and encourage tumor growth. The PD-L1/PD-1 axis is believed to play an important role as an inhibitor of immune activation. Studies have demonstrated PD-L1 expression in a wide variety of solid tumors, suggesting that the PD-1 pathway is the prevailing mechanism for permitting cancer cells to escape host immune response (Zou 2008). This assumption is supported by early phase clinical trials demonstrating potent activity of PD-1 inhibitors, including a recently reported study of pembrolizumab in recurrent metastatic HNSCC (Seiwert 2014). A logical inference from these observations is that radiation induces an inflammatory response in the tumor microenvironment; however, it is possible that a PD-L1/PD-1 inhibitor can restore anti-tumor immunity. Deng and colleagues demonstrated in a pre-clinical model that PD-L1 was upregulated in the tumor microenvironment following radiation and that anti-PD-L1 enhanced the efficacy of radiation through a cytotoxic T cell-dependent mechanism (Deng 2014). Moreover, synergism between radiation and immune checkpoint targeting appears to be more pronounced when multiple large radiation fractions are used (Dewan 2009); hence, the rationale for SBRT. This phenomenon has not been examined in humans; demonstration of this proof of concept in a clinical trial will be a critical component in understanding the therapeutic utility of PD-L1/PD-1 inhibition. Closely associated with these questions is whether the sequence of radiation relative to PD-L1/PD-1 inhibition influences optimal anti-tumor activity. To date no clinical trials have examined the effects of pembrolizumab in conjunction with radiation therapy for HNSCC. However, the recently reported results of a phase I trial of pembrolizumab as a single modality/agent in patients with metastatic and recurrent HNSCC provide evidence as to the activity of this agent (Seiwert 2014). Stemming from these favorable early phase results, a large Merck-sponsored phase III trial comparing pembrolizumab with conventional systemic therapy will be opening soon.

We propose a randomized phase II study to test the hypothesis that PD-1 inhibition

enhances effects of radiation in HNSCC. In addition, we will examine exploratory endpoints as to whether the detrimental tumor micro-environmental effects of radiation may be overcome by PD-1 inhibition. Proposed studies will provide valuable insight regarding the correlation between characteristics of HNSCC tumor micro-environment and tumor response given the PD1 inhibitor. We hypothesize that the presence of high density of tumor infiltrating immune cells detected by multiplex immunohistochemistry (mIHC) using anti-CD3, -CD4, -CD8, -CD68, -PD-1 and –PD-L1 antibodies will predict response given IR and PD-1 inhibitor.

In addition, it will be particularly interesting to evaluate the effect of pembrolizumab in HPV-positive patients with HNSCC and the potential extension of the findings to other virus-induced cancer. HPV-positive HNSCC arises from deep crypts in lymphoid tissue of tonsil and tongue base and has characteristic tumor infiltrating lymphocytes in the stroma and tumor nests (Westra 2009). Expression of PD-L1 is noted within deep tonsillar crypts as well as in 70% of HPV-positive HNSCC (Lyford-Pike 2013) While PD-L1 expression is suggested to correlate with the likelihood of response in early clinical studies with anti-PD1 and anti-PD-L1 antibodies (Brahmer 2012, Topalian 2012 the response rate of HPV-positive HNSCC to pembrolizumab is approximately 20% which seems lower than HPV-negative HNSCC with response rate of 27% (Chow, ECCO 2015). Therefore, further evaluation of PD-L1 expression and other mechanism of resistance in the tumors is important. Furthermore, Saloura and colleagues presented at ASCO that tumors with "T cell-inflamed phenotype" —defined by the 12-gene cytokine expression profile—comprise about 1/3 of HNSCC and are associated with enrichment of CD8+ cells and tumor PD-L1 expression (Saloura 2014). We will further evaluate this signature using qRT-PCR and correlate with outcomes. In addition, based on the recent data in pembrolizumab sensitivity in NSCLC tumors with a high mutation burden and mutations in DNA repair pathway (Rizvi, N, Science, 2015), whole exome sequencing using a Next Generation Sequencing platform also will be performed.

This study exploits the expertise gained by the RTOG. The group has developed standardized methods for radiation therapy planning and delivery as well as high quality data collection that is obligatory for reliable outcome analysis and safety assessment. RTOG has pioneered methods for credentialing institutions for radiation delivery using advanced technologies. These capabilities, transferred to NRG Oncology and the RTOG Foundation, are critical for safety and efficient conduct of a trial such as that proposed here.

The results of this trial are critically important as proof of biologic principle for the effect of radiation on the tumor micro-environment, specifically, whether PD-1 inhibition offsets negative effects of radiation upon the tumor micro-environment. The findings of this trial may have significant bearing upon the design of future trials for combining radiation with PD-1/PD-L1 inhibitors.

The trial has the potential for producing practice changing results. RTOG opened a phase III trial (RTOG 0421) of re-irradiation and chemotherapy versus chemotherapy alone, building upon the positive results of RTOG 99-11. RTOG 0421, as well as a

contemporary GETTEC/GORTEC phase III trial did not complete accrual, due to an a priori physician bias toward re-irradiation. Since RTOG 0421, it has seemed unlikely that this question could be resolved. However, a positive result from the study proposed here could provide a scientific basis for a future definitive trial comparing SBRT + PD-1 inhibitor versus PD-1 inhibitor alone for recurrent/metastatic HNSCC. It is conceivable that pembrolizumab may have significant clinical effects that overshadow and are not enhanced by radiation therapy. Findings that strongly support this conclusion would be useful in allowing us to pursue directions, other than radiation therapy, for enhancing the immunologic effects of anti- PD-1 therapy.

## 2.2 Biomarker Studies (11-MAR-2019)

### 2.2.1 High Density of Tumor Infiltrating Immune Cells in HNSCC Tumor Microenvironment and Its Association With PD-1 Inhibitor Response

The assertion that the PD-1 pathway is the prevailing mechanism for permitting cancer cells to escape host immune response is supported by studies that have demonstrated PD-L1 expression in a wide variety of solid tumors (Zou 2008). This assertion also is supported by a growing number of reported clinical trials demonstrating unequivocal anti-tumor activity of PD-1/PD-L1 inhibition. We speculate that higher baseline cytotoxic Th1 T-cell markers are associated with favorable response to anti-PD1 therapy. To test these hypotheses we will examine tumor biopsy specimens obtained at baseline for PD-L1 expression by multiplex immunohistochemical staining (mIHC). We hypothesize that high expression of PD1/PD-L1 and high density of tumor infiltrating immune cells in the microenvironment detected by mIHC using anti-CD3, -CD4, -CD8, -CD68, -PD-1 and –PD-L1 antibodies will predict response given IR and PD-1 inhibitor. To test this hypothesis, we will examine tumor biopsy specimens obtained before starting the radiation.

### 2.2.2 12-Gene Cytokine Expression Profile and Its Association With PD-1 Inhibitor Response

Tumors with "T cell-inflamed phenotype" defined by the 12-gene cytokine expression profile comprise about 1/3 of HNSCC and are associated with enrichment of CD8+ cells and tumor PD-L1 expression (Saloura 2014). We hypothesize that the presence of the 12-gene cytokine expression profile in tumors will associate with the response to anti-PD1 therapy. To test this hypothesis, we will isolate RNA from paraffin-embedded tumors and perform qRT-PCR to detect the relative expression levels of CCL2, CLL3, CLL4, CCL5, CCL8, CCL18, CCL19, CCL21, CXCL9, CXCL10, CXCL11 and CXCL13 across the tumors obtained at pre-radiation.

### 2.2.3 Assessment of Mutational Landscape in HNSCC

In advanced NSCLC, the response rate of anti-PD1/PDL1 monotherapy ranges 17-21% which is similar in HNSCC. When the mutational landscape of the tumors were evaluated by whole exome sequencing, molecular smoking signature, higher neoantigen burden, and DNA repair pathway mutations were associated with clinical benefits (Rizvi, NA, Hellmann, MD, et al Science, 2015). Because HNSCC patients share similar risk factors with NSCLC, we hypothesize the similar mutational landscape found in NSCLC will also be present in HNSCC and will associate with clinical benefits.

## 3. PATIENT SELECTION, ELIGIBILITY, AND INELIGIBILITY CRITERIA

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

### 3.1 Patient Selection Guidelines

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

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

**3.1.2** Women of childbearing potential and male participants must agree to use a medically effective means of birth control throughout their participation in the treatment phase of the study (until at least 4 months following the end of therapy); nursing women must agree to refrain from nursing throughout their participation in the treatment phase of the study (until at least 4 months following the end of therapy)

**3.1.3** Investigators should review the planning constraints listed in Section 5.2.7 and have a strong expectation that they are achievable prior to enrolling a patient on study.

### 3.2 Eligibility Criteria (11-MAR-2019)

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

**3.2.1** Pathologically (histologically or cytologically) confirmed diagnosis of locoregional recurrent or any new primary squamous cell carcinoma of the head and neck that is not amenable to curative resection. A new primary HNSCC is defined where any one of the following criteria are met:

- Metachronous invasive SCC developing ≥ 6 months after an index HNSCC, more than 3 cm from the index lesion;
- SCC developing in the same region as the index SCC if ≥ 36 months after the index diagnosis and if within 3 cm of a site where disease was completely resected or complete response was documented;
- New SCC that is cytologically or molecularly distinct from index SCC (eg new HPV negative SCC with prior index SCC that was HPV positive).

**3.2.2** Tumor tissue testing for p16 status is required for base of tongue, soft palate, and tonsil cancer. If a p16 testing has been previously performed on an oropharynx cancer that has recurred, then repeat testing for p16 status is not required. Participants whose first cancer was an unknown primary must have p16 testing performed and documented at the time of enrollment from either the new primary tumor or the recurrent cancer.

**3.2.3** Patients must have had prior radiotherapy (RT) to the head and neck (minimum of 30 Gy) with overlap of at least 25% of the current PTV with the previously treated area. Obtaining

and reviewing prior radiation treatment plans is strongly encouraged. In the event that they are unavailable, and the area in question was clearly in the previous radiation field (e.g. in a conventional 3 field arrangement), that patient will be considered eligible for trial.

**3.2.4** Disease must be limited to a single site or adjacent sites that can be treated in a single contiguous target volume for which the maximum total tumor dimension (GTV) must be <7.5cm. Examples of eligible patients include

1) A primary site recurrence in the oropharynx with a concurrent level 2 nodal mass, or a laryngeal recurrence with a level 3 nodal mass
2) Multiple nodes in the same (level 2) or adjacent nodal levels (levels 2 and 3)
3) Skull base recurrence with a lateral pharyngeal or high level 2 node

**Note:** These cases will be eligible provided that the maximum total tumor dimension is <7.5cm. For cases in which a tumor biopsy was performed and there is a biopsy/tumor debulking bed adjacent to the gross residual disease, all of the preoperative radiographic abnormalities must be included in the GTV and meet the <7.5cm maximal dimension criteria to meet eligibility.

**Note:** Patients who meet these criteria only after surgical removal of a portion of the patient's disease (e.g. removal of level 4 nodal mass in a patient with a tongue base primary; or of a contralateral nodal mass in an N2c patient) are ineligible.

**3.2.5** Patients who have undergone a recent biopsy (e.g. incisional) are eligible. Any preceding surgical procedure beyond a biopsy (e.g. debulking) must be reviewed as follows:

- Patients rendered free of gross disease are not eligible.
- Patients with gross residual disease postoperatively, must be reviewed by the Surgical Co-PI, Dr. John Ridge (drew.ridge@fccc.edu) for determination of eligibility. The operative report, pathology report and radiographic image(s) of the preoperative and postoperative target lesion must be included in the email along with the eligibility inquiry. These will be addressed within 3 business days.
- Patients eligible for study must have cutaneous wounds healed for 4-6 weeks prior to the initiation of SBRT.

**3.2.6** The following diagnostic evaluation is required:

- History/physical examination within 56 days prior to registration
  Examination by a Radiation Oncologist and Medical Oncologist within 56 days prior to registration; [Note: Baseline dental assessment is strongly recommended prior to start of therapy but is not required for eligibility (See Section 4)]
- Contrast enhanced CT or MRI, of the tumor and neck within 56 days prior to registration.
- Chest CT scan or full body PET/CT within 56 days prior to registration; patients with equivocal pulmonary nodules that are < 1.5 cm, that cannot be safely biopsied, or that are negative on PET/CT imaging are eligible;

**3.2.7** Zubrod Performance Status 0-1 within 28 days prior to registration;

**3.2.8** Age ≥ 18;

**3.2.9** The trial is open to all genders;

**3.2.10** Adequate bone marrow, liver function, renal function, and laboratory parameters within 28 days prior to registration defined as follows:

- Hematologic: Absolute neutrophil count (ANC) ≥ 1,500 cells/mm$^3$, Platelets ≥ 100,000 cells/mm$^3$, Hemoglobin ≥ 9 g/dL
- Hepatic: Total bilirubin ≤ 1.5 x ULN OR Direct bilirubin ≤ ULN for subjects with total bilirubin levels > 1.5 x ULN, AST (SGOT) and ALT (SGPT) ≤ 2.5 xULN
- Creatinine ≤ 1.5 x ULN, OR measured or calculated creatinine clearance > 60 mL/min for subject with creatinine levels > 1.5 x institutional ULN [NOTE: Calculated creatinine per institutional standard; GFR may be used in place of creatinine or CrCl]

**3.2.11** Negative serum pregnancy test within 14 days prior to registration for women of childbearing potential. (Note: A pregnancy test must be repeated within 3 days prior to the administration of the first dose of pembrolizumab)

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

## 3.3 Ineligibility Criteria (11-MAR-2019)

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

**3.3.1** Patients with distant metastases;

**3.3.2** Tumors that involve more than 180 degrees of the carotid artery on diagnostic CT or MRI of the neck within 56 days prior to registration. Investigators are encouraged to review the CT simulation imaging and ensure that tumor progression has not occurred whereby patients who were initially eligible based on diagnostic imaging, would be rendered ineligible based on CT simulation imaging (e.g. tumor size >7.5cm, skin involvement, >180 degrees of carotid encasement by tumor). If this does occur, the patient should be removed from the study and the Radiation Oncology Co-PIs should be notified via email. **Note:** It is strongly recommended that CT simulation be performed prior to registration.

**3.3.3** Patients with gross skin involvement (i.e. tumor ulceration through the skin) are excluded. Patients with tumor approaching the skin but in which the overlying skin remains intact are eligible, providing that planning constraints per Section 5.2.8 can be achieved without the use of bolus;

**3.3.4** Disease that requires two or more discontiguous target volumes will be ineligible. Examples of such cases include:

1. Bilateral nodal targets
2. Level 2 and level 4 nodes
3. An oropharyngeal recurrence with a low level 4 node;

**3.3.5** Patients for whom the maximal total tumor dimension (GTV) is >7.5cm

**3.3.6** Prior radiation to primary tumor within 6 months of registration

**3.3.7** Prior systemic therapy, investigational agent or investigational device within 28 days of start of study treatment.

**3.3.8** Surgical resection of the qualifying cancer is not permitted. (Patients who have undergone biopsies are eligible). Patients without radiographically apparent gross tumor are ineligible. For cases where an operation more extensive than a biopsy was performed but radiographically apparent gross residual tumor remains, please email the Surgical Co-PI, Dr. John Ridge (drew.ridge@fccc.edu) for determination of eligibility. The operative report, pathology report and radiographic image(s) of the postoperative target lesion must

be included in the email along with the eligibility inquiry. These will be addressed within 3 business days.

**3.3.9** No concurrent treatment with other investigational agent or investigational device

**3.3.10** Prior therapy with a checkpoint inhibitor (eg anti-CTLA-4, anti-PD-1 or anti-PD-L1 therapy);

**3.3.11** Severe, active co-morbidity defined as follows:

- Patients with immunodeficiency, or receiving systemic steroid, or any form of immunosuppressive therapy at the time of registration (eg history of human immunodeficiency virus--HIV). Use of physiologic doses corticosteroids may be approved with consultation with study chairs.
- Active autoimmune disease that has required systemic treatment in the past 2 years (ie with use of disease modifying agents, corticosteroids or immunosuppressive drugs). Replacement therapy (eg thyroxin, insulin, or physiologic corticosteroid replacement therapy for adrenal or pituitary insufficiency etc.) is not considered a form of systemic therapy
- Known active hepatitis B (positive test for virus surface antigen--HBsAg) or hepatitis C virus (eg positive HCV RNA qualitative test);
- History of (non-infectious) pneumonitis that required steroids or current pneumonitis;
- Treatment with a live vaccine within 30 days of registration. Note: Seasonal influenza vaccines for injection are generally inactivated flu vaccines and are allowed; however intranasal influenza vaccines (e.g., Flu-Mist®) are live attenuated vaccines and are not allowed
- Unstable angina and or congestive heart failure requiring hospitalization in the last 6 months;
- Transmural myocardial infarction within the last 6 months;
- Active bacterial or fungal infection requiring intravenous antibiotic at the time of registration; Note: If the infection resolves and the patient is on p.o. and still within, the required registration timeframe, then the patient is eligible
- Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy within 30 days of registration.

**3.3.12** Other significant medical, surgical or psychiatric conditions or requirements for any medication or treatment that in the opinion of the investigator may interfere with compliance, make administration of anti-PD-L1 therapy hazardous, or obscure interpretation of adverse events (AEs), such as a condition associated with frequent diarrhea;

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

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

(11-MAR-2019)

**PRE-TREATMENT ASSESSMENTS**

| Assessments | Prior to Registration (calendar days) | Prior to Treatment (calendar days) |
|---|---|---|
| CBC w/diff & ANC | 28 days | |
| Sodium, potassium, chloride glucose, calcium, magnesium, albumin | | 21 days |
| Creatinine or creatinine clearance | 28 days | |
| Total bilirubin; AST, ALT | 28 days | |
| Serum pregnancy test (if applicable) | 14 days | 3 days prior to first dose of pembrolizumab |
| CT or MRI of neck, with contrast | 56 days | |
| PET/CT skull base to mid-thigh | | Recommended 56 days |
| Dental assessment | | Recommended prior to treatment start |
| CT scan of chest (Not necessary if whole-body PET is performed; see section 3.2 for further details) | 56 days | |
| History/physical exam | 56 days | |
| Performance status | 28 days | |
| Rad onc exam | 56 days | |
| Med onc exam | 56 days | |
| Tissue for research, if patient consents | | X |
| Blood for research, if patient consents | | X |

**ASSESSMENTS DURING SBRT or SBRT + PEMBROLIZUMAB TREATMENT**

NOTE: See Appendix IA for Cross-Over Patients

| **Assessments** | **Arm 1 (SBRT+ Pembrolizumab)** | **Arm 2 (SBRT Alone)** |
|---|---|---|
| Brief history/physical exam | Weekly[a] | Weekly[a] |
| Weight | Weekly[a] | Weekly[a] |
| Zubrod PS | Weekly[a] | Weekly[a] |
| CBC w/diff & ANC | Weekly[a,d] | IS[b] |
| Sodium, potassium, chloride glucose, calcium, magnesium, albumin | Weekly[a,d] | IS[b] |
| Serum creatinine or creatinine clearance | Weekly[a,d] | IS[b] |
| Total bilirubin; AST, ALT | Prior to each dose of pembrolizumab[d] | |
| TSH with reflex to T4[c] | Prior to initial dose of pembrolizumab, then prior to every other dose[d] | |
| Serum pregnancy test (if applicable) | Prior to first dose of pembrolizumab[d] | |
| Adverse Event Eval, including mucosal assessment | Weekly[a] | Weekly[a] |

[a] Note: Assessment required weekly during SBRT for both arms, with one of the weekly assessments to be performed prior to pembrolizumab administration for Arm 1.
[b] Note: For Arm 2 (SBRT alone), labs and frequency to be performed according to institutional standards (IS).
[c] T3 and T3-resin uptake to be added as necessary if screening thyroid function tests are abnormal.
[d] Within 3 days prior to pembrolizumab administration

**ASSESSMENTS IN MAINTENANCE PEMBROLIZUMAB/FOLLOW UP**

NOTE: For Arm 1, maintenance pembrolizumab begins with first infusion post completion of RT. For Arm 2, follow up begins 30 days after the completion of SBRT. See Appendix IA for Cross-Over Patients.

| **Assessments** | **Arm 1 (SBRT+ Pembrolizumab)** | **Arm 2 (SBRT Alone)** |
|---|---|---|
| | **From end of RT: q3 mos. x 2 yrs.; q6 mos. x 3 years; unless otherwise indicated (+/- 1 month)** | |
| History/physical exam | X [a] | X |
| Weight | X [a] | X |
| Zubrod PS | X [a] | X |
| CBC w/diff & ANC | X [a] | IS [b] |
| Total bilirubin; AST, ALT | X [a, d] | IS[b] |
| Sodium, potassium, chloride glucose, calcium, magnesium, albumin | X [a] | IS [b] |
| Serum creatinine or creatinine clearance | X [a] | IS [b] |
| TSH with reflex to T4 | X [a, d] | IS [b] |
| Adverse Event Eval, including mucosal assessment | X [a] | X |
| Contrast enhanced CT (or MRI) of tumor site and neck nodes | At 3 mos x 2 years, then q 6 mos x 1year, then annually up to year 5 | |
| PET/CT skull base to mid-thigh | Recommended at 3 mos after RT [c] | |
| CT of Chest | At 3 mos x 2 years, then q 6 mos x 1year, then annually up to year 5 | |
| Blood for research, if patient consents | Only if blood was not collected prior to the first treatment. | |

a. For Arm 1: During maintenance treatment with pembrolizumab (every 3 weeks), directed history and physical exam, lab studies and adverse event assessment will be performed prior to each drug dose, in addition to the schedule specified in the table above. Unresolved abnormal labs that are drug related AEs should be followed until resolution. After completion or discontinuation of maintenance pembrolizumab lab tests are not required but should be performed according to institutional standards. Thyroid testing is required during maintenance pembrolizumab every other cycle (ie every 6 weeks)
b. For Arm 2: Lab studies are not required but should be performed according to institutional standards (IS).
c. For the 3 month follow-up imaging, PET/CT scan is highly recommended if the Pre-Treatment imaging of the tumor was also performed with this modality
d. Within 3 days prior to pembrolizumab administration

NOTE: See Section 5.4.1 for Patient Discontinuation Criteria

## 4.1 Definition of Disease Assessments

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

### 4.1.1 Response Criteria

| Evaluation of Target and Response Definitions | |
|---|---|
| Complete Response **(CR)** | Disappearance of the target lesion; ideally, this determination will be made based on CT (MRI, or PET/CT) image evaluation. |
| Partial Response **(PR)** | At least a 30% decrease in the LD of the target lesion, taking as reference the baseline LD; ideally, this determination will be made based on CT (MRI, or PET/CT) image evaluation. |
| Stable Disease **(SD)** | Neither sufficient shrinkage to qualify for CR/PR above nor sufficient increase to qualify for LE below, taking as reference the smallest LD since the treatment started |
| Local Enlargement **(LE)** | At least a 20% increase in the LD of target lesion, taking as reference the smallest LD recorded since the treatment started; Ideally, this determination will be made based on CT (MRI, or PET/CT) image evaluation. |
| Primary Tumor Failure **(PTF)** | Refers to the primary treated tumor after protocol therapy and corresponds to meeting both of the following two criteria: 1) Increase in tumor dimension of 20% as defined above for local enlargement (LE); 2) The measurable tumor with criteria meeting LE should be avid on PET/CT imaging with uptake of a similar intensity as the pretreatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma. For outcome analysis, Marginal Failures (MF; see below) will also be counted as PTF; however, they should be distinguished specifically as MF, not PTF, on all report forms. The EORTC criteria for post-treatment PET evaluation will be used as a basis for evaluation in cases more difficult to assign as to whether the uptake is pathological for cancer recurrence vs. inflammation.4 |
| Marginal Failure **(MF)** | Refers to the appearance after protocol radiation therapy of a measurable tumor appearing since treatment within 1.0 cm of the treated PTV (see Section 5.2.4) and meeting the |

| | |
|---|---|
| | following two criteria: 1) Enlarging tumor dimensions corresponding to a 20% increase in the longest diameter compared to initial appearance on imaging evaluation. Ideally, this determination will be made based on MRI, PET/CT, or CT image evaluation; 2) The measurable tumor within 1.0 cm of the treated PTV should be avid on PET imaging with uptake of a similar intensity as the pre-treatment staging PET, OR the measurable tumor should be biopsied confirming viable carcinoma. |
| Primary Tumor Control **(PTC)** | The absence of Primary Tumor Failure. |
| Local Failure | Either PTF or MF |
| Local Control | Absence of Local Failure |
| Regional Failure **(RF)** | Refers to the appearance after protocol therapy of measurable tumor within lymph nodes along the natural lymphatic drainage typical for the location of the treated primary disease only with dimension of at least 1.0 cm on imaging studies (preferably CT scans). Equivocally appearing enlarged lymph nodes should be positive on PET/CT imaging or biopsied to confirm involvement with carcinoma. |
| Metastatic dissemination (**MD**) | Refers to the appearance after protocol therapy of cancer deposits characteristic of metastatic dissemination from HNSCC. Appropriate evaluations for making this determination include physical examination and imaging studies. PET/CT scan OR biopsy to confirm MD is encouraged but not required. |
| Progressive Disease (PD) | Refers to the appearance after protocol therapy of PTF, MF, RF, or MD as defined above |
| **NOTE:** Response assessment for patients who progress after SBRT alone and are treated with pembrolizumab on crossover component of the study will be identically defined. However, events will be calculated starting from the first dose of salvage pembrolizumab. | |

## 5. TREATMENT PLAN/REGIMEN DESCRIPTION

**5.1** **Pembrolizumab** (see Section 9 for agent and supply information)
**Run-In/Arm 1: Pembrolizumab treatment must begin within 7 days after the site receives the study drug shipment.**
Systemic therapy with pembrolizumab will be administered for Run-In Cohort and for patients randomized to Arm 1 following completion of Run-In Phase of the study.

**5.1.1** Dose: 200 mg

**5.1.2** Administration and Route: Intravenous over 30 minute infusion. Every effort should be made to target infusion time to be as close to 30 minutes as possible. However, a

window between -5 minutes and +10 minutes is permitted (i.e. infusion time is 30 minutes -5 minutes/+10 minutes).

**5.1.3** Dose Frequency: Every 3 weeks

**5.1.4** Regimen: Day 1 of each cycle (3 week cycles) Cycle 1 Day 1 to start at least 14 days prior to initiation of SBRT.

**5.1.5** Duration: Maximum duration of treatment for up to two years of therapy

**5.1.6** Timing of Dose administration: Pembrolizumab may be administered up to 3 days before or after the scheduled Day 1 of each cycle due to administrative reasons (for example due to holidays).

**5.1.7** Cross-Over Following Progressive Disease on Arm 2: Please refer to Appendix I regarding patients who cross-over following SBRT alone.

## 5.2 Radiation Therapy

**Run-In/Arm 1: Radiation Treatments must begin at least 14 days after the first dose of pembrolizumab.**

**Arm 2: Radiation Treatments must begin within 14 days after registration.**

**Note 1:** Pre-treatment reviews will be required for each case from each institution. The patient cannot begin treatment until complete data from each case are received, reviewed and approved **Sites need to allow 3 business days for the pre-treatment review, and if necessary, 3 additional business days if a revision and re-plan is requested by the Reviewer** (See Section 5.2.11).

**Note 2:** All participating institutions must be credentialed for extracranial SBRT, which consists of credentialing for IMRT and IGRT, prior to registering patients to the study. Daily IGRT is mandatory (See Section 5.2.1).

**Radiation Therapy Schema**

Before reading this section, please refer to the schema at the beginning of the protocol.

**5.2.1** Treatment Technology

This protocol requires the use of photon treatment. Proton therapy is not allowed. IMRT techniques, including step and shoot or volumetric arc techniques are allowed. Tomotherapy and CyberKnife are allowed. All patients are required to have daily image guidance as described below in section 5.2.10. Photon beams with energies of 6-10 MV are allowed. The photon energy of 6 MV is preferred. Minimum field size should be larger than the field size for small field used for beam commissioning. Beam shaping for treatment delivery shall be via conical collimator or multi-leaf collimator (MLC). Treatment shall be via linear accelerator (LINAC) commissioned and equipped to deliver stereotactic radiosurgery. All participating institutions must be previously credentialed for extracranial SBRT which consists of credentialing for IMRT and IGRT. Previous credentialing for one or both of these treatment techniques will be accepted when requirements have been met through other RTOG/NRG head and neck studies, or the lung, liver or spine SBRT protocols.

**5.2.2** Immobilization and Simulation

Patients will be treated supine and must have a secure head and neck immobilization (e.g. aquaplast mask) made prior to the treatment planning CT scan. Bite blocks may be utilized for tongue position control or immobilization when the targets involve the pharyngeal axis. The treatment planning CT scan should be performed with IV contrast unless contraindicated, obtained in the immobilization device and in the treatment position with a slice thickness of ≤1.5 mm. For patients in whom contrast is contraindicated, PET/CT and MRI based imaging should be used to guide tumor and normal organ volume definition.

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

In addition to the planning CT, additional imaging can be fused to the planning CT data set to aid in target delineation. While not mandatory, we strongly recommend obtaining and fusing an FDG PET/CT as well as accompanying diagnostic contrast enhanced CT images. Contrast enhanced MRI can also be extremely valuable and are strongly encouraged for tumors near the skull base. All image sets used for structure delineation must be submitted with the RT digital data.

**5.2.4** Definition of Target Volumes and Margins

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

**Gross Tumor Volume (GTV)**

The GTV represents clinically or radiographically areas grossly involved with tumor and will be designated as GTV_4000. These volumes are defined based on physical exam and review of available imaging. FDG-PET may assist in GTV identification but specific GTV border delineation should not rely exclusively on PET signal given the known variable association between gross tumor extent and PET signal cutoff. Grossly Positive Nodes must be included in the GTV and are defined as those greater than 1.5 cm in long axis and/or > 1 cm in short axis, a cluster of 3 or more borderline size nodes, radiographic evidence of extranodal extension (ENE), a node of any size with evidence of necrosis, or a node with a standard uptake value (SUV) above 4 on PET/CT. A patient who underwent aggressive biopsy or subtotal resection (and meets eligibility criteria as defined in section 3.2.3) with a biopsy/resection bed in association with the radiographically visible gross target disease, must have the entire biopsy bed/resection bed included in the GTV. This residual tumor + biopsy/resection bed GTV must have its largest maximum dimension <7.5cm to meet eligibility criteria.

**Clinical Target Volume (CTV)**

There will be no high dose clinical target volume expansion used on this protocol.

**Planning Target Volume (PTV)**

GTV_4000 will have an associated PTV_4000 which represents the volumes to which radiation dose will be prescribed, delivered and evaluated. The PTV is an isotropic expansion of the GTV to account for internal motion and residual set-up error. The **PTV**

**is defined as a 3 mm expansion of the GTV in all planes.**

The simple isotropic expansion can result in a dosimetric challenge when the GTV expansion results in a PTV that overlaps a critical OAR (spinal cord and/or brainstem) and its associated PRV, hence dose delivered to this PTV will exceed the acceptable dose limits for the OAR. In this case, the PTV coverage can be reduced from the desired ≥95% coverage to ≥85%, as per the dose constraints table in Section 5.2.7.

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

| **Standard Name** | **Description** | **Validation** |
|---|---|---|
| GTV_4000 | GTV to receive 40 Gy | **Required** |
| PTV_4000 | PTV to receive 40 Gy | **Required** |

**5.2.5** Definition of Critical Structures and Margins

Note: All structures must be named for digital RT data submission as listed in the table below. The structures marked as "Required" in the table must be contoured and submitted with the treatment plan. Structures marked as "Required if…" must be contoured and submitted when applicable.

Resubmission of data may be required if labeling of structures does not conform to the standard DICOM name listed. Capital letters, spacing and use of underscores must be applied exactly as indicated.

| OAR Standard Name | Description | Validation |
|---|---|---|
| SpinalCord | Spinal Cord | Required |
| SpinalCord_05 | PRV=5mm expansion on spinal cord | Required |
| BrainStem | Brain stem | Required |
| BrainStem_03 | PRV=3mm expansion on brainstem | Required |
| Lips | Lips | Required |
| Cavity_Oral | Oral cavity | Required |
| Parotid_R | Right parotid gland | Required |
| Parotid_L | Left parotid gland | Required |
| Glnd_Submand_R | Right submandibular gland | Required |
| Glnd_Submand_L | Left submandibular gland | Required |
| Pharynx | Non treated pharynx | Required |
| Esophagus_S | Cervical esophagus | Required |
| Larynx | Larynx | Required |
| Bone_Mandible | Mandible | Required |
| A_Carotid_R | Right carotid artery | Required |
| A_Carotid_L | Left carotid artery | Required |
| External | External border of the patient | Required |
| Skin | Inner ring of all tissue within 3mm of the skin | Required |
| E-PTV_4000 | Unspecified tissue, external minus PTV | Required |
| Eye_R | Right globe | Required for targets near* the skull base |
| Eye_L | Left globe | Required for targets near* the skull base |
| Lens_R | Right lens | Required for targets near* the skull base |
| Lens_L | Left lens | Required for targets near* the skull base |
| Glnd_Lacrimal_R | Right lacrimal gland | Required for targets near* the skull base |
| Glnd_Lacrimal_L | Left lacrimal gland | Required for targets near* the skull base |
| OpticNrv_R | Right optic nerve | Required for targets near* the skull base |
| OpticNrv_L | Left optic nerve | Required for targets near* the skull base |
| OpticChiasm | Optic Chiasm | Required for targets near* the skull base |
| Cochlea_R | Right cochlea | Required for targets near* the skull base |
| Cochlea_L | Left cochlea | Required for targets near* the skull base |
| Brain | Whole Brain | Required for targets near* the skull base |
| Lobe_Temporal_R | Right temporal lobe | Required for targets near* the skull base |
| Lobe_Temporal_L | Left temporal lobe | Required for targets near* the skull base |
| BrachialPlex_R | Right brachial plexus | Required for targets below cricoid cartilage |
| BrachialPlex_L | Left brachial plexus | Required for targets below cricoid cartilage |

*Near is defined as any point on the contour coming within 5 mm of the base of the skull.

- **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:** The definition of the globe of the eye is self-explanatory with an R or L used to specify each side of the body
- **Optic Nerve:** The definition of optic nerve is self-explanatory with an R or L used to specify each side of the body
- **Optic Chiasm:** The definition of optic chiasm is self-explanatory
- **Cochlea:** The definition of cochlea is self-explanatory with an R or L used to specify each side of the body
- **Temporal Lobe:** The temporal lobe is bounded by the sylvian fissure cranially, the base of the middle cranial fossa caudally, the temporal bone anteriorly, the tentorium of the cerebellum and incisura preoccipitalis posteriorly, the temporal bone laterally and the cavernous and sphenoid sinus and sylvian fissure medially.
- **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_S**: This will be defined as the cervical or superior (S) esophagus, a tubular structure that starts at the bottom of pharynx (cricopharyngeal inlet) and extends to the thoracic inlet.
- **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_4000)**: 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.

**5.2.6** Dose Prescription

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

The prescribed dose of 40Gy will be delivered over 5 fractions using 8Gy per fraction. Treatments will typically be delivered over 10-15 days with a minimum of 40 hours in between fractions and a maximum of 5 days in between fractions. The recommended fractionation is every other weekday (e.g. Monday, Wednesday, Friday, Monday and Wednesday). However, twice weekly treatment (e.g. Mondays and Thursdays) is also acceptable and can be used for patients in whom an every other weekday schedule is not logistically feasible.

| **Target Standard Name** | **Dose (Gy)** | **Fraction Size** (Gy) | **# of fractions** | **Dose specification technique** |
|---|---|---|---|---|
| PTV_4000 | 40 | 8 | 5 | Covering >=95% of PTV |

**5.2.7** Compliance Criteria

The compliance criteria listed here will be used to score each case. Given the limitations inherent in the treatment planning process, the numbers given in this section can be different than the prescription table. The Per Protocol and Variation Acceptable categories are both considered to be acceptable. The Per Protocol cases can be viewed as ideal plans, and the Variation Acceptable category can include more challenging plans

that do not fall at or near the ideal results. A final category, called Deviation Unacceptable, results when cases do not meet the requirements for either Per Protocol or Variation Acceptable. Plans falling in this category are considered to be suboptimal and additional treatment planning optimization is recommended.

**Normalization of Dose:** The plan is normalized such that 95% of the PTV_4000 volume receives the prescription dose of 40 Gy. The treatment plan should be initially normalized such that 100% corresponds to the maximum dose within the PTV. While this point will typically correspond to the PTV center of mass, it can be located elsewhere within the PTV. For this SBRT approach, the recommended isodose prescription line chosen should be between 80%-90% but may range from 75%-95%. As a result, a ―hotspot will exist within the PTV that is equal to the prescription dose divided by the prescription isodose line (i.e., 40Gy/0.75 = 54Gy when 40Gy is prescribed to the 75% isodose). Doses higher than the prescription isodose (i.e., hotspots) should be manipulated to occur within the target and away from critical structures. Any dose > 105% of the prescription dose should occur within the PTV and not within the normal tissues outside the PTV.

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

**Target Volume and Critical Normal Structure Constraints and Compliance Criteria**

| Name of Structure | Dosimetric parameter | Per Protocol | Variation Acceptable | Notes |
|---|---|---|---|---|
| GTV_4000 | $V_{40Gy}$ | >=99% | >=90 and <99 | Required for all cases. |
| PTV_4000 | $V_{40Gy}$ | >= 95% | >=85 and <95 | |
| | $D_{95\%}$*(Gy) | 40 | >34 and <45 | |
| | $D_{max}$**(Gy) | <=50 | <=56 | |
| SpinalCord | $D_{max}$** (Gy) | <=8 | >8 and <10 | |
| SpinalCord_05 | $D_{max}$** (Gy) | <=10 | >10 and <12 | |
| BrainStem | $D_{max}$** (Gy) | <=10 | >10 and <12 | |
| BrainStem_03 | $D_{max}$** (Gy) | <=12 | >12 and <14 | |
| Optic nerve/chiasm | $D_{max}$** (Gy) | <=8 | >8 and <10 | Required when treating lesions near skull base |
| BrachialPlexus | $D_{max}$** (Gy) | <=10 | >10 and <12 | Required when treating lesions low neck |
| CarotidArtery | $D_{max}$** (Gy)<br>$D_{50\%}$***(Gy) | <=42<br><=32 | >42 and <44<br>>32 and <34 | Required for all cases |
| Esophagus | $D_{max}$ ** (Gy) | <=25 | >25 and <30 | Required when treating lesions low neck |
| Skin | $D_{max}$ ** (Gy) | <=30 | >30 and <35 | Required for all cases |

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

*$D_{95\%}$(Gy) = Dose to 95% of volume
**$D_{max}$ (Gy) = Maximum dose to 0.03 cc of the volume
***$D_{50\%}$(Gy) = Dose to 50% of the volume

**Recommended <u>Dose Spillage Criteria, Not for Plan Score</u>**

- Volume: Acceptable isodose distributions should be as conformal as possible. To this end the ratio of prescription isodose volume to PTV should be as small as possible.
  CI = Ratio of the prescription isodose volume to the PTV volume [Note: These criteria will not be required in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension). The prescription line will be contoured for calculation of this ratio and labeled as V_4000]
- Guidelines for the ratio of the 50% prescription isodose volume to the PTV volume (R50%) and for the maximum dose at 2cm ($D_{2cm}$) from the PTV are given in Table below. The 50% isodose volume may be elongated deliberately in order to avoid OAR thereby making it difficult to meet the guidelines in Table below. This is acceptable as long as normal tissue constraints are met.

| PTV Volume (cc) | Recommended CI | Recommended ratio of the 50% prescription isodose volume to the PTV volume (R50%) | Recommended maximum dose (Gy) at 2cm from the PTV in any direction ($D_{2cm}$) |
|---|---|---|---|
| PTV volume (cc)* < 25 cc | <=1.5 | < 7.5 | < 26 |
| 25cc <=PTV volume (cc) < 50 | <=1.5 | < 6.5 | < 31 |
| 50cc <=PTV volume (cc) < 75 | <=1.5 | < 5.7 | < 34 |
| 75cc <=PTV volume (cc) < 100 | <= 1.5 | < 5.5 | < 36 |
| 100cc <=PTV volume | <=1.5 | < 5.3 | < 37 |

**Note *:** These criteria will not be required in treating very small tumors (< 2.5 cm axial GTV dimension or < 1.5 cm craniocaudal GTV dimension).

**Recommended Dose Acceptance Criteria for non-critical OAR, Not for Plan Score**

| **Structure*** | **Recommended dose acceptance criteria** |
|---|---|
| E-PTV_4000 | $D_{1cc}$ <=42 Gy |
| Mandible | $D_{0.03cc}$ <= 42 Gy |
| OralCavity | $D_{mean}$ <= 25 Gy |
| Submandibular | $D_{mean}$ <= 25 Gy |
| Larynx | $D_{mean}$ <=20 Gy |
| Pharynx | $D_{mean}$ <= 20 Gy |
| Parotid | $D_{mean}$ <= 15 Gy |
| Globe | $D_{mean}$ <=10 Gy |
| Temporal Lobe | $D_{mean}$ <=10 Gy |

*All of these structures are evaluated after ensuring PTV is removed.

**Delivery Compliance criteria**

| Parameter | Per Protocol | Variation Acceptable |
|---|---|---|
| Start date | Between14 and 21 days after start of pembrolizumab | >21 and <27 days after start of pembrolizumab |
| Overall Treatment time | >=10 and <=15 days | >=9 and <=18 days |
| Interruptions | <=4 days in between fractions | 5 days in between fractions |

A **Deviation Unacceptable** will be scored when the Variation Acceptable limits are not met, unless there is a medically appropriate indication for the delay.

**5.2.8** Treatment Planning Priorities and Instructions

**IMRT Dose Prescription to PTVs**

It is recognized that a portion of the PTV that is close to the skin or critical PRVs (e.g. spinal cord, brainstem, brachial plexus, carotid artery) may receive significantly less than the prescription dose. This is acceptable in these regions even if cold spots exist within the GTV, as meeting constraints of certain critical OARs must take precedence over tumor coverage. A minimum of 90% of the GTV for the case to be scored as a Variation Acceptable, and a minimum of 85% of the PTV must be covered by the prescription dose for the plan to be scored as Variation Acceptable. Patients with skin involvement, or with PTVs so close to the skin that tissue equivalent bolus must be utilized to ensure adequate dose are ineligible for registration on this protocol.

**Prioritization for IMRT Planning (in order of decreasing importance)**

1. Spinal Cord
2. Brainstem
3. Optic nerve/chiasm
4. Brachial Plexus
5. Ipsilateral Carotid Artery
6. Skin
7. Esophagus
8. PTV_4000 & GTV_4000
9. Pharynx
10. Larynx
11. Oral Cavity
12. Mandible
13. Parotid glands
14. Submandibular glands

**Dose Calculations**

The primary data set for dose calculation is CT. In the case in which contrast is present during the treatment planning CT, the density of the contrast should be overridden to a representative background electron density. The dose grid size should be ≤ 2 mm in all

directions, however the CT slice thickness should be ≤ 1.5 mm.

Dose calculation algorithms have been credentialed by IROC Houston. To find whether your commercial treatment planning system has been credentialed by IROC Houston, please see the list from the following website:
http://rpc.mdanderson.org/rpc/Services/Anthropomorphic_%20Phantoms/TPS%20-%20algorithm%20list%20updated.pdf

Any other dose calculation algorithms not listed on the web site must be credentialed by IROC Houston prior to the use for this study. All doses should be reported in terms of dose-to-water and not in terms of dose-to-medium.

**5.2.9** Patient-Specific QA

Patient specific QA is required. Any patient-specific QA that needs to be acquired should follow institutional guidelines. QA is performed by delivering the plan onto a phantom and measuring the dose using an ion chamber/film set, an ion chamber array or other 2D/3D device. Measured dose distribution will be compared to planned dose distribution using a Gamma criterion of 3% dose difference and 3 mm distance-to-agreement. Absolute dose difference should be used to compute the Gamma value. The pass rate should be at least 90% measured for the entire plan with a threshold set to 10% of the maximum dose on the plane. For the ion chamber measurement imbedded into a low dose-gradient region inside the target region, the dose difference should be within 5%.

**5.2.10** Daily Treatment Localization/IGRT

IGRT is radiation therapy using imaging to facilitate accuracy and precision throughout its entire process from target and normal tissue delineation, to radiation delivery, to adaptation of therapy to anatomic and biological changes over time in individual patients. In this section we use the terminology IGRT to focus on image-guidance at the time of radiation delivery to ensure its adherence to the planned treatment.

At beginning of treatment for every fraction, capability should exist to define the positions of targets within the patient anatomy according to 3-D coordinate system. By doing that, the patient could be set up for each delivery with the intention of directing the radiation toward an isocenter or target. Angular as well as translational couch corrections are strongly recommended. The following techniques are acceptable for image-guided radiation delivery.

a) Cone-Beam CT device mounted on the linear accelerator. The CT images can be generated by using either MV treatment beam or kV auxiliary equipment attached to the accelerator. Before delivering radiation, on-board imaging might be obtained at every fraction on the treatment unit for verifying the isocenter of treatment fields. Cone-beam CT is strongly recommended.
b) Fan-Beam CT device equipped to the helical beam delivery accelerator, which uses the MV beam to acquire helical CT images for localization.
c) Diagnostic CT device sharing the treatment couch with the linear accelerator.
d) kV x-ray devices mounted on wall or floor that produce orthogonal or near-orthogonal projection views of a patient in the treatment position.

The accuracy of localization should be ≤ 2.5mm during the treatment. Any shifts made to align the pretreatment IGRT imaging ≥ 5mm requires repeat imaging and confirmation of alignment prior to the administration of SBRT.

**5.2.11** Pre-Treatment Case Review

As this is the first RTOG study of head and neck SBRT, a pre-treatment review of each case from each institution will be required. These pre-treatment reviews must be completed prior to the initiation of treatment. Contours and planning requirements will be assessed within 3 business days of the complete RT data submission. Any case that does not meet protocol compliance requirements as per section 5.2.7 above will require revision and replan as well as a repeat pre-treatment review prior to SBRT administration. The resubmitted data will be reviewed within 3 business days once complete data have been received.

## 5.3 Concomitant Medications/Vaccinations

Medications and vaccinations specifically prohibited in the exclusion criteria are not allowed during study protocol therapy. If during the course of study protocol therapy a clinical indication arises for the use of any medication or vaccination specifically prohibited, then discontinuation from protocol therapy may be required. The final decision of any supportive therapy or vaccination will occur at the discretion of the investigator and/or the patient's care physician. However, the decision to continue the patient on protocol therapy requires mutual agreement with the investigator, the RTOG chair/co-chairs, and the study participant.

**5.3.1** Permitted Supportive/Ancillary Care and Concomitant Medications

All supportive therapy for optimal medical care will be given during the study period at the discretion of the attending physician(s) within the parameters of the protocol and documented on each site's source documents as concomitant medication. All concomitant medications will be recorded in the case report forms including prescriptions, over-the-counter medications or herbal supplements and IV medications and fluids.

**5.3.2** Prohibited Concomitant Therapies

Study participants are prohibited from receiving long therapies during screening and the treatment phase of the study:

- Anti-neoplastic systemic chemotherapy or biologic therapy
- Immunotherapy not specified in this protocol
- Investigational agents other than pembrolizumab
- Live vaccines within 30 days prior to the first dose of trial treatment and while participating in this trial. Examples of live vaccines include, but are not limited to, the following: Measles, mumps, rubella, chickenpox, yellow fever, rabies, BCG, and typhoid (oral) vaccine. Seasonal influenza vaccines for injection are generally killed virus vaccines and are allowed. However, intranasal influenza vaccines (e.g. Flu–Mist®) are live attenuated vaccines and are not allowed.
- Systemic glucocorticoids for any purpose other than to modulate symptoms from an event of suspected immunologic etiology. The use of physiologic replacement doses of corticosteroids may be approved after consultation with the study chairs/co-chairs.

- Note: inhaled steroids are allowed for management of asthma
- Note: Use of prophylactic corticosteroids to avoid allergic reactions (e.g., to IV contrast dye) is permitted.

Study participants who, in the assessment by the investigator, require use of any of the above treatments for clinical management should be discontinued from study protocol therapy.

No prohibited therapies are stipulated during the post-treatment follow-up phase of the study.

**5.3.3** Participation in Other Trials

Study patients are not permitted to participate in another concurrent intervention clinical trial in which they will receive treatment with an investigational agent or investigational device.

## 5.4 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- Disease progression,
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw consent for participation in the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

**5.4.1** Patient Discontinuation of Therapy

See also section 4.1 for Definition of Disease Assessments

Immunotherapeutic agents such as pembrolizumab may produce antitumor effects by potentiating endogenous cancer-specific immune responses. The response patterns seen with such an approach may extend beyond the typical time course of responses seen with cytotoxic agents, and can manifest as a clinical response after an initial increase in tumor burden or even the appearance of new lesions

**5.4.1.1** Arm 1 (SBRT + pembrolizumab) If a patient achieves CR, PR, or SD as per Definition of Disease Assessment in Section 4.1 then treatment with pembrolizumab will continue. If radiographic imaging shows Primary Tumor Failure (PTF) then follow Delayed Immune Response Assessment (DIRA) below. If PTF is confirmed following DIRA, then the patient should be discontinued from protocol treatment. If PTF is not confirmed following DIRA, then protocol therapy and protocol assessments should continue.

*Delayed Immune Response Assessment (DIRA)*--If radiologic imaging shows PTF, tumor assessment may be repeated by the site ≥28 days later in order to confirm PTF with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the

initial scan demonstrating PTF, treatment may be continued as per treatment calendar. If repeat imaging confirms progressive disease, then the date of PTF will be considered the date of the initial scan suggesting PTF and the patient will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

The decision to continue study treatment after the first evidence of PTF is at the Investigator's discretion based on the clinical status of the patient as described in the Evaluation of Target and Response Definitions table in Section 4.1.1

Patients may receive study treatment while waiting for confirmation of PTF if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in Zubrod performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention
- No significant, unacceptable, or irreversible toxicities related to study treatment

If a patient on Arm 1 experiences RF, MF, or MD then Delayed Immune Response Assessment (see below), as described above should be followed. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy. In this case the date of RF, MF, or MD will be considered the date of the imaging study that suggested progression. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

*Delayed Immune Response Assessment (DIRA)*--If radiologic imaging shows RF, MF, or MD tumor assessment may be repeated by the site ≥28 days later in order to confirm RF, MF, or MD with the option of continuing treatment per below while awaiting radiologic confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating RF, MF, or MD treatment may be continued as per treatment calendar. If repeat imaging confirms progressive disease, subjects will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

**5.4.1.2** Arm 2 (SBRT Alone) If a patient achieves CR, PR, or SD as per Definition of Disease Assessment in section 4.1.1, then protocol follow-up assessments should be continued. If radiographic imaging confirms PTF, RF, MF, or MD then histologic confirmation is suggested, but not mandatory, and the patient is eligible for cross-over to pembrolizumab, if the patient experiences PTF, RF, MF, or MD within 2 years after start of SBRT (see Appendix I for further instructions).

## 6. TREATMENT MODIFICATIONS/MANAGEMENT

### 6.1 Pembrolizumab

Note: pembrolizumab dose should not be modified for toxicity. See the pembrolizumab investigator brochure, available on the RTOG 3507 Foundation webpage, for additional toxicity management information.

Pembrolizumab will be held for drug–related toxicities and severe life–threatening AEs as per Table 6.1 below. Held doses will not be replaced. When pembrolizumab is restarted, this dose would be considered day 1 of the subsequent cycle and should be in alignment with the new schedule.

Participants with adverse toxicity or persistent laboratory AE at grade 2 following 12 weeks of therapy may continue on the trial only if asymptomatic, controlled and with agreement of the investigator and the RTOG chair/co–chair.

Table 6.1: Modification Guidelines For Pembrolizumab Drug-Related Adverse Events

| Toxicity | Hold Treatment For Grade | Timing For Restarting Treatment | Discontinue Pembrolizumab |
|---|---|---|---|
| AST, ALT, Or Increased Bilirubin | 2 | Toxicity resolves to grade 0-1 | Toxicity does not resolve within 12 weeks of last dose |
| | 3-4[1] | Permanently discontinue (see exceptions below) | Permanently discontinue |
| Diarrhea/Colitis | 2-3 | Toxicity resolves to grade 0-1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or last of prednisone or equivalent per day within 12 weeks |
| | 4 | Permanently discontinue | Permanently discontinue |
| Hyperthyroidism | 3 | Toxicity resolves to grade 0 -1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or last of prednisone or equivalent per day within 12 weeks |
| | 4 | Permanently | Permanently |

| | | | |
|---|---|---|---|
| | | discontinue | discontinue |
| Hypothyroidism | 2-4 | Therapy with pembrolizumab can be continued while treatment for the thyroid disorder is instituted | Therapy with pembrolizumab can be continued while thyroid replacement is instituted |
| Hypophysitis | 2-4 | Toxicity resolves to grade 0-1. Therapy with pembrolizumab can be continued while endocrine replacement therapy is instituted | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or last of prednisone or equivalent per day within 12 weeks |
| | | | |
| Infusion reaction | 2[2] | Toxicity resolves to Grade 0-1 | Permanently discontinue if toxicity develops despite adequate premedication |
| | 3–4 | Permanently discontinue | Permanently discontinue |
| Pneumonitis | 2 | Toxicity resolves to grade 0 -1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or last of prednisone or equivalent per day within 12 weeks |
| | 3-4 | Permanently discontinue | Permanently discontinue |
| Renal Failure Or Nephritis | 2 | Toxicity resolves to grade 0 -1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or last of prednisone or equivalent per day within 12 weeks |
| | 3-4 | Permanently discontinue | Permanently discontinue |

| | | | |
|---|---|---|---|
| Tumor Site Bleeding (in the absence of tumor progression) | 2 | Toxicity resolves to grade 0-1 | |
| | 3 | Hold pembrolizumab until ALL of the following criteria are met:<br>-the bleeding has resolved and Hgb is stable<br>-bleeding diathesis is resolved and/or ruled out<br>-anatomic or pathologic condition that could increase risk for bleed has been ruled out<br>If interventional radiology procedure is performed to stop bleeding, patients may resume therapy if ALL of the above criteria are met | Permanently discontinue if recurrent grade 3 bleeding |
| | 4 | Permanently discontinue | Permanently discontinue |
| Tumor Site Edema Causing Airway Compromise | 3 | Toxicity resolves to grade 0-1 or a tracheostomy is placed and airway is secure | Toxicity does not resolve within 12 weeks of last dose; recurrent grade 3 tumor site edema following tracheostomy |
| | 4 | Permanently discontinue | Permanently discontinue |
| All Other Drug—Related Toxicity[3] | 3 | Toxicity resolves to grade 0 -1 | Toxicity does not resolve within 12 weeks of last dose or inability to reduce corticosteroid to 10 mg or last of prednisone or equivalent per day |

| | | | |
|---|---|---|---|
| | | | within 12 weeks |
| | 4 | Permanently discontinue | Permanently discontinue |

**Note: Permanently discontinue for any severe or Grade 3 drug-related AE that recurs or any life-threatening event.**
1. For patients on Arm 2 who cross over to pembrolizumab with liver metastasis and who begin treatment with Grade 2 AST or ALT, if AST or ALT increases by greater than or equal to 50% relative to baseline and lasts for at least 1 week then patient should be discontinued.
2. If symptoms resolved within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate for the next scheduled dose.
3. Patients with intolerable or persistent Grade 2 drug-related AE may hold study medication at physician discretion. Permanently discontinue study drug for persistent Grate 2 adverse reactions for with treatment with study drug has been held, that do not recover to Grade 0-1 within 12 weeks of the last dose.

**6.2 Supportive Care Guidelines for Pembrolizumab** (see also dose modification Section 6.1 and Table 6.1) (11-MAR-2019)

See the pembrolizumab investigator brochure, available on the RTOG 3507 Foundation webpage, for additional information.

Patient should receive appropriate supportive care measures as deemed necessary by the treating investigator including, but not limited to, the items outlined below:

**6.2.1** Diarrhea/Colitis

Subjects should be carefully monitored for signs and symptoms of enterocolitis (such as diarrhea, abdominal pain, blood or mucus in stool, with or without fever) and of bowel perforation (such as peritoneal signs and ileus).

- All subjects who experience diarrhea/colitis should be advised to drink liberal quantities of clear fluids. If sufficient oral fluid intake is not feasible, fluid and electrolytes should be substituted via IV infusion. For Grade 2 or higher diarrhea, consider GI consultation and endoscopy to confirm or rule out colitis.
- For **Grade 2 diarrhea/colitis** that persists greater than 3 days, administer oral corticosteroids.
- For **Grade 3 or 4 diarrhea/colitis** that persists > 1 week, treat with intravenous steroids followed by high dose oral steroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

**6.2.2** Pneumonitis

- For **Grade 2 events**, treat with systemic corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- For **Grade 3-4 events**, immediately treat with intravenous steroids. Administer additional anti-inflammatory measures, as needed.

- Add prophylactic antibiotics for opportunistic infections in the case of prolonged steroid administration.

**6.2.3** Hypophysitis

- For **Grade 2** events, treat with corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.
- For **Grade 3-4** events, treat with an initial dose of IV corticosteroids followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks. Replacement of appropriate hormones may be required as the steroid dose is tapered.

**6.2.4** Hyperthyroidism or Hypothyroidism

- Thyroid disorders can occur at any time during treatment. Monitor patients for changes in thyroid function (at the start of treatment, periodically during treatment, and as indicated based on clinical evaluation) and for clinical signs and symptoms of thyroid disorders.
- **Grade 2** hyperthyroidism events (and **Grade 2-4** hypothyroidism):
    - In hyperthyroidism, non-selective beta-blockers (e.g. propranolol) are suggested as initial therapy.
    - In hypothyroidism, thyroid hormone replacement therapy, with levothyroxine or liothyroinine, is indicated per standard of care.
- **Grade 3-4** hyperthyroidism
    - Treat with an initial dose of IV corticosteroid followed by oral corticosteroids. When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.
- Replacement of appropriate hormones may be required as the steroid dose is tapered.

**6.2.5** Type 1 Diabetes Mellitus (if new onset, including diabetic ketoacidosis [DKA]) or **≥Grade 3 Hyperglycemia**, if associated with ketosis (ketonuria) or metabolic acidosis (DKA)

- For **T1DM** or **Grade 3-4 Hyperglycemia**
    - Insulin replacement therapy is recommended for Type I diabetes mellitus and for Grade 3-4 hyperglycemia associated with metabolic acidosis or ketonuria.
    - Evaluate patients with serum glucose and a metabolic panel, urine ketones, glycosylated hemoglobin, and C-peptide.

**6.2.6** Hepatic

- For **Grade 2** events, monitor liver function tests more frequently until returned to baseline values (consider weekly).
    - Treat with IV or oral corticosteroids
- For **Grade 3-4** events, treat with intravenous corticosteroids for 24 to 48 hours.
- When symptoms improve to Grade 1 or less, a steroid taper should be started and continued over no less than 4 weeks.

**6.2.7** Renal Failure or Nephritis

- For **Grade 2** events, treat with corticosteroids.
- For **Grade 3-4** events, treat with systemic corticosteroids.
- When symptoms improve to Grade 1 or less, steroid taper should be started and continued over no less than 4 weeks.

**6.2.8** Infusion Reaction

**6.2.8.1** Hypersensitivity infusion reactions should be reported to the sponsor within 24 hours of the event regardless of grade. The following AE terms constitute hypersensitivity infusion reactions:

- Allergic reaction
- Anaphylaxis
- Cytokine release syndrome
- Serum sickness
- Infusion reactions
- Infusion—like reactions

**6.2.8.2** Management of infusion reactions

Infusion reactions should be treated as summarized in Table 6.2 as follows:

Table 6.2 Management of infusion reaction

| | | |
|---|---|---|
| Grade 1<br>Mild reaction; infusion interruption not indicated; intervention not indicated | Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator. | None |
| Grade 2<br>Requires infusion interruption but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, IV fluids); prophylactic medications indicated for < =24 hrs | **Stop Infusion and monitor symptoms.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>If symptoms resolve within one hour of stopping drug infusion, the infusion may be restarted at 50% of the original infusion rate (e.g., from 100 mL/hr to 50 mL/hr).<br>Otherwise dosing will be held until symptoms resolve and the subject should be premedicated for the next scheduled dose.<br>**Subjects who develop Grade 2 toxicity despite adequate premedication should be permanently discontinued from further trial treatment administration.** | Subject may be premedicated 1.5h (± 30 minutes) prior to infusion of pembrolizumab with:<br><br>Diphenhydramine 50 mg po (or equivalent dose of antihistamine).<br><br>Acetaminophen 500-1000 mg po (or equivalent dose of antipyretic). |
| Grades 3 or 4<br><br>Grade 3:<br>Prolonged (i.e., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for other clinical sequelae (e.g., renal impairment, pulmonary infiltrates)<br><br>Grade 4:<br>Life-threatening; pressor or ventilatory support indicated | **Stop Infusion.**<br>Additional appropriate medical therapy may include but is not limited to:<br>IV fluids<br>Antihistamines<br>NSAIDS<br>Acetaminophen<br>Narcotics<br>Oxygen<br>Pressors<br>Corticosteroids<br>Epinephrine<br><br>Increase monitoring of vital signs as medically indicated until the subject is deemed medically stable in the opinion of the investigator.<br>Hospitalization may be indicated.<br>**Subject is permanently discontinued from further trial treatment administration.** | No subsequent dosing |
| Appropriate resuscitation equipment should be available in the room and a physician readily available during the period of drug administration. | | |

### 6.3 Radiation Therapy Management/Supportive Care Guideline

Radiation therapy toxicity management will be per institutional standards of practice, including but not limited to initial and ongoing assessment during SBRT, ENT evaluation and tracheostomy (including prophylactic tracheostomy).

## 7. ADVERSE EVENTS REPORTING REQUIREMENTS

### 7.1 Protocol Agents

Investigational Agents

The investigational agent administered in RTOG 3507 is pembrolizumab, which is being made available under an IND sponsored by RTOG Foundation and distributed by a third party drug distributor. For pembrolizumab, determination of whether an adverse event meets expedited reporting criteria, see the reporting table in section 7.4 of the protocol.

Commercial Agents

Not applicable

#### 7.1.1 Adverse Events for Investigational Study Agents

Investigators must obtain the current version of the pembrolizumab Investigator Brochure (IB) for comprehensive pharmacologic and safety information. The IB can be accessed on the RTOG Foundation 3507 protocol page of the RTOG website, www.rtog.org. Sites must use their username and password to access the protocol page and the IB.

#### 7.1.2 Adverse Events for Commercial Study Agents

**Not applicable**

### 7.2 Adverse Events (AEs)** (11-MAR-2019)

This study will use the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 for adverse event reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0.

Report all AEs regardless of relationship to protocol treatment or procedures from the time of consent until 90 days after last dose of pembrolizumab, then only report AEs reasonably related to protocol treatment. For patients randomized to Arm 2, SBRT only, report all AEs from time of consent until 30 days from end of SBRT, then only report AEs reasonably related to protocol treatment. Adverse events that meet seriousness and expedited reporting criteria should be reported per Section 7.4.

AEs and SAEs that occur from time of consent to time of registration should be recorded in the patient's study chart and then reported in RAVE after the patient is registered. In addition, during this timeframe SAEs that meet expedited reporting requirements must be submitted to RTOG within the designated timelines per Section 7.4. The SAE Report Form (found under RAVE forms on the study-specific page of the RTOG website www.rtog.org) must be manually completed and submitted to RTOG at RTOG3507SAE@acr.org.

#### 7.2.1 Definition of an Adverse Event (AE)

Any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related. Therefore, an AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not considered related to the medicinal (investigational) product (attribution of unrelated, unlikely, possible, probable, or definite). (International Conference on Harmonisation [ICH], E2A, E6).

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

AEs, as defined above, experienced by patients accrued to this protocol should be reported on the AE section of the appropriate case report form (see Section 12.1).

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

**7.2.2** Adverse Events of Clinical Interest

Report adverse events of clinical interest within 24 hours using the SAE report form in RAVE. RTOG will notify Merck within 2 business days.

Events of clinical interest for this trial include:

*Overdose*

An overdose of pembrolizumab is any dose of 1,000 mg or greater (≥5 times the indicated dose). In the event of overdose, the participant should be observed closely for signs of toxicity. Appropriate supportive treatment should be provided if clinically indicated.

The overdose without any associated clinical symptoms or abnormal laboratory results is reported as a "accidental or intentional overdose without adverse effect." If an adverse event(s) is associated with ("results from") the overdose, the adverse event(s) is reported as a serious adverse event, even if no other seriousness criteria are met.

*Elevated AST or ALT*

An elevated AST or ALT lab value that is greater than or equal to 3X the upper limit of normal and an elevated total bilirubin lab value that is greater than or equal to 2X the upper limit of normal and, at the same time, an alkaline phosphatase lab value that is less than 2X the upper limit of normal, as determined by way of protocol-specified laboratory testing or unscheduled laboratory testing* require 24 hour reporting to RTOG via the SAE report form.

*Note: These criteria are based upon available regulatory guidance documents. The purpose of the criteria is to specify a threshold of abnormal hepatic tests that may require an additional evaluation for an underlying etiology.

### 7.3 Serious Adverse Events (SAEs) (11-APR-2018)

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

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

- Death;
- A life-threatening adverse drug experience;
- Inpatient hospitalization or prolongation of existing hospitalization ≥24 hours;
- A persistent or significant disability/incapacity;
- A congenital anomaly/birth defect;
- Other serious/important medical events;
- Important medical events that may not result in death, be life threatening, or require hospitalization may be considered an SAE, when, based upon medical judgment, they may jeopardize the patient and may require medical or surgical intervention to prevent one of the outcomes listed in the definition.

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

**Note:** In addition to the above criteria, adverse events meeting either of the following criteria are reportable as SAEs to meet study requirements and, therefore, are considered serious:

- Is a new cancer (that is not a condition of the study);
- Is associated with an overdose.

### 7.4 Serious Adverse Event (SAE) Reporting Requirements (11-MAR-2019)

It is the responsibility of the investigator to document all adverse events which occur during the study. All serious adverse events that meet expedited reporting criteria defined in the reporting table below will be reported via the RTOG SAE Report Form in RAVE. RTOG will report unexpected and related SAEs to the FDA and Merck via the MedWatch Form per the requirements set forth in the Code of Federal Regulations, Section 312.32.

#### 7.4.1 Reporting SAEs

Expeditiously report SAEs, regardless of relationship to protocol treatment or procedures, according to the reporting table below from the time of consent until 90 days after last dose of pembrolizumab. After 90 days, only report SAEs reasonably related (possibly, probably, or definitely) to protocol treatment per the reporting table below. For patients randomized to Arm 2, SBRT only, expeditiously report SAEs from time of consent until 30 days from end of treatment, then only report SAEs reasonably related to protocol treatment per the reporting table below.

In addition, any SAEs which occur as a result of protocol specific diagnostic procedures or interventions also must be reported. NOTE: please see specific protocol exceptions to expedited reporting.

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

**All SAEs must be reported in RAVE using the SAE Report Form within the designated timeframe outlined in the reporting table below. RTOG will complete a preliminary review of the SAE details and will contact the site with queries as needed. RTOG will report the SAE to Merck global safety within two business days (no later than 3 calendar days) of notification of the event. RTOG will report to FDA per 21 CFR 312.**

*Pregnancy*

Pregnancies and infant exposures during breastfeeding that occur from the time of randomization through 120 days following cessation of pembrolizumab must be reported by the investigator. All reported pregnancies must be followed to the completion/termination of the pregnancy.

Patients who become pregnant during the study should discontinue the study immediately. Investigators should report the pregnancy, including a male participant's impregnation of his partner, within 24 hours of awareness as a grade 3 SAE coded in the CTCAE v.5 as "pregnancy, puerperium and perinatal conditions, other—pregnancy" on the SAE Report Form (in RAVE) and submit the Pregnancy Report Form in Rave within 14 days of notification. RTOG will report the pregnancy to Merck. Patients must be instructed to notify the investigator if it is determined after completion of the study that they become pregnant (including a male participant's impregnation of his partner) either during the treatment phase of the study or within 120 calendar days after the end of treatment. The pregnancy outcome for patients on study must be reported to RTOG as a serious adverse event. RTOG will report the status to Merck.

**For Safety Run-In**
**Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur within 90 Days of the Last Administration of the Investigational Agent/Intervention[1]**

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

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

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

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

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to RTOG via the SAE Report Form within the timeframes detailed in the table below.

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

**Expedited AE reporting timelines are defined as:**

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

[1]Serious adverse events that occur more than 90 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 3, 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

**Additional Inclusions to Expedited Reporting**: Hypersensitivity infusion reactions should be reported to the sponsor within 24 hours of the event regardless of grade. See Section 6.2.8.1 for what constitutes hypersensitivity infusion reactions. Adverse events of clinical interest should be reported to the sponsor within 24 hours regardless of grade (see Section 7.2.2).

**For Arm 1: SBRT + Pembrolizumab**

**Late Phase 2 and Phase 3 Studies: Expedited Reporting Requirements for Adverse Events that Occur within 90 Days of the Last Administration of the Investigational Agent/Intervention [1]**

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

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

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

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

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to RTOG via the SAE Report Form within the timeframes detailed in the table below.

<table>
<tr><th>Hospitalization</th><th>Grade 1 Timeframes</th><th>Grade 2 Timeframes</th><th>Grade 3 Timeframes</th><th>Grade 4 & 5 Timeframes</th></tr>
<tr><td>Resulting in Hospitalization ≥ 24 hrs</td><td colspan="3">10 Calendar Days</td><td rowspan="2">24-Hour 5 Calendar Days</td></tr>
<tr><td>Not resulting in Hospitalization ≥ 24 hrs</td><td colspan="2">Not required</td><td>10 Calendar Days</td></tr>
</table>

**Expedited AE reporting timelines are defined as:**

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

[1]Serious adverse events that occur more than 90 days after the last administration of investigational agent/intervention and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 4, and Grade 5 AEs

**Expedited 10 calendar day reports for:**

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

**Additional Inclusions to Expedited Reporting**: Hypersensitivity infusion reactions should be reported to the sponsor within 24 hours of the event regardless of grade. See Section 6.2.8.1 for what constitutes hypersensitivity infusion reactions. Adverse events of clinical interest should reported to the sponsor within 24 hours regardless of grade (see Section 7.2.2).

**For Arm 2: SBRT only**

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

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

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

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

**ALL SERIOUS** adverse events that meet the above criteria **MUST** be immediately reported to RTOG via the SAE Report Form within the timeframes detailed in the table below.

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

**Expedited AE reporting timelines are defined as:**

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

[1]Serious adverse events that occur more than 30 days after the last administration of investigational agent/intervention and have an attribution of **possible, probable, or definite** require reporting as follows:

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

- Unexpected Grade 4 and all Grade 5 AEs

## 8. REGISTRATION AND STUDY ENTRY PROCEDURES

### 8.1 Regulatory Requirements

See the study-specific guide on the RTOG Foundation 3507 protocol page of the RTOG website, www.rtog.org.

### 8.2 RT-Specific Pre-Registration Requirements

See the study-specific guide on the RTOG Foundation 3507 protocol page of the RTOG website, www.rtog.org.

### 8.3 Patient Enrollment

See the study-specific guide on the RTOG Foundation 3507 protocol page of the RTOG website, www.rtog.org for enrollment instructions.

## 9. DRUG INFORMATION

### 9.1 Pembrolizumab

To supplement the toxicity information contained in this document, investigators must obtain the current version of the Pembrolizumab IB for comprehensive pharmacologic and safety information.

**The IB can be accessed on the RTOG Foundation 3507 protocol page of the RTOG website, www.rtog.org. Sites must use their username and password to access the protocol page and the IB.**

Agent Information:
Refer to the Pharmacy Manual in Appendix IV for detailed agent information.

Drug Ordering and Accountability
See the study-specific guide on the RTOG Foundation 3507 protocol page of the RTOG website, www.rtog.org.

## 10. PATHOLOGY/BIOSPECIMENS

See Appendix II for specimen kit and processing instructions

### 10.1 Optional Specimen Collection for Banking (11-MAR-2019)

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

**Optional Study #1A: High Density of Tumor Infiltrating Immune Cells in HNSCC Tumor Microenvironment and Its Association With PD-1 Inhibitor Response**

**Optional Study #1B: 12-gene cytokine expression profile and its association with PD-1 inhibitor response**

**#1A** Specimens are being collected to test the hypothesis that high expression of PD1/PD-L1 and high density of tumor infiltrating immune cells in the microenvironment detected by mIHC will predict response given IR and PD-1 inhibitor.

**#1B** Specimens are being collected to test the hypotheses that the presence of the 12-gene cytokine expression profile in tumors will associate with the response to anti-PD1 therapy.

- Required Forms: RTOG Foundation 3507 ST form and pathology reports with accession number, date of procedure, and p16 staining result; any other personal health information (PHI) should be redacted.
- Shipping costs: Submitting site pays cost of shipping FFPE samples.
- Return Requests. Do not ship FFPE material that cannot be kept at the Biospecimen bank. All blocks will be punched prior to returning. Sites must submit a return request and provide a return airbill.

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

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

| Specimen Type | Collection Time Points | Collection Information and Requirements | Shipping |
|---|---|---|---|
| One H&E slide and one FFPE Block from Tumor (OPTIONAL for the patient). | Any archived tumor tissue obtained pre-SBRT. | H&E slide must correspond to the same Block being submitted. H&E slide can be a duplicate cut slide, does not have to be the diagnostic slide. If site is unable to submit whole blocks then two FFPE embedded 3mm punches with corresponding H&E is acceptable alternative. | Slide and block/punches shipped ambient. Use of cold packs is recommended during warm weather seasons. |

**Optional Study #2: Assessment of mutational landscape by whole exome sequencing**

Specimens are being collected to test the hypotheses that the presence of greater than 200 nonsynonymous mutations per tumor will associate with the response to anti-PD1 therapy.

- Required Forms: RTOG Foundation 3507 ST form and pathology reports with accession number, date of procedure, and p16 staining result; any other personal health information (PHI) should be redacted.
- Shipping: Whole blood must be frozen at -70C to -90C and shipped on Dry Ice. Whole blood kits and return labels for batch shipping frozen specimens can be requested in advance from the Biospecimen bank. Batch shipping with other cases is encouraged. Frozen shipments should only be made on Monday-Wednesday.
- Return Requests. Do not ship FFPE material that cannot be kept at the Biospecimen bank. All blocks will be punched prior to returning. Sites must submit a return request and provide a return airbill.

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

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

| Specimen Type | Collection Time Points | Collection Information and Requirements | Shipping |
|---|---|---|---|
| One H&E slide and one FFPE Block from Tumor | Any archived tumor tissue obtained pre-SBRT. | H&E and block can be in addition to, or the same FFPE samples submitted for optional study #1 above. OPTIONAL for the patient | Slide and block/punches shipped ambient. Use of cold packs is recommended during warm weather seasons. |
| Whole Blood in one EDTA tube. See Appendix II for instructions. (OPTIONAL for the patient) | Pre-treatment.<br><br>If site misses the pre-treatment collection, site may collect and submit the whole blood samples at any time during the study | Mix Blood and aliquot a minimum of 1.5 ml into each of three 2 ml cryovials. Freeze at -70C to -90C until shipped. | Shipped frozen on Dry Ice to Biospecimen Bank at UCSF |

## 11. SPECIAL STUDIES (NON-TISSUE)

Not applicable to this study.

## 12. MODALITY REVIEWS

### 12.1 Radiation Therapy Quality Assurance Reviews

The Radiation Oncology Co-Chairs, Shlomo Koyfman, MD and Quynh-Thu Le, MD, or RTOG Foundation approved designees will perform a pre-treatment review of each case's treatment plan data from each institution prior to the institution's delivering any treatment using SBRT. Sites must allow 3 business days for the complete case data to be received, processed and reviewed. If a revision and re-plan is necessary an additional 3 business days will be needed to complete another pre-treatment review of the resubmitted data.

The goal of the review is to evaluate protocol compliance. The scoring mechanism is: Per Protocol, Variation Acceptable, and Deviation Unacceptable.

### 12.2 Drug Quality Assurance Reviews (11-APR-2018)

The Principal Investigator/Medical Oncologist, Stuart J. Wong, MD, or RTOG Foundation approved designee will perform a Chemotherapy Assurance Review of all patients who receive or are to receive drug therapy in this trial. The goal of the review is to evaluate protocol compliance. The review process is contingent on timely submission of chemotherapy treatment data. The scoring mechanism is: **Per Protocol/Acceptable Variation, Unacceptable Deviation, and Not Evaluable**.

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

### 12.3 Surgical Quality Assurance Reviews

See Sections 3.2.5 and 3.3.8 for details.

## 13. DATA AND RECORDS

**This study will utilize Medidata Rave.** See the Data Management Plan in the study-specific guide on the RTOG Foundation 3507 protocol page of the RTOG website, www.rtog.org, for further details.

### 13.1 Summary of Data Submission and Dosimetry Digital Data Submission

See the study-specific guide on the RTOG Foundation 3507 protocol page of the RTOG website, www.rtog.org.

## 14. STATISTICAL CONSIDERATIONS

### 14.1 Study Design (11-MAR-2019)

**14.1.1** Stratification for Phase II

Patients will be stratified by having oropharyngeal with positive p16, oropharyngeal with negative p16 or non-oropharyngeal before being randomized between the 2 arms.

**14.1.2** Randomization for Phase II

The treatment allocation scheme described by Zelen (1974) will be used as it balances patient factors other than treating institution. The randomization ratio between the 2 arms will be 1:1.

### 14.2 Study Endpoints (11-MAR-2019)

**14.2.1** Run-In Component

Primary Endpoint

Dose-limiting toxicity (DLT), which is defined as:

- Any ≥ Grade 4 non-immune-related adverse event due to therapy, **except**:
  - Grade 4 hypomagnesemia, hypokalemia, or hypophosphatemia without life-threatening consequences, which corrects to Grade ≤ 2 with observation or replacement therapy;
  - Grade 4 infusion-related reaction (first occurrence and in the absence of steroid prophylaxis) that resolves within 6 hours with appropriate clinical management.
- Any ≥ Grade 3 immune-related due to systemic therapy adverse event that does not downgrade to Grade 2 within 3 days despite optimal medical management including systemic corticosteroids or does not downgrade to ≤ Grade 1 or baseline within 14 days. **Note, grade ≥ 3 colitis or pneumonitis, regardless of response to therapy, is a DLT.**

Adverse events will be graded according to NCI CTCAE version 5.0.

DLT Observation Window

The DLT observation period will start at the first dose of pembrolizumab and extend for 28 days after the completion of SBRT.

**14.2.2** Phase II

*Primary Endpoint:* Progression-free survival (PFS)

*Secondary Endpoints*

- Overall survival (OS);
- Acute toxicities (≤ 90 days after the start of radiation therapy) and late toxicities (> 90 days after the start of radiation therapy);
- Radiographic response, PFS and OS in patients who receive cross-over treatment to pembrolizumab following disease progression on SBRT alone;
- Correlative studies.

### 14.3 Primary Objectives Study Design (11-MAR-2019)

**14.3.1** Primary Hypothesis and Endpoints

For the phase II portion of the study, it is hypothesized that re-irradiation of SBRT plus anti-PD-1 antibody pembrolizumab will improve PFS after randomization for patients with locoregionally recurrent or second primary head and neck carcinoma, as compared with SBRT alone.

**14.3.2** How Primary Endpoints Will Be Analyzed

*Run-In Component*

Although PD-1 inhibition is not expected to increase the toxicity of radiation therapy, clinical trials of pembrolizumab combined with SBRT reirradiation HNSCC have not been conducted. In order to protect against unexpected problems a safety run-in analysis will be performed prior to proceeding to the phase II portion of the study. This safety analysis will occur after the first 6 analyzable patients are entered on the experimental arm; we will accrue 8 patients to ensure that there will be 6 analyzable patients. Pembrolizumab will be administered initially at the recommended phase II dose of 200 mg. The data that will be collected for analysis will include all the adverse events reported through 28 days after the completion of SBRT. If there are more than 2 dose limiting toxicities (DLTs) in the cohort of 6 patients, then pembrolizumab will be de-escalated by delaying first cycle of pembrolizumab until 7 days following the completion of SBRT. In the event of 0-2 DLT events, the study will proceed to the phase II portion of the study with the dose being tested. The probability of the SBRT + pembrolizumab arm being judged to be too toxic when the true toxicity rate is 45% or higher is at least 56%. If the true toxicity rate is 20% or lower, the probability that the therapy will be safe is 90%.

*Phase II*

The primary endpoint for the phase II portion of this study is progression-free survival (PFS). The study is designed for an improvement in the 1-year PFS from 25% to 45%. A difference in PFS of at least 20% at 1 year was chosen as the lowest acceptable PFS improvement after taking into consideration PFS rate seen in previous SBRT studies (Langer 2007, Unger 2010, Lartigau 2013). Under the assumption of exponential distribution for PFS time, this is corresponding to a median PFS comparison of 6.0 vs. 10.6 months, with a hazard ratio of 0.57 for PFS in favor of the experimental arm.

**Progression-Free Survival (PFS)** is defined as the time from randomization to the first documented progressive disease (PD) per RECIST 1.1 or death due to any cause, whichever comes first. Because disease progression is assessed periodically it is possible for disease progression to occur at a time between the last assessment, when disease progression was not present, and the assessment when disease progression was evident. For the primary endpoint analysis, the true date of disease progression will be approximated by the date of the first assessment at which PD is objectively documented per RECIST 1.1 or death due to any cause, whichever comes first. Data reported by sites on PD determination will be used for the primary endpoint analysis. PFS will be estimated using the Kaplan-Meier method. PFS at 1 year from the Kaplan-Meier curve with its respective 90% confidence interval based on a log-log transformation and Greenwood's formula will be also calculated. Patients who progress within 2 years after start of SBRT and who are then treated with pembrolizumab in the crossover cohort will have their outcomes separately investigated related to response rates of pembrolizumab.

**Overall survival (OS)** is defined as the time from randomization to death due to any cause. Study participants without documented death at the time of final analysis will be censored at the date of last follow-up. OS will be estimated using the Kaplan-Meier method. OS at 1 year from the Kaplan-Meier curve with its respective 90% confidence interval based on a log-log transformation and Greenwood's formula will be also calculated.

**14.3.3** Sample Size and Power Calculations for Phase II

The total sample size for phase II portion of the study is 102 patients, 51 per arm. Overall 89 PFS failures will be required for a one-sided type 1 error rate of 0.05 with 85% statistical power to detect the projected difference in PFS (median PFS from 6.0 months to 10.6 months, corresponding to a hazard ratio of 0.57), resulting in a required sample size of 102 analyzable patients for both arms.

## 14.4 Study Monitoring of Primary Objectives

**14.4.1** Analysis for Reporting the Initial Treatment Results

The analysis reporting these treatment results will be carried out after 89 PFS failures have been observed. At the specified accrual and event rates, it is anticipated that this analysis will occur approximately 4 years after accrual to the phase II portion of the study commences. All eligible and randomized patients will be included in the primary treatment analysis. Eligible and randomized patients who do not start protocol treatment will be included in the analysis under the intent-to-treat principle. The usual components of this analysis are:

- Tabulation of all cases entered and exclusion rates;
- Patient accrual rate;
- Distribution of important baseline prognostic variables;
- Frequency and severity of adverse events;
- Observed results with respect to the primary endpoints described above.

PFS rates will be estimated using the Kaplan-Meier method (1958). Hazard ratio for the treatment effect on PFS will be calculated using the stratified Cox proportional hazard model and tested using the stratified log-rank test at the significance level of 0.05 (one-sided), with the stratification factor as strata. A point-wise comparison will be performed to test PFS at 1 year between the 2 arms. Multivariable analysis adjusting for important pretreatment characteristics, such as age, p16 status, clinical stages, etc., will be conducted using the Cox proportional hazard model.

**14.4.2** Interim Analysis for the Data Monitoring Committee (DMC)

Interim reports will be prepared twice each year until the final analysis has been accepted for presentation or publication. In general, these reports will contain information about the accrual rate with projected completion date for the accrual phase, exclusion rates, pretreatment characteristics of patients accrued, and the frequency and severity of adverse events. The RTOG Foundation DMC will review the study twice a year with respect to patient accrual and morbidity. The DMC also will review the study on an "as needed" basis.

One interim futility analysis will be performed when 44 PFS events have been observed.

The analysis will be performed on an intent-to-treat basis, with all eligible cases included in the treatment arm to which they were randomized regardless of what treatment the patients actually received. The primary efficacy comparison will be tested. If the observed hazard ratio for PFS is $\geq 1.0$ favoring the SBRT alone arm, then early stopping will be considered, with the conclusion being that the experimental regimen would not be a candidate for further evaluation in a definitive phase III trial.

### 14.4.3 Study Monitoring for the Safety Run-in Component

After the start of the accrual, the study team, including the study chairs, study statisticians, data managers and protocol administrator, will hold monthly calls to review the overall conduct of the safety run-in component of the study. Data on treatment dose delivery, adverse events reported, patient demographics and eligibility will be assembled and reviewed. When a decision to de-escalate or continue a dose level must be made, the study team will hold a conference call to review information including the categorization and grading of reported adverse events, determination of the dose-limiting toxicities, etc. The decision to de-escalate or continue is made by consensus of the study team in accordance with the decision rules outlined in the protocol. At each meeting, consideration is also given to the rate of accrual. Brief minutes of each meeting will be written to document the review of information and any decision made.

## 14.5 Accrual/Study Duration Considerations

Based upon historical accrual rates for this patient population (3 patients per month), the projected accrual time is 34 months for the phase II portion of the study. The primary analysis for the phase II portion of the study is projected to be performed approximately 4 years after the start of accrual. Prior to the phase II portion of the study, 8-16 patients will be entered on the experimental arm for a run-in safety analysis.

## 14.6 Dose Level Guidelines (11-MAR-2019)

This safety analysis will occur after the first 6 analyzable patients are entered on the experimental arm; we will accrue 8 patients to ensure that there will be 6 analyzable patients. Pembrolizumab will be administered initially at the recommended fixed dose of 200 mg. If there are more than 2 dose limiting toxicities (DLTs) in the cohort of 6 patients, then the dose will be de-escalated. In the event of 0-2 DLT events, the study will proceed to phase II. (see the DLT definition in Section 14.2.1)

## 14.7 Secondary or Exploratory Endpoints (including correlative science aims) (11-MAR-2019)

Based on results from previous studies (Unger 2010, Lartigau 2013), it is estimated that the median survival time for the SBRT alone arm is about 12 months. Assuming that the projected hazard ratio of the pembrolizumab + SBRT arm with respect to the SBRT alone arm is around 0.75, by the time of the primary analyses, there will be approximately 75 deaths from the 102 randomized patients on both arms. OS rates will be estimated using the Kaplan-Meier method (1958). Hazard ratio for the treatment effect on OS will be calculated using the stratified Cox proportional hazard model and tested using the stratified log-rank test, with the stratification factor as strata. A point-wise comparison will be performed to test OS at 1 year between the 2 arms. Multivariable analyses adjusting for important pretreatment characteristics such as age, p16 status, clinical

stages, etc. will be conducted using the Cox proportional hazard model.

For toxicity analysis, only adverse events (AEs) assessed to be definitely, probably, or possibly related (if relationship is missing, it will be assumed to be definitely, probably, or possibly) to protocol treatment will be considered. The rates of adverse events in terms of $<$ versus $\geq$ grade 3 will be estimated using a binomial distribution along with their associated 95% confidence intervals and will be compared between the treatment arms using Fisher's exact test.

Patients from the SBRT alone arm who progress within 2 years after start of SBRT are allowed to cross over to receive pembrolizumab at disease progression. The efficacy of cross-over from the SBRT alone arm will be investigated, as evaluated by radiographic response rate, PFS and OS since the initial disease progression. PFS will be measured from the date of initial disease progression to the date of the first documented progressive disease (PD) per RECIST 1.1 after cross-over or death due to any cause, whichever comes first. OS will be measured from the date of initial disease progression to the date of death due to any cause. PFS and OS rates will be estimated using the Kaplan-Meier method. The incidence rates of radiographic response and toxicity will also be calculated.

Tumor infiltrating immune cell profile, cytokine profile, or whole exomes sequence profile from pre-radiation tumors for the pembrolizumab + SBRT arm (Arm 1) will be determined by mIHC, Nanostring, or NGS, respectively. The biomarker profiles that may associate with pembrolizumab + SBRT sensitivity will be generated by comparing profiles between patients with and without PFS events on Arm 1. Presence of the each selected profile also will be determined in pre-radiation tumors for the SBRT alone arm (Arm 2). Each molecular profiles will be summarized by means and standard deviations for each arm. Proportions of the tumors with each profile and associated 95% CIs will be summarized based on binomial distributions. Each profile status for each patient will be correlated with survival outcomes to examine its prognostic effects. PFS and OS will be evaluated using the Kaplan-Meier method (1958) by mutation status. Hazard ratios on the effect of each profile will be calculated using the Cox proportional hazard model and tested using the log-rank test. The adjusted effect of each profile can be estimated using the Cox proportional hazard model adjusting for covariates, such as age, smoking history, tumor stage, etc.

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**APPENDIX I** (11-APR-2018)

**Provisions for Cross-Over Treatment to Pembrolizumab Following SBRT Alone (Arm 2 Patients Experiencing Disease Progression)**

## 1.0 SUMMARY

**1.1** Patients on Arm 2 who experience progressive disease within 2 years after start of SBRT by definitions in section 4.1 and as described in Section 5.4.1.2, may cross over to pembrolizumab.

**1.2** Pembrolizumab will be administered as per Section 5.1.1, and treatment modifications/management as described in section 6.0. Pembrolizumab may continue for a total of up to 2 years.

**1.3** Pembrolizumab will be supplied to the patient free of charge by Merck via distribution by McKesson Specialty Health. See the study-specific guide on the RTOG Foundation 3507 protocol page of the RTOG website, www.rtog.org.

**1.4 Steps To Receive Pembrolizumab at Disease Progression**

**1.4.1** A Disease Assessment form is first completed electronically confirming progression.

**1.4.2** The treating institution will then electronically submit a Cross-Over Treatment Guideline Questionnaire, which will trigger an auto-generated email message transmitting a clinical drug request to McKesson Specialty Health. Drug supplies will not be sent until the form has been submitted.

**1.5** Toxicity and efficacy will be monitored for all patients as specified in the full protocol.

**1.6** Treatment on the cross-over study will continue as follows:

**1.6.1** Discontinuation Criteria Following Cross-Over to Pembrolizumab
The imaging studies used to define progression prior to cross over will be used for determination of new reference target lesion measurements. Repeat imaging of Chest, Abdomen, Liver, and Adrenal Glands will be required if not already obtained prior to cross-over. The Evaluation of Target and Response Definitions table in Section 4.1 will be used for response criteria for cross-over patients treated with pembrolizumab.

**1.6.2** If a patient achieves CR, PR, or SD as per Definition of Disease Assessment in section 4.1 then treatment with pembrolizumab will continue.

**1.6.3** If radiographic imaging shows Progressive Disease (PD) (RTF, RF, MF, or MD--see definitions section 4.1.1) then follow Delayed Immune Response Assessment (DIRA) below (see also section 5.4.1.1). If PD is confirmed following DIRA, then the patient should be discontinued form protocol treatment. If PD is not confirmed following DIRA, then protocol therapy and protocol assessments should continue.

Delayed Immune Response Assessment (DIRA)--If radiologic imaging shows PD, tumor assessment may be repeated by the site ≥4 weeks later in order to confirm PD with the option of continuing treatment per below while awaiting radiologic

confirmation of progression. If repeat imaging shows a reduction in the tumor burden compared to the initial scan demonstrating PD, treatment may be continued as per treatment calendar. If repeat imaging confirms progressive disease, then the date of PD will be considered the date of the initial scan suggesting PD and the patient will be discontinued from study therapy. In determining whether or not the tumor burden has increased or decreased, investigators should consider all target lesions as well as non-target lesions.

The decision to continue study treatment after the first evidence of PD is at the Investigator's discretion based on the clinical status of the patient as described in the Evaluation of Target and Response Definitions table in Section 4.1

Patients may receive study treatment while waiting for confirmation of PD if they are clinically stable as defined by the following criteria:

- Absence of signs and symptoms (including worsening of laboratory values) indicating disease progression
- No decline in Zubrod performance status
- Absence of rapid progression of disease
- Absence of progressive tumor at critical anatomical sites (e.g., cord compression) requiring urgent alternative medical intervention

## 2.0 PRE-TREATMENT EVALUATIONS/ELIGIBILITY GUIDELINES FOR ARM 2 PATIENTS CROSSING OVER TO PEMBROLIZUMAB AT DISEASE PROGRESSION

**2.1** Pre-therapy evaluations must occur as follows and as described in the table in Appendix IA:

**2.1.2** The following diagnostic evaluation is required:

- History/physical examination within 28 days prior to pembrolizumab start Examination by a Radiation Oncologist and Medical Oncologist within 28 days prior to pembrolizumab start;
- Contrast enhanced CT or MRI, of the tumor and neck within 28 days prior to pembrolizumab start;
- Chest CT scan or full body PET/CT within 28 days prior to pembrolizumab start;

**2.1.3** Zubrod Performance Status 0-1 within 28 days prior to pembrolizumab start;

**2.1.4** Adequate bone marrow, liver function, renal function, and laboratory parameters within 28 days prior to pembrolizumab start defined as follows:

- Hematologic: Absolute neutrophil count (ANC) $\geq$ 1,500 cells/mm$^3$, Platelets $\geq$ 100,000 cells/mm$^3$, Hemoglobin $\geq$ 9 g/dL
- Hepatic: Total bilirubin $\leq$ 1.5 x ULN OR Direct bilirubin $\leq$ ULN for subjects with total bilirubin levels $\geq$ 1.5 x ULN, AST (SGOT) and ALT (SGPT) $\leq$ 2.5 x ULN
- Creatinine $\leq$ 1.5 x ULN, OR measured or calculated creatinine clearance > 60 mL/min for subject with creatinine levels > 1.5 x institutional ULN [NOTE: Calculated creatinine per institutional standard; GFR may be used in place of

creatinine or CrCl]

**2.1.5** Negative serum pregnancy test within 3 days prior to pembrolizumab start for women of childbearing potential.

## 3.0 PEMBROLIZUMAB THERAPY

### 3.1 Treatment Specifications

The dose of pembrolizumab will be per Section 5.1. Monitoring and treatment modifications should be performed as outlined in Section 6 of the full protocol and Appendix IA below.

### 3.2 Agent Information

See protocol Section 9

### 3.3 Supply

Pembrolizumab will be supplied to the patient free of charge by Merck via distribution through McKesson Specialty Health. See the study-specific guide on RTOG Foundation 3507 protocol page of the RTOG website, www.rtog.org.

### 3.4 Accountability

Sites should start a study case-specific accountability record for the cross over portion of treatment.

## 4.0 ADVERSE EVENT REPORTING: See protocol section 7

**APPENDIX IA** (11-MAR-2019)

**Pre-Treatment Assessments for Arm 2 Patients Crossing Over to Pembrolizumab at Disease Progression**

| **Assessments** | **Prior to Pembrolizumab Start (calendar days)** |
|---|---|
| CBC w/diff & ANC | 28 days |
| Sodium, potassium, chloride glucose, calcium, magnesium, albumin. | 28 days |
| Creatinine or creatinine clearance | 28 days |
| Total bilirubin; AST, ALT | 28 days |
| TSH with reflex to T4 | 28 days |
| Serum pregnancy test (if applicable) | 3 days |
| CT or MRI of neck, with contrast | 28 days |
| PET/CT | Recommended 28 days |
| CT scan of chest (Not necessary if Whole-body PET is performed; see section 3.2 for further details) | 28 days |
| History/physical exam | 28 days |
| Performance status | 28 days |

**Assessments During Treatment for Arm 2 Patients Crossing Over to Pembrolizumab at Disease Progression**

| **Assessments** | **Prior to Each Treatment (every 3 weeks)** |
|---|---|
| Brief history/physical exam | X |
| Weight | X |
| Zubrod PS | X |
| CBC w/diff & ANC[a,c] | X |
| Sodium, potassium, chloride glucose, calcium, magnesium, albumin[a,c] | X |
| Serum creatinine or creatinine clearance[a,c] | X |
| Total bilirubin; AST, ALT[a,c] | X |
| TSH with reflex to T4[b,c] | Every 6 weeks |
| Tumor Imaging-CT of neck (or MRI), CT of chest and abdomen | Every 9 weeks |
| Adverse Event Eval, including mucosal assessment | X |

**[a] Pre-treatment lab assessments for cross-over can be used for the initial pembrolizumab dose.**

**[b] T3 and T3-resin uptake to be performed as necessary if abnormal thyroid screening tests are encountered.**

**[c] Within 3 days prior to pembrolizumab administration.**

**NOTE: For Follow-Up Assessments, please refer to the Follow-Up Assessment Table in Protocol Section 4.0**

**APPENDIX II** (11-MAR-2019)

**RTOG 3507: Kit and Processing Instructions for Whole Blood Collection and FFPE Punch Kits**

**This Kit is for collection, processing, storage, and shipping of <u>whole blood.</u>**

**<u>Kit contents</u>: Supplies for 1 case, 1 timepoint for Shipping Back to Bank**

- Three (3) 1 ml cryovials
- Biohazard bags (1)
- ST Form and Kit Instructions
- Return label for frozen specimen shipment
- Absorbent shipping material (1)
- 1 Styrofoam container (inner) and Cardboard shipping (outer) box
- UN1845 DRY Ice Sticker and UN3373 Biological Substance Category B Stickers

**<u>PREPARATION AND PROCESSING OF WHOLE BLOOD:</u> Sites are required to supply their own blood draw tubes unless otherwise noted in the protocol.**

**(A) <u>Whole Blood for DNA: Use 5 or 10 ml Purple Top EDTA tubes:</u>**

- ❑ Label three 2ml cryovials as necessary for the whole blood collected. Label them with the study and case number, collection date/time, and time point, and clearly mark cryovials "blood" or "WB". Do not collect more than 3 cryovials.

**<u>Process</u>:**

1. After collection, invert tube(s) multiple times to ensure adequate mixing of EDTA. Blood can also be mixed for 5 minutes on a mixer at room temperature.
2. Carefully pipette and aliquot a minimum of 1.5 ml blood the labeled cryovials as are necessary for the blood collected (up to 3). Make sure tubes are labeled as specified above.
3. Place cryovials into biohazard bag and immediately freeze tubes upright at -70 to -90° C. Store frozen until ready to ship on dry ice. See below for storage conditions

**PLEASE make sure EVERY SPECIMEN IS LABELED and include collection time point on ST Form.**

**<u>Freezing and Storage</u>:**

- ☐ Freeze Blood samples in a -80°C Freezer or on Dry Ice or snap freeze in liquid nitrogen.
- ❑ Store at –80°C (-70°C to -90°C) until ready to ship.
  If a -80°C Freezer is not available,
  - Samples can be stored short term in a -20°C freezer (non-frost free preferred) for up to one week (please ship out Monday-Wednesday only; Canada: Monday-Tuesday only).

  **<u>OR</u>:**
  - Samples can be stored in plenty of dry ice for up to one week, replenishing daily (please ship out on Monday-Wednesday only; Canada: Monday-Tuesday only).

  **<u>OR</u>:**

- Samples can be stored in liquid nitrogen vapor phase (ship out Monday-Wednesday only; Canada: Monday-Tuesday only).
- Please indicate on Specimen Transmittal Form the storage conditions used and time stored.

**Shipping/Mailing: Ship to the Biospecimen bank in each box.**

- Ship specimens on Dry Ice overnight **Monday-Wednesday (Monday-Tuesday from Canada)** to prevent thawing due to delivery delays. Saturday and holiday deliveries cannot be accepted.
- Include all required paperwork in sealed plastic bag taped on outside top of the Styrofoam box.
- Wrap frozen specimens of same type (i.e., all serum together, plasma together and whole bloods together) in absorbent shipping material and place each specimen type in a separate biohazard bag. Place specimen bags into the Styrofoam cooler and fill with plenty of dry ice (7-10 lbs/3.5kg minimum). ***Add padding to avoid the dry ice from breaking the tubes.***
- Place Styrofoam coolers into outer cardboard box, and attach shipping label and UN3373 and UN1895 dry ice stickers to outer cardboard box. Fill out the UN1895 Label COMPLETELY.
- *Multiple cases may be shipped in the same cooler, but make sure each one is in a separate bag and that there is enough room for plenty of dry ice.* ***Add padding to avoid the dry ice from breaking the tubes.***
- **For questions regarding collection, shipping or to order a Blood Collection Kit, please e-mail RTOG@ucsf.edu or call (415) 476-7864.**
- **For kit orders include the following information:** Ship to address; IRB approval in place; # patients already enrolled in study, date kit needed (allow 5-10 business days) and if site has access to a -80° C freezer for batch shipping.

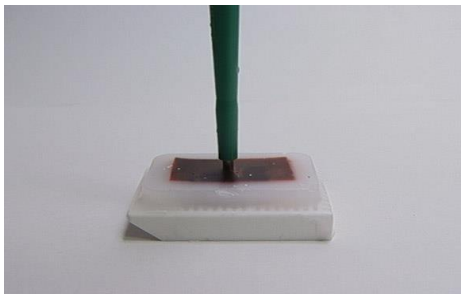
**Shipping Address:**

**Courier Address (FedEx, UPS, etc.): For all Frozen Specimens**
**Biospecimen Bank at UCSF**
**Dept of Radiation Oncology**
**2340 Sutter Street, Room S341**
**San Francisco, CA 94115**
**For questions: e-mail: RTOG@ucsf.edu or phone: 415-476-7864**

**RTOG 3507 FFPE SPECIMEN PLUG KIT INSTRUCTIONS**

This Kit allows sub-sampling of an FFPE block for submission to the Biospecimen Bank at UCSF. The plug kit contains a shipping tube and a punch tool.

Step 1: Have the local pathologist review the H&E slide and identify two areas with tumor to be punched.

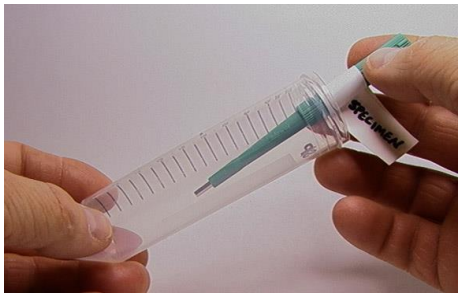


Step 2: Punch the block. If the block is stored cold, allow it to equilibrate for 30 minutes at room temperature. Place the 3mm punch tool on the paraffin block over the selected tumor area. (Ask a pathologist to select area with tumor.) Push the punch into the paraffin block. Twist the punch tool once around to separate the plug from the block. Then pull the punch tool out of the block. The punch should be filled with tissue sample. Repeat with a second punch tool.

Step 3: Embed both punches into a new paraffin block. Create new H&E from the new block. All embedded punches must be shipped with a corresponding H&E slide.

For sites unable to embed the punches at their facility proceed with Steps 1 & 2 above then Step 4.

Step 4: Label punch tool with proper specimen ID and block number. DON'T remove specimen from the punch unless you are embedding the punch in paraffin before shipping. (step 3 above)



Step 5:
A) For sites that are unable to embed the punches into blocks: Once punch tool is labeled, place in shipping tube and mail to address below. Please do not mix specimens in the same tube.
B) For sites submitting punch blocks with H&Es, please ship as for tissue blocks. Do not wrap blocks in bubble wrap.

We will remove core specimen from the punch, embed in a paraffin block, and label with specimen ID

*NOTE: If your facility is uncomfortable obtaining the plug but wants to retain the tissue block, please send the entire block to the Biospecimen Bank at UCSF and we will sample a plug from the block and return the remaining block to your facility. Please indicate on the submission form the request to perform the plug procedure and return of the block and include a return shipping label.
Ship: Specimen plug kit, specimen in punch tool, and all paperwork to the Biospecimen Bank at UCSF

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- For Questions regarding collection/shipping or to order an FFPE Specimen Plug Kit, please contact the Biospecimen Bank at UCSF: RTOG@ucsf.edu 415-476-7864

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

## APPENDIX III

| *Type of Initial Tumor* | *Type of Eligible Lesion* | *Patients will be stratified to:* |
|---|---|---|
| non-oropharynx | non-oropharynx or regional | non-oropharynx |
| oropharynx p16- | local or regional | oropharynx p16- |
| oropharynx p16+ | non-oropharynx ($2^{nd}$ primary) | non-oropharynx |
| oropharynx p16+ | local or regional | oropharynx p16+ |
| unknown primary | oropharynx p16 - (emerged) | oropharynx p16- |
| unknown primary | oropharynx p16+ (emerged) | oropharynx p16+ |
| unknown primary | regional p16- | oropharynx p16- |
| unknown primary | regional p16+ | oropharynx p16+ |

The table above is provided to assist in the assignment of p16 status for stratification. Utilize Column 1(describing the initial head and neck cancer diagnosis) and column 2 (describing the recurrent head and neck or new second primary tumor diagnosis), in order to determine the correct group to which the patient will be stratified. Testing for p16 on the archived original primary tumor specimen may be required if the patient had an oropharynx primary that was not originally tested for p16 status.

**APPENDIX IV** (11-APR-2018)

**PHARMACY MANUAL**
**PEMBROLIZUMAB (MK-3475)**

## 1. DRUG PREPARATION – PEMBROLIZUMAB (MK-3475) SOLUTION FOR INFUSION

### 1.1 DRUG PRODUCT

**Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/ 4 mL vial**

- Pembrolizumab (MK-3475) Solution for Infusion is a sterile, non-pyrogenic aqueous solution supplied in single-use Type I glass vial containing 100 mg/4 mL of pembrolizumab (MK-3475). The product is preservative-free, latex free solution which is essentially free of extraneous particulates.

- Cap color of MK-3475 (Pembrolizumab) 100 mg vials:

    - Both red, salmon, and blue color caps may be used. Though the cap color may be different, the product inside the vial is the same MK-3475 drug product.

- Pembrolizumab (MK-3475) Solution for Infusion vials are filled to a target of 4.25mL (106.25mg) to ensure recovery of 4.0mL (100mg).

### 1.2 STABILITY AND HANDLING OF DRUG PRODUCT

- **Pembrolizumab (MK-3475) Solution for Infusion, 100 mg/ 4 mL vial**: pembrolizumab (MK-3475) Solution for Infusion vials should be stored at refrigerated conditions 2 – 8 °C (36 - 46 °F) and protected from light.

- To determine whether to report a temperature excursion, the temperature values should be rounded to whole numbers.

- Rounding:

    - Decimal values from 0.1 to 0.4 round down to the nearest whole number (e.g., 8.3 = 8)
    - Decimal values from 0.5 to 0.9 round up to the nearest whole number (e.g., 8.7 = 9)

- Then compare the rounded values to the required temperature range to determine if there's an excursion.
- All temperature excursions, however small, must be reported by the site to the Clinical Complaint Intake mailbox (clinical.complaints.intake@merck.com) for investigation within

1 business day using the Clinical Supply Complaint & GCP Inquiry Form (excel version) and attached temperature data. Please also notify your CRA. All Clinical Supply stock that is subject to an investigation must be placed in quarantine and remain unavailable to dispense to patients until disposition has been determined.

- Please note temperature excursions after drug product is prepared are out of scope of the clinical complaint process. Please contact HQ clinical study team for further guidance.

**Note**: vials should be stored in the original box to ensure the drug product is protected from light.

- Pembrolizumab (MK-3475) infusion solutions should be prepared in **0.9% Sodium Chloride Injection, USP** (normal saline) or regional equivalent or 5% Dextrose Injection, USP (5% dextrose) or regional equivalent and the final concentration of pembrolizumab (MK-3475) in the infusion solutions should be between 1 mg/mL and 10 mg/mL.

- Please note, the preferred diluent is 0.9% Sodium Chloride and 5% dextrose is only permissible if normal saline is not available.

- Local guidelines should be followed for collection of diluent information such as manufacturer, lot and expiry. When the diluent is provided by Merck, the drug accountability log should be used for collection of diluent information.

- Pembrolizumab (MK-3475) SHOULD **NOT** BE MIXED WITH OTHER DILUENTS.

- Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. The 6 hour countdown begins when the vial is pierced, and includes room temperature storage of admixture solutions in the IV bags and the duration of infusion. (Please note this 6 hour timeframe is to provide a microbial control strategy. The microbial clock only starts when the product stopper is pierced and not when the vial is removed from the refrigerator.)

- In addition, IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours.

- If refrigerated, allow the IV bags to come to room temperature prior to use.

- Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration. Discard the drug product vial if visible particles are observed.

- Sites should follow their SOPs for drug transport and delivery, with all possible effort to minimize agitation of the drug product between the pharmacy and the clinic

- **DO NOT USE PEMBROLIZUMAB (MK-3475) IF DISCOLORATION IS OBSERVED**.

- **DO NOT SHAKE OR FREEZE THE VIAL(S).**

- **DO NOT ADMINISTER THE PRODUCT AS AN INTRAVENOUS (IV) PUSH OR BOLUS.**

- **DO NOT COMBINE, DILUTE OR ADMINISTER IT AS AN INFUSION WITH OTHER MEDICINAL PRODUCTS.**

- **Any departure from the guidance listed in this manual, must be discussed with sponsor**

## 1.3 DOSE CALCULATION

Follow directions applicable to the dose level of the study.

**200 mg Fixed Dose**

- **2 vials (100 mg/4 mL)**
- **8 mL total**

## 1.4 PREPARATION OF INFUSION SOLUTION

- Aseptic technique must be strictly observed throughout the preparation procedure

- Use of a biosafety cabinet is preferred since no anti-microbial preservative is present in the product; however, it is not mandatory unless specified by site standard operating procedure.

- Equilibrate required number of pembrolizumab MK-3475 vials to room temperature

- The preferred method of dose preparation is the volumetric method

- Sponsor recommends reconstitution and administration of pembrolizumab (MK-3475) that follows the parameters in this manual, however if use of gravimetric preparation is mandatory due to local site procedures, the following requirements must be satisfied and documented:
    - Draw the required volume up to 4.0 mL (100 mg) of pembrolizumab from each vial
    - Limit the number of punctures of each vial to one

- For gravimetric preparation method using density of pembrolizumab solution, a value of 1.03 g/mL should be used

- Merck does not support methods of preparation of non-Merck agents beyond what is stated in the product literature. Sites should reference the SmPCs or packaging inserts for preparation instructions

- If the site procedures require use of spikes or other closed system transfer devices (CSTDs), please contact sponsor for approval

- Choose a suitable infusion bag size so that the following conditions are met:
    - Concentration of pembrolizumab MK-3475 is between 1 mg/mL and 10 mg/mL
    - The infusion volume to bag capacity ratio should not be less than 0.3. In other words, the bag must be filled to at least 30% of its capacity.

- Choose a suitable infusion bag material. The bag may be empty or it may contain normal saline The following infusion bag materials are compatible with pembrolizumab (MK-3475):
    - PVC plasticized with DEHP
    - Non-PVC (polyolefin)
    - EVA
    - PE lined polyolefin

- Calculate the volume of pembrolizumab (MK-3475) and normal saline required to prepare the infusion (admixture) bag

  Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL)

  Volume of normal saline = total infusion volume – volume of pembrolizumab (MK-3475) from above

- If a bag pre-filled with normal saline is being used, remove the excess volume of normal saline using a sterile syringe (Polypropylene, latex-free) attached to a suitable needle. Keep in consideration the excess bag fill volume as well as the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution. This helps ensure that the concentration in the bag can be accurately calculated and falls within the acceptable range of 1 mg/mL to 10 mg/mL. If the site would like to proceed without removing excess saline they must ensure that the concentration of MK-3475 would still fall within acceptable range.

- If an empty bag is being used, withdraw the necessary volume of normal saline from another appropriate bag and inject into the empty bag. Keep in consideration the volume of pembrolizumab (MK-3475) to be added to the bag to prepare the infusion solution.

- Withdraw the required volume of pembrolizumab (MK-3475) from the vial(s) (up to 4 mL from each vial) using a sterile syringe attached to a suitable needle. The vial(s) may need to be inverted to remove solution.

  Volume of pembrolizumab (MK-3475) (mL) = required dose amount (mg) / 25 (mg/mL)

  **Note:** If it is necessary to use several vials, it is advisable to withdraw from several vials into a suitable size single use syringe using a new needle for each vial.

- Add the required pembrolizumab (MK-3475) into the infusion IV bag containing normal saline and gently invert the bag 10-15 times to mix the solution.

- Pembrolizumab (MK-3475) solutions may be stored at room temperature for a cumulative time of up to 6 hours. This includes room temperature storage of admixture solutions in the IV bags and the duration of infusion.

- In addition, IV bags may be stored under refrigeration at 2 °C to 8 °C (36 °F to 46 °F) ), total cumulative storage time at room temperature and refrigeration should not exceed 24 hours.

- If refrigerated, allow the IV bags to come to room temperature prior to use.

- If the infusion bag is excessively handled or shaken, particulates may form. If this occurs discard the bag and create a new bag taking care not to shake. Please contact your HQ clinical study team if particulates are noticed for further instructions. Be prepared to provide the following information:
    - IV bag manufacture, lot and expiry
    - Target volume of admixture solution in the IV bag (e.g. 100 mL, 200 mL etc.)
    - Amount of drug product (mL or mg) added to the bag
    - Drug product lot
    - Brief description of the nature of visible particles (color, shape, size, numbers etc.).

- **DO NOT FREEZE THE PEMBROLIZUMAB (MK-3475) INFUSION SOLUTION.**

- Discard any unused portion left in the vial as the product contains no preservative

### 1.5 ADMINISTRATION

- Pembrolizumab (MK-3475) infusions should be administered in 30 minutes, with a window of -5 and +10 minutes, using an infusion pump. A central catheter is not required for infusion; however if a subject has a central venous catheter in place, it is recommended that it be used for the infusion.

- The following infusion set materials are compatible with (pembrolizumab) MK-3475:

    - PVC Infusion set that is plasticized using DEHP
    - PVC and tri-(2-ethylhexyl) trimellitate (TOTM) infusion set
    - Polyethylene lined PVC infusion set
    - PVC Infusion set that is plasticized using Di-2-ethylhexyl Terephthalate (DEHT)
    - Polyurethane set

- A sterile, non-pyrogenic, low-protein binding 0.2 to 5 µm in-linefilter made of polyethersulfone (PES) must be used during administration to remove any adventitious particles. If the infusion set does not contain 0.2 to 5 µm in-line filter, it is recommended to use 0.2 to 5 µm add-on filter which may contain an extension line (Note: the materials of the extension line and filter should be as mentioned above).

- Attach the infusion line to the pump and prime the line, either with normal saline (at least 25 mL) or with infusion solution as per local SOP, before starting the infusion.

- Infuse pembrolizumab (MK-3475) over approximately 30 minutes, with a window of -5 and +10 minutes, through a peripheral line or indwelling catheter.

- Ensure the entire contents of the bag are dosed and all remaining drug solution in the line is administered through saline flushing.

- Document volume administered according to data entry guidelines.

- *In case of infusion reactions, infusion rate may differ; refer to protocol for specific instructions.*

- Whenever possible, the lowest infusion rate should be used that will allow completion of the infusion within the 30 minutes.

- **DO NOT CO-ADMINISTER OTHER DRUGS THROUGH THE SAME INFUSION LINE.**

- **UNUSED INFUSION SOLUTION FOR INJECTION SHOULD NOT BE USED FOR ANOTHER INFUSION OF THE SAME SUBJECT OR DIFFERENT SUBJECT.**

- **Caution: Do not shake the vials/bags otherwise this may result in formation of foam. If foam is noticed in either vial or bag, the drug product will need to be discarded. A new preparation should be made, taking care not to shake or agitate the product.**

### 1.6 RETURN AND DISCARDING OF PEMBROLIZUMAB (MK-3475) VIALS

Refer to the RTOG 3507 Study Guide for management instructions for unused pembrolizumab (MK-3475) Solution for Infusion vial(s)