Quad-Shot Radiotherapy in Combination with Immune Checkpoint Inhibition for Advanced/Recurrent Head and Neck Cancer
Wake Forest Baptist Comprehensive Cancer Center
WFBCCC60320

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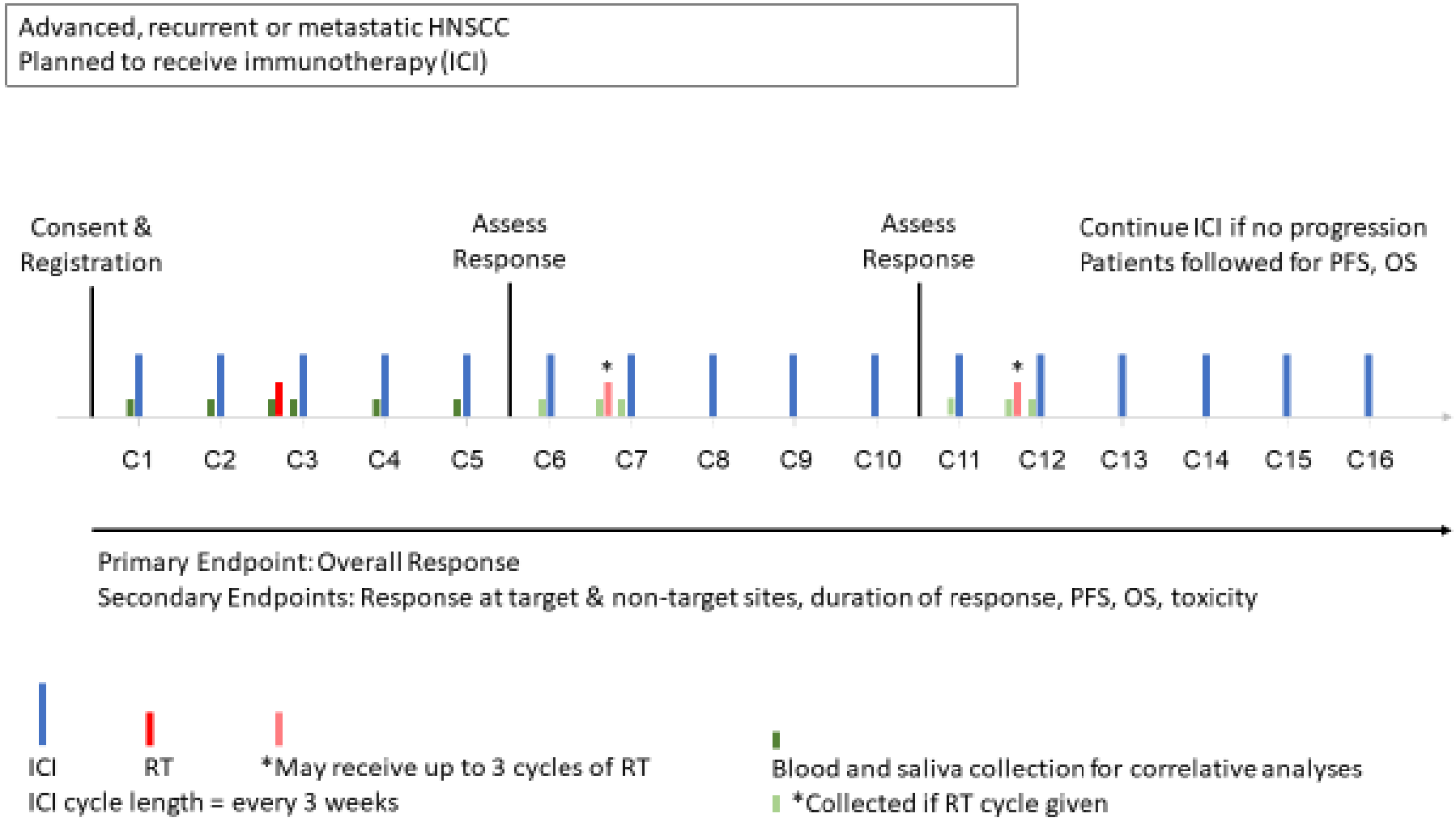
Advanced, recurrent or metastatic HNSCC
Planned to receive immunotherapy (ICI)
Consent & Registration
Assess Response
Assess Response
Continue ICI if no progression
Patients followed for PFS, OS
*
*
C1
C2
C3
C4
C5
C6
C7
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C9
C10
C11
C12
C13
C14
C15
C16
Primary Endpoint: Overall Response
Secondary Endpoints: Response at target & non-target sites, duration of response, PFS, OS, toxicity
ICI
RT
*May receive up to 3 cycles of RT
ICI cycle length = every 3 weeks
Blood and saliva collection for correlative analyses
*Collected if RT cycle given

1.0 Introduction and Background

1.1 Introduction

Head and neck cancer is diagnosed in approximately 65,000 patients per year in the United States and causes over 14,000 deaths per year (1). Approximately 90% of all head and neck cancers are squamous cell carcinoma (SCC) of the autodigestive mucosal lining, with other histologies including cutaneous SCC/basal cell carcinoma, melanoma, salivary gland tumors, and others. Generally, 10% of patients have metastatic disease at presentation, 20-30% will develop metastatic disease after definitive treatment, and 40-60% of patients progress within 3-years after curative therapy (2-7). Head and neck cancer is the cause of death in the majority of patients, whether locoregional disease (42.5%) or distant disease (17.9%) (8). Therefore, for those with recurrent or metastatic (R/M) head and neck squamous cell carcinoma (HNSCC), there is strong rationale for the use of second line strategies aimed to: 1) impact disease control on a systemic level and 2) maximize local control at the primary site.

Role for Immunotherapy in the Management of Head and Neck Cancer

The first-line standard of care (SOC) management for patients with recurrent/metastatic HNSCC includes combination platinum-based chemotherapy plus cetuximab, platinum-based chemotherapy plus pembrolizumab, pembrolizumab alone (for those with combined positive score [CPS] ≥1) (9). Second-line systemic therapy regimens include immune checkpoint inhibitors (ICIs) such as nivolumab or pembrolizumab as single agents after progression on platinum-based therapy (10-14). However, overall response rates (ORR) remain low (Table 1). Additional interventions are direly needed to improve rates of disease response with ICI (with or without chemotherapy), particularly at the primary tumor site, progression of which often leads to significant morbidity and possibly mortality.

Table 1: Overall Response Rates for Immunotherapy in R/M Head and Neck Squamous Cell Carcinoma

Study	Overall Response Rate	Agent
KEYNOTE-012	18%	Pembrolizumab
KEYNOTE-040	15%	Pembrolizumab
KEYNOTE-048	17% 36%	Pembrolizumab Pembrolizumab + chemotherapy
Checkmate 141	13%	Nivolumab

Quad-Shot Palliative Radiotherapy for Head and Neck Cancer

Palliative radiotherapy (RT) is a mainstay in the SOC treatment of recurrent or metastatic HNSCC (15). Palliative RT is primarily delivered using external-beam techniques over short courses using larger doses per fraction (≥3 Gy per fraction) than conventionally fractionated radiotherapy (1.8-2 Gy per fraction) in an attempt to effect local tumor regression and relief of

malignancy-related morbidity while limiting acute toxicity. While various fractionations have been reported for this purpose, the quad-shot regimen is a commonly used SOC radiotherapy schedule derived from prior palliative experiences in advanced pelvic malignancy (16, 17). This regimen is comprised of four 3.5 to 3.7-Gy fractions delivered twice daily (BID) over the course of two consecutive days (17-22). This regimen is associated with favorable palliative response rates at the treated site (Table 2). It can also be given concurrently with cytotoxic chemotherapy as reported in two studies detailed in Table 2 (21, 23). Additionally, due to the nature of the hypofractionated regimen and its delivery in split-course cycles, acute toxicity is modest.

Table 2: Quad-Shot Palliative Radiotherapy for Head and Neck Cancer

Study	Dose/Number of Fractions	Response Rate	Toxicity Rate	Note
Paris et al. (17)	14.8 Gy / 4	CR: 28% PR: 49%	N/A	1-3 cycles delivered with 3-4 weeks between cycles
Corry et al. (19)	14 Gy / 4	CR: 6% PR: 47%	Mucositis G1: 33%; G2: 11%; G3: 0%	1-3 cycles delivered with 3-4 weeks between cycles
Lok et al. (18)	14.8 Gy / 4	Pain response: 66%	Mucositis/dermatitis G3: 5%	1-3 cycles delivered with 3-4 weeks between cycles
Finnegan et al. (20)	14.8 Gy / 4	Pain CR: 39% Pain PR: 22%	Mucositis/dermatitis G2+: 26%/17%	1-3 cycles delivered with 3-4 weeks between cycles
Chen et al. (22)	14.8 Gy / 4	Palliative response: 83%	G3+: 9%	1-3 cycles delivered with 3-4 weeks between cycles.
Carrascosa et al.	14.8 Gy / 4	CR: 14% PR: 71%	Mucositis G3: 14%	1-3 cycles delivered with 3-4 weeks between cycles. Concurrent paclitaxel administered 1 hour prior to the first fraction of each cycle.
Gamez et al.	14.8 Gy / 4	CR: 24% PR: 62%	Mucositis/xerostomia G2: 35%	1-3 cycles delivered with 3-4 weeks between cycles. Concurrent carboplatin or cetuximab administered 1 hour prior to the first fraction of each cycle.

However, the quad-shot regimen is not sufficient to provide a definitive dose for durable disease control. The equivalent dose in 2-Gy fractions (EQD2) (assuming $\alpha/\beta=10$ [tumor]) for a single cycle is 16.9 Gy, 33.8 Gy for 2 cycles, and 50.7 Gy for 3 cycles. In prior studies, approximately

64% of patients are eligible to receive more than one quad-shot cycle, and palliative response rates correlate with number of cycles delivered: 55% for 1 cycle, 44% for 2 cycles, 88% for 3 cycles (correlation coefficient 0.29, p=0.012) (18). Despite its fairly favorable rates of achieving palliation at the treated site, this palliative (rather than curative) regimen is insufficient for long-term disease control at the target site. Duration of control (DOC) has been reported in a phase II study also included in Table 2 (19). Median DOC was 5.7 months at the primary and 5.2 months at nodal sites for those with CR/PR and 1.8 months at the primary and 9.5 months at nodal sites for those with stable disease. Considering that advancements in systemic therapy using ICI have prolonged median survival for this patient cohort to 12 months or more, most patients will experience local and/or regional progression that may result in significant morbidity or even mortality. Therefore, there is strong rationale for combination therapy with PRT + immunotherapy for both patients with recurrent, advanced, incurable local disease or metastatic disease with an untreated primary.

Rationale for the Combination of Quad-Shot Radiotherapy and Immunotherapy

The mechanism of conventionally-fractionated RT (1.8-2 Gy per fraction) is to induce clonogenic cell death in target cells by generating irreparable DNA damage. This is achieved indirectly through the generation of reactive oxygen species or directly by ionizing the DNA itself. For palliation, more hypofractionated regimens such as quad-shot are often utilized. It is now apparent in preclinical data that hypofractionated radiotherapy impacts many components of the tumor microenvironment including CD8 T-cells, dendritic cells/antigen-presenting cells, cytokine expression, MHC expression, regulatory T-cells, interferon-gamma expression, MHC expression, and others (24).

Immune checkpoint inhibition has been studied in combination with radiotherapy in preclinical models with the goal of increasing efficacy through RT-mediated increase in tumor immunogenicity (25). The combination of hypofractionated radiotherapy with anti-CTLA-4 antibodies or with PD-1 pathway blockade seems to enhance the effects of RT on tumor kill (26-28). RT has been shown to induce a significant increase in major histocompatibility complex (MHC) molecular expression in tumor cell lines and may re-sensitize tumors resistant to anti-PD-1 therapy causing regression in the target primary and non-irradiated (non-target) tumors (29). Additionally, tumor cells and other cells in the tumor microenvironment upregulate PD-L1 expression after RT, and the combination of ICI and RT may increase tumor kill by enhancing the efficacy of established T-cell mediated tumor immunity (30).

It appears that RT regimens using hypofractionated radiotherapy (a few fractions of doses higher than 2 Gy per fraction) improve tumor control when combined with ICI. Because T cells are sensitive to low doses of radiation, it is thought that conventionally fractionated radiotherapy over the course of several weeks may deplete the tumor immune response by local depletion of tumor-specific immune cells (31). In a mouse model, synergistic effects are increased when RT is given in the days prior to ICI or on the same day (32). Other preclinical evidence points to a benefit with ICI is administered prior to radiotherapy (30, 33). No clear clinical evidence exists to support the timing of ICI combined with RT, and currently, administration of ICI and radiotherapy on the same day is avoided given concerns for increased RT and immune-mediated adverse effects. It is worth noting that this practice is borne from an abundance of caution among oncologists and that it is not clear there is increased toxicity with concurrent administration of ICI

and RT—recent and ongoing clinical trials are testing the efficacy of conventionally fractionated concurrent with ICI (RTOG 3504: NCT02764593, HN-005: NCT03952585).

Current standards of care for patients receiving palliative RT while on ICI or chemo-ICI is to deliver the RT between administrations of systemic therapy. The half-life of pembrolizumab is on the order of 14-27 days and reaches steady-state after approximately 6 every-3-weekly cycles (34). We hypothesize that this combination and the timing detailed in the schema will provide sufficient PD-L1 blockade at the time of quad-shot radiotherapy. It has been suggested that RT doses in the range of 14-24 Gy in 2-3 fractions with concurrent ICI may be the most appropriate to utilize in further study (25). It is important to note that the quad-shot regimen falls close to this optimal range (14.4 Gy in 4 fractions). Additionally, prior reports indicate this dosage may be able to produce an abscopal effect in patients treated with ICI in metastatic head and neck squamous cell carcinoma (35). In all, this regimen is well-established in the literature to be safe and effective for head and neck cancer, can be delivered safely as RT alone or in combination with cytotoxic chemotherapy.

The combination of ICI with radiotherapy has been found to be safe for patients with intermediate- or high-risk squamous cell carcinoma of the head and neck in preliminary studies (36, 37). Early-phase studies have also demonstrated safety with hypofractionated (3 Gy per fraction) regimens and stereotactic body radiotherapy (SBRT), a technique which employs larger fraction sizes (8 Gy per fraction) (38, 39). The data presented herein provide strong rationale for further clinical study into the efficacy of quad-shot radiotherapy combined with ICI.

2.0 Objectives

This pilot study aims to assess the efficacy and tolerability of short-course quad-shot radiotherapy in combination with immunotherapy. Both of these standard-of-care treatments have the potential to act synergistically to improve response rates to systemic therapy. This study will study the effects of combining these standard treatments in a novel sequence. For the purposes of this study, the term immunotherapy will be used to specifically reference the use of the immune checkpoint inhibitor pembrolizumab.

The hypothesis is that the delivery of palliative quad-shot radiotherapy in combination with immunotherapy is feasible and improves the response rates at the treated site.

2.1 Primary Objective(s)

2.1.1 Measure the overall response rate for immunotherapy given with quad-shot radiotherapy

2.2 Secondary Objective(s)

2.2.1 Measure the response rate at the target lesion.

2.2.2 Measure the response rate at non-target sites *in patients with non-target sites*.

2.2.3 Evaluate the durability of response at the target lesion.

2.2.4 Evaluate progression-free survival.

2.2.5 Evaluate overall survival.

2.2.6 Assess the tolerability of the combination of quad-shot radiotherapy with immunotherapy in order to assess the feasibility of this treatment regimen.

2.3 Exploratory Objectives

2.3.1 Evaluate the effect of quad- shot administration on increasing the immune activation by treatment with pembrolizumab and investigate possible mechanisms.

3.0 Patient Selection

In this pilot study of quad-shot radiotherapy in combination with pembrolizumab immunotherapy, patients with advanced, recurrent or metastatic head and neck cancer will be enrolled. Participants will be identified and selected for eligibility screening during routine clinical practice in either the medical oncology or radiation oncology clinics at WFBCCC.

3.1 Inclusion Criteria

3.1.1 Advanced, recurrent or metastatic head and neck squamous cell carcinoma, as defined by clinical or pathological diagnosis of any of the following:

3.1.1.1 Locally advanced head and neck squamous cell carcinoma not suitable for curative local treatment.

3.1.1.2 Locally recurrent head and neck squamous cell carcinoma not suitable for curative local treatment within or outside a previously irradiated tissue.

3.1.1.3 Metastatic head and neck squamous cell carcinoma.

3.1.2 Target site in the head and neck region amenable to quad-shot palliative radiotherapy, for which palliative radiotherapy is recommended, as determined by the treating radiation oncologist.

3.1.3 Age 18 years or greater at time of registration

3.1.4 ECOG Performance Status of 0-2.

3.1.5 Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.

3.1.6 Ability to understand and the willingness to sign an IRB-approved informed consent document (either directly or via a legally authorized representative).

3.1.7 Willingness to provide blood and saliva samples for exploratory research purposes

3.1.8 Organ and Marrow Function as defined below:

3.1.8.1 Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L

3.1.8.2 Platelet count ≥ 100 x 10^9/L

3.1.8.3 Hemoglobin ≥ 9.0 g/dL

3.1.8.4 Serum bilirubin ≤ 1.5 x ULN (institutional upper limit of normal)

3.1.8.5 AST and ALT ≤ 2.5 x ULN (institutional upper limit of normal)

3.1.8.6 Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance:

Males:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females:

$$\text{Creatinine CL (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{Age})}{72 \times \text{serum creatinine (mg/dL)}} \times 0.85$$

3.2 Exclusion Criteria

3.2.1 Radiation therapy to the planned quad-shot radiotherapy target region within 30 days of registration.

3.2.2 Prior radiotherapy to the head and neck that precludes safe delivery of study radiotherapy, as determined by the treating radiation oncologist.

3.2.3 Active medical conditions that are contraindications to study radiotherapy (i.e. scleroderma), as determined by the treating radiation oncologist.

3.2.4 Pregnant or lactating women are excluded from this study because radiotherapy is contraindicated in pregnancy and because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with immunotherapy.

3.2.5 Participation in another clinical study with an investigational product during the last 3 months.

3.2.6 Any previous treatment with a PD1 or PD-L1 inhibitor.

3.2.7 Any anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) within the last 30 days. Note: this excludes palliative radiotherapy to the non-target site.

3.2.8 Mean QT interval corrected for heart rate (QTc) ≥470 ms.except for patients with pacemaker who have a paced ventricular rhythm

3.2.9 Current or prior use of immunosuppressive medication within 30 days, with exceptions of intranasal and inhaled corticosteroids, a brief, non-sustained corticosteroids treatment for incidental problems such as allergies (at the discretion of the treating physician) or sustained systemic corticosteroids treatment at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid except for s short course of prednisone that is prescribed for acute allergic situations or for prevention of an allergy to contrast substance utilized for imaging studies.

3.2.10 Any unresolved toxicity (>CTCAE grade > 2) from previous anti-cancer therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy).

3.2.11 Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1.

3.2.12 Active or prior documented autoimmune disease within the past 2 years
NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.

3.2.13 Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).

3.2.14 History of primary immunodeficiency.

3.2.15 History of allogeneic organ transplant.

3.2.16 History of hypersensitivity to any excipient in pembrolizumab.

3.2.17 History of pneumonitis or interstitial lung disease.

3.2.18 Subjects with uncontrolled seizures.

3.2.19 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses, evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.

3.2.20 Known history of active tuberculosis.

3.2.21 Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving pembrolizumab.

3.2.22 Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.

3.3 Inclusion of Women and Minorities

Men and women of all races and ethnicities who meet the above-described eligibility criteria are eligible to participate in this study.

Based on WFBCCC population estimates, we expect approximately 30% of participants to be women. Similarly, we expect approximately 1% of study participants to be Hispanic/Latino. We plan to enroll at least 15% Black or African American. Should we not meet or exceed these estimates, the PI will engage the Cancer Center Health Equity Advisory Group to discuss strategies to enhance recruitment in these target populations.

4.0 Methods

4.1 Registration Procedure

All patients entered on any WFBCCC trial, whether treatment, companion, or cancer control trial, **must** be linked to the study in EPIC within 24 hours of Informed Consent. Patients **must** be registered prior to the initiation of treatment.

You must perform the following steps in order to ensure prompt registration of your patient:

1. Complete the Eligibility Checklist (Appendix A)
2. Complete the Protocol Registration Form (Appendix B)
3. Alert the Cancer Center registrar by phone, *and then* send the signed Informed Consent Form, Eligibility Checklist and Protocol Registration Form to the registrar, either by fax or e-mail.

*Protocol Registration is open from 8:30 AM - 4:00 PM, Monday-Friday.

4. Fax/e-mail ALL eligibility source documents with registration. Patients **will not** be registered without all required supporting documents.

Note: If labs were performed at an outside institution, provide a printout of the results. Ensure that the most recent lab values are sent.

To complete the registration process, the Registrar will:

- assign a patient study number
- register the patient on the study

4.2 Study Design

This is a single-arm, non-randomized pilot study to evaluate the efficacy and tolerability of combination of **two standard of care interventions** (quad-shot palliative radiotherapy and pembrolizumab immunotherapy) for patients with advanced/recurrent/metastatic head and neck cancer.

Fifteen patients will be enrolled who have no curative localized treatment options, are eligible for palliative immunotherapy (pembrolizumab), have a lesion that can be targeted by radiotherapy, and are eligible for palliative radiotherapy as recommended by their radiation oncologist.

Patients eligible for this study will be those scheduled to receive palliative immunotherapy with the immune checkpoint inhibitor pembrolizumab (which is standard of care) for advanced, R/M head and neck SCC according to standard of care practice. They will also be eligible for palliative quad-shot radiotherapy according to the standard of care for advanced/recurrent/metastatic HSNCC. Quad-shot radiotherapy will be applied between immunotherapy cycle 2-3 or between immunotherapy cycle 3-4, within the last week of the cycle, and not to be delivered on the same day as ICI administration. Up to two additional quad-shot cycles will be delivered between cycles 6-7 or 7-8 (prior to cycle 8) and 11-12 or 12-13 (prior to cycle 13) of immunotherapy. The additional quad-shot treatments will be delivered in a similar fashion, in the last week of the ICI cycle.

Restaging imaging with CT, MRI or PET/CT will be obtained every 5-6 immunotherapy treatments. For the purposes of lesion measurements, follow-up imaging must be performed using the same modality (CT or MRI) as was used for initial baseline imaging. PET/CT may be utilized for follow-up imaging at the clinician's discretion. The maximum response in the targeted lesion and in the non-targeted lesions will be assessed. Subsequent immunotherapy cycles will be delivered after quad-shot radiotherapy until tumor progression or treatment intolerance.

Palliative local (non-systemic) interventions to other sites that are not quad-shot radiotherapy target sites is allowable while on study protocol treatment for the management of cancer symptoms. This should not be utilized for progression of disease at that site.

The study treatment portion ends for all patients with the last administration of the immunotherapy.

We will monitor and document clinical toxicity per NCI Common Terminology Criteria for Adverse Events version 5.0 during the treatment and for two additional visits 30 days apart from the end of treatment with immunotherapy. Subjects who decline to return to the site for evaluations will be offered follow-up by phone up to 2 months as an alternative and the PI will make every effort to collect toxicity data from medical records.

Patients will be subsequently followed for progression-free survival and overall survival outcomes. Subsequent visits can be accomplished in person or over the phone and clinical and imaging data will be collected from medical records as available.

Patient-reported outcomes will be obtained at each time point using a tailored checklist of PRO-CTCAE head and neck cancer-specific items.

Saliva and blood for correlative studies will be collected before each treatment with immunotherapy for the first 5 administrations and before the quad-shot administration. Saliva and blood samples will only need to be collected on the first day of Quadshot treatment. In the cases in which the patients will receive a 2nd quad-shot and possibly a third quad-shot, blood and saliva will be collected before the respective radiation treatments as well as before the immunotherapy cycles that proceed and follow the quad-shot treatments.

PD-L1 receptors will be tested in all patients as per standard of care. Next generation sequencing is encouraged and will be done whenever possible from the blood or tumor if available.

If any patient does not complete the study treatment and investigations, the patient will be replaced.

4.3 Radiotherapy

4.3.1 Patient Positioning and Simulation: Patients will be simulated using CT simulation with or without contrast at the discretion of the treating physician. Immobilization will be employed at the discretion of the treating radiation oncologist.

4.3.2 Target Delineation:
- Gross Tumor Volume (GTV): the target lesion will be identified and delineated as GTV.
- Clinical Target Volume (CTV): areas at risk of subclinical disease around the GTV may be delineated at the discretion of the treating radiation oncologist.
- Planning Target Volume (PTV): 0.3-1 cm isotropic expansion from the GTV or CTV (if present).
- Diagnostic imaging including but not limited to CT, MR, and PET/CT imaging may be utilized to guide target delineation

4.3.3 Radiotherapy Planning:
- Each cycle of quad-shot radiotherapy will be comprised of 14.8 Gy in 4 fractions (3.7 Gy per fraction) delivered twice daily (at least 6 hours apart) over two consecutive days.
- All patients will receive 1 cycle of quad-shot radiotherapy between ICI cycles 2-3.
- Subsequent cycles may occur between immunotherapy cycles 6-7 and 11-12, if more than 1 cycle can be safely delivered at the discretion of the treating radiation oncologist. The eligibility for subsequent cycles will be at the discretion of the treating radiation oncologist.
  Therefore, the total prescription dose will be:
  - 14.8 Gy in 4 fractions for those that complete 1 cycle (all patients will receive 1 cycle)
  - 29.6 Gy in 8 fractions for those that complete 2 cycles
  - 44.4 Gy in 12 fractions for those that complete 3 cycles
- Upon planning the initial cycle of quad-shot radiotherapy, a composite plan will be generated to assess the total dose to the target/organs at risk (see below).
  - If deemed appropriate by the treating radiation oncologist, the same plan may be delivered for up to 3 cycles.
  - If deemed appropriate by the treating radiation oncologist, re-simulation may be performed in order to plan subsequent cycles. This may be necessary to account for anatomic changes that may have occurred in the interim (between quad-shot cycles) which would otherwise impact dose to the target or organs at risk.

4.3.4 Organs at Risk (OAR): Organs at risk will vary depending on the location of the target lesion and will be delineated at the discretion of the treating radiation oncologist. No target or normal tissue constraints are mandated by this protocol. However, optional clinical goals are below:

Structure	**Treatment Planning Goals**	**Treatment Planning Limit (if target is close to structure, higher doses may be accepted)**
Spinal Cord	Max dose ≤ 37.2 Gy	same
Spinal Cord + 5mm	Max dose ≤ 39.2 Gy	39.2-40.6Gy to <0.03cc
Brachial Plexus	No more than 5% >44.6 Gy	No more than 5% >49.2 Gy
	Max dose ≤47.4 Gy	Max dose ≤50Gy
GTV	97% of GTV receives the prescription dose	95% of GTV receives the prescription dose
	maximum dose no more than 110% of the prescription dose	maximum dose no more than 115% of the prescription dose
	100% of GTV receives 95% of prescription dose	99% of GTV receives 93% of prescription dose
Parotid gland ipsilateral to primary tumor site[a]	Mean dose <26 Gy	Mean dose <30 Gy
Parotid gland contralateral to primary tumor site[a]	Mean dose <25.3 Gy	Mean dose <31.8 Gy
Constrictors[a]	Mean dose <37.2 Gy; V39.6 < 33%; V44.5 <15%	Mean dose <44.5 Gy; V46.9 <50%;
Larynx[a]	Mean dose <28.2 Gy	Mean dose <37 Gy
Esophagus[a]	Mean dose <28.1Gy; no hot spots in the esophagus	Mean dose <31.2 Gy; no hot spots in the esophagus
Lips[a]	Mean dose <20 Gy	Mean dose <25 Gy
Oral Cavity[a]	Mean dose <28.1 Gy; avoid hot spots >44.5 Gy	Mean dose <34.2 Gy; avoid hot spots >44.5 Gy
Mandible[a]	V44.5 <20%; Max 47.4 Gy to mandible	V44.5 <20%; Max 47.4Gy; minimize hot spots in the mandible
Submandibular gland(s) [a]	Mean <33.6 Gy	None
[a] GTV involving a non-critical OAR will be excluded from OAR contour – if applicable, OAR_x structure contour will represent X-GTV.		

4.3.5 Radiotherapy Delivery:

- External beam radiotherapy (photon or electron) will be delivered using 3D-conformal or intensity-modulated radiotherapy according to the treating radiation oncologist.
- Image guidance will be performed at the discretion of the treating physician.
- One cycle of quad-shot radiotherapy will be comprised of 14.8 Gy in 4 fractions (3.7 Gy per fraction) delivered twice daily (at least 6 hours apart) over two consecutive days.

4.3.6 Radiotherapy Timing:

- Radiation Therapy will be given as outlined in the Study Schema and according to the Study Calendar in Section 6.1:
    - Quad-shot Cycle #1: prior to cycle 4 (between pembrolizumab cycle 2-3 or 3-4) for all patients
    - Quad-shot Cycle #2 (if delivered): prior to cycle 8 (between pembrolizumab cycles 6-7 or 7-8)
    - Quad-shot Cycle #3 (if delivered): prior to cycle 13 (between pembrolizumab cycles 11-12 or 12-13).
- Radiotherapy is **NOT** to be given on the same day as immunotherapy/ICI infusion.
- Outside of this restriction, the timing of the delivery of 4 radiotherapy fractions that make up each cycle is not required.
- Though specific days are not mandated, it is **strongly recommended** that at least 1 day of the two consecutive days (including 2 of the 4 planned RT fractions per cycle) falls within 7 days prior to the delivery of an immunotherapy infusion.

4.4 Immunotherapy

Systemic immunotherapy will be delivered according to the standard of care for patients with recurrent/metastatic head and neck cancer.

4.4.1 Pembrolizumab Formulation/packaging/storage

Pembrolizumab will be obtained, stored, and administered in accordance with institutional guidelines.

4.4.2 Pembrolizumab Doses and treatment regimens

Pembrolizumab 200 mg will be given every 3 weeks to tumor progression or treatment tolerance.

4.4.3 Preparation of Pembrolizumab doses for administration with an IV bag

4.4.3.1 The dose of pembrolizumab for administration must be prepared by the Investigator's or site's designated IP manager using aseptic technique. Total time from needle puncture of the pembrolizumab vial to the end of administration should not exceed: 24 hours at 2°C to 8°C (36°F to 46°F) or 8 hours at room temperature (up to 25°C (77°F)). If in-use storage time exceeds these limits, a new dose must be prepared from new vials. Infusion solutions must be allowed to equilibrate to room temperature prior to commencement of administration.

4.4.3.2 Pembrolizumab will be administered at room temperature (approximately 25°C) by controlled infusion via an infusion pump into a peripheral or central vein. Following preparation of pembrolizumab, the entire contents of the IV bag should be administered as an IV infusion over approximately 30 minutes (±5 minutes), using a 0.2, or 0.22-µm in-line filter. Less than 25 minutes is considered a deviation.

4.4.3.3 The IV line will be flushed with a volume of IV solution (0.9% [w/v] saline) equal to the priming volume of the infusion set used after the contents of the IV bag are

fully administered, or complete the infusion according to institutional policy to ensure the full dose is administered and document if the line was not flushed.

4.4.3.4 Standard infusion time is 30 minutes. However, if there are interruptions during infusion, the total allowed time should not exceed 8 hours at room temperature.

4.4.4 Monitoring of dose administration

4.4.4.1 Subjects will be monitored before, during and after the infusion with assessment of vital signs at the times specified in the Schedule of Assessment. Subjects are monitored (pulse rate, blood pressure) every 30 minutes during the infusion period (including times where infusion rate is slowed or temporarily stopped).

4.4.4.2 In the event of a ≤Grade 2 infusion-related reaction, the infusion rate of study drug may be decreased by 50% or interrupted until resolution of the event (up to 4 hours) and re-initiated at 50% of the initial rate until completion of the infusion. For subjects with a ≤Grade 2 infusion-related reaction, subsequent infusions may be administered at 50% of the initial rate. Acetaminophen and/or an antihistamine (e.g., diphenhydramine) or equivalent medications per institutional standard may be administered at the discretion of the investigator. If the infusion-related reaction is Grade 3 or higher in severity, study drug will be discontinued. The standard infusion time is thirty minutes, however if there are interruptions during infusion, the total allowed time from infusion start to completion of infusion should not exceed 8 hours at room temperature, with maximum total time at room temperature not exceeding 8 hours (otherwise requires new infusion preparation).

4.4.4.3 As with any antibody, allergic reactions to dose administration are possible. Appropriate drugs and medical equipment to treat acute anaphylactic reactions must be immediately available, and study personnel must be trained to recognize and treat anaphylaxis. The study site must have immediate access to emergency resuscitation teams and equipment in addition to the ability to admit subjects to an intensive care unit if necessary.

4.4.5 Accountability and dispensation

Drug accountability logs will be maintained for the investigative agent used under this protocol. These logs shall record quantities of study drug received and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the medication.

4.4.6 Dose Modification and Toxicity Management

4.4.6.1 For adverse events (AEs) that are considered at least partly due to administration of pembrolizumab, the following dose adjustment guidance may be applied:

4.4.6.1.1 Treat each of the toxicities with maximum supportive care (including holding the agent suspected of causing the toxicity where required). Isolated increase in amylase has been noted after radiotherapy for the head and neck cancer, being released

from the salivary glands included in the radiation field. In addition, asymptomatic increase in the lipase has been reported. If the patient does not have symptoms of pancreatitis, treatment with pembrolizumab does not need to be stopped when increase in amylase and/or lipase are identified. Follow up of the lab values until normalization is recommended.

4.4.6.1.2 If the symptoms promptly resolve with supportive care, consideration should be given to continuing the same dose of pembrolizumab along with appropriate continuing supportive care.

4.4.6.1.3 Otherwise, pembrolizumab should be permanently discontinued. Dose reductions are not permitted.

4.4.6.2 Based on the mechanism of action of pembrolizumab leading to T-cell activation and proliferation, there is the possibility of observing immune related Adverse Events (irAEs) during the conduct of this study. Potential irAEs include immune-mediated enterocolitis, dermatitis, hepatitis, and endocrinopathies. Subjects should be monitored for signs and symptoms of irAEs. In the absence of an alternate etiology (e.g., infection or PD) signs or symptoms of enterocolitis, dermatitis, hepatitis, and endocrinopathy should be considered to be immune-related.

4.4.6.3 All toxicities will be graded according to NCI CTCAE v 5.0.

4.4.7 Restrictions during the study

4.4.7.1 Contraception

Females of childbearing potential who are sexually active with a nonsterilised male partner must use 2 methods of effective contraception from screening, and must agree to continue using such precautions for 180 days after the final dose of investigational product. Periodic abstinence, the rhythm method, and the withdrawal method are not acceptable methods of birth control.

- Females of childbearing potential are defined as those who are not surgically sterile (i.e., bilateral tubal ligation, bilateral oophorectomy, or complete hysterectomy) or postmenopausal (defined as 12 months with no menses without an alternative medical cause).
- Subjects must use 2 acceptable methods of effective contraception as described in the table below.
- Nonsterilised males who are sexually active with a female partner of childbearing potential must use 2 acceptable methods of effective contraception (see Table 1) from Day 1 and for 90 days after receipt of the final dose of investigational product.

Effective methods of contraception (two methods must be used)

Barrier Methods	Intrauterine Device Methods	Hormonal Methods
Male condom plus spermicide	Copper T	Implants
Cap plus spermicide	Progesterone T[a]	Hormone shot or injection
Diaphragm plus spermicide	Levonorgestrel-releasing intrauterine system (e.g., Mirena®)[a]	Combined pill Minipill Patch

[a] This is also considered a hormonal method.

4.4.7.2 Blood donation:

Subjects should not donate blood while participating in this study and for at least 90 days following the last infusion of pembrolizumab.

4.4.7.3 Concomitant treatments

Permitted concomitant medications
Investigators may prescribe concomitant medications or treatments (e.g., acetaminophen, diphenhydramine) deemed necessary to provide adequate prophylactic or supportive care except for those medications identified as “excluded” as listed below.

Excluded Concomitant Medications
The following medications are considered exclusionary during the study.

1. Any investigational anticancer therapy
2. Any concurrent chemotherapy, radiotherapy (except palliative radiotherapy), immunotherapy, biologic or hormonal therapy for cancer treatment. Concurrent use of hormones for noncancer-related conditions (e.g., insulin for diabetes and hormone replacement therapy) is acceptable.
3. Immunosuppressive medications including, but not limited to systemic corticosteroids at doses exceeding 10 mg/day of prednisone or equivalent, methotrexate, azathioprine, and TNF-α blockers. Use of immunosuppressive medications for the management of investigational product-related AEs or in subjects with contrast allergies is acceptable. In addition, use of inhaled and intranasal corticosteroids is permitted. A temporary period of steroids will be allowed for different indications, at the discretion of the principal investigator (e.g., chronic obstructive pulmonary disease, nausea, a short course of prednisone that is prescribed for acute allergic situations or for prevention of an allergy to contrast substance utilized for imaging studies, etc).
4. Live attenuated vaccines within 30 days of pembrolizumab dosing (ie, 30 days prior to the first dose, during treatment with pembrolizumab and for 30 days post discontinuation of pembrolizumab. Inactivated vaccines, such as the injectable influenza vaccine, are permitted.

Prohibited and Rescue Medications	
Rescue/supportive medication/class of drug:	**Usage:**
Concomitant medications or treatments (eg, acetaminophen or diphenhydramine) deemed necessary by the Investigator to provide adequate prophylactic or supportive care, except for those medications identified as "prohibited" as listed above	To be administered as prescribed by the Investigator
Best supportive care (including antibiotics, nutritional support, correction of metabolic disorders, optimal symptom control, and pain management.	Should be used when necessary for all patients

4.5 Other Non-study Treatments

Other local treatments (including but not limited to radiation therapy, surgery, interventional procedures) to sites outside the QuadShot target region are allowed for local symptom palliation or in the case of limited oligometastatic or oligoprogressive disease.

5.0 Study Outcomes and Study Measures

5.1 Primary Outcome

5.1.1 The overall response rate will be measured according to RECIST 1.1 (Section 7.1.3).

5.2 Secondary Outcomes

5.2.1 The response rate in the target lesion measured according to RECIST 1.1 (Section 7.1.3).

5.2.2 The response rate in the non-target lesions (if applicable) will be measured according to RECIST 1.1 (Section 7.1.3).

5.2.3 The duration of response at the target lesion will be defined as the duration from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date of recurrent or progressive disease as defined in Section 7.1.4.

5.2.4 Progression-free survival (PFS) will be defined as in Section 7.1.5.

5.2.5 Overall survival (OS) will be defined as in Section 7.1.5.

5.2.6 Tolerability will be measured using the Patient-Reported Outcomes version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE).

5.3 Exploratory Objectives

Blood will be utilized to measure the effect of immunotherapy alone as well as in combination with quad-shot therapy on increase of the circulating immune microRNA.

In addition, blood and saliva specimens will be utilized for mechanistic investigations of the effects of quad-shot on the response to immune checkpoint inhibitors. Detailed and comprehensive single cell RNA sequencing and multi-omics analysis of both plasma and exosomes fractions will be performed.

Saliva will be utilized for metabolomics and miRNA and RNAseq analysis of oral microbiome

6.0 Treatment Plan

6.1 Study Calendar

	Screening/ Pre-Registration[i]	**Cycle 1-3 ICI**	**QuadShot #1**	**Cycles 4-6 ICI**	**QuadShot #2**	**Cycles 7-11 ICI**	**Quadshot #3**	**Maintenance ICI Every 3 Weeks**
Initial Screening for Eligibility	X							
Informed Consent	X							
Demographics	X							
Medical and Surgical History	X							
Medication List	X							
Comorbidities	X							
Tobacco Use History	X							
Pre-Toxicity Form	X							
Hepatitis A antibody Hepatitis B surface Ag, Hepatitis C antibody and HIV	X							
Urine hCG or serum βhCG[a]	X	As clinically indicated						
Pembrolizumab Administration		X		X		X		X
Quad-shot Radiotherapy[h]			X		X		X	
Physical Examination[b]	X	X		X		X		X
Vital Signs	X	X[c]		X		X		X

Electrocardiogram[d]	X	X	As clinically indicated					
Concomitant Medications	X	X		X		X		X
Adverse event/serious adverse event assessment				X		X		X
ECOG Performance Status	X	X	X[m]	X	X[m]		X[m]	
Liver enzyme panel	X	X[j]		X		X		X
Serum Chemistry	X	X[j]		X		X		X
Magnesium	X	As clinically indicated						
Uric Acid	X	As clinically indicated						
LDH	X	X[j]	As clinically indicated					
Amylase, Lipase	X	X[j]		X		X		X
Thyroid function tests (TSH and fT3 and fT4)[e]	X	X[j]		X		X		X
Hematology	X	X[j]		X		X		X
Urinalysis	X	As clinically indicated						
Coagulation parameters	X	As clinically indicated						
Tumor Assessment with CT scan or MRI[f]	X			X		X		X
Tumor assessment with PET scan[g]	X			X		X		X
Blood Collection for Correlatives		X	X	X[k]	X[k]	X[k]	X[k]	X[k]
Saliva Collection for Correlatives		X	X	X[k]	X[k]	X[k]	X[k]	X[k]
PRO-CTCAE QOL Questionnaire[l]		X		X		X		X

a. Female subjects of childbearing potential only
b. Full physical examination at baseline; targeted physical examination at other timepoints
c. With first administration of pembrolizumab only and then as clinically indicated. Subjects will have their blood pressure and pulse measured before, during and after the infusion at the following times (based on a 60-minute infusion):

- At the beginning of the infusion (at 0 minutes)
- At 30 minutes during the infusion (±5 minutes)
- At the end of the infusion (at 60 minutes ±5 minutes)
- In the 1 hour observation period post-infusion: 30 and 60 minutes after the infusion (ie, 90 and 120 minutes from the start of the infusion) (±5 minutes) – for the first infusion only and then for subsequent infusions as clinically indicated
- If the infusion takes longer than 60 minutes then blood pressure and pulse measurements should be collected every 30 minutes (±5 minutes) and as described above or more frequently if clinically indicated.

d. ECG during screening and at Day1 –baseline. Thereafter as clinically indicated. Baseline and abnormal ECG at any time in triplicate others single. Triplicate EKG is only needed at screening, and not on Cycle 1 Day 1 unless something clinically significant was seen at screening.
e. Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.
f. CT (preferred) or MRI scans, preferably with IV contrast, are collected during screening (for baseline) and as close to and prior to initiation of study treatment but not more than 14 days +/- 5 days prior to first treatment. Will then be performed every 5 cycles (+/- 1 cycle) for tumor response measurement
g. PET scan will be performed in all cases if reimbursed by Medical Insurance or funded. It will be performed as close to the initiation of treatment but not more than 28 days prior to treatment. Will then be performed in follow up as clinically indicated and if approved by medical insurance.
h. Prior to cycle 4 (between pembrolizumab cycle 2-3 or 3-4) for all patients. Subsequent quad-shot cycles, if applicable, will be given as follows: quad-shot cycle #2: prior to cycle 8 (between pembrolizumab cycles 6-7 or 7-8); quad-shot cycle #3: prior to cycle 13 (between pembrolizumab cycles 11-12 or 12-13). Radiotherapy shall not be given on the same day as immunotherapy administration. Though specific days are not mandated, it is recommended that at least 1 day of each quad-shot cycle is given within 7 days of the upcoming ICI administration. Only one quad-shot cycle is mandated by the protocol; the 2nd and 3rd cycles may be completed at the discretion of the treating radiation oncologist as per Section 4.3.
i. Pre-study requirements listed in table must be completed **within** 30 days prior to registration.
j. If screening laboratory assessments are performed within 3 days prior to Day 1 they do not need to be repeated at Day 1. Results for safety bloods must be available and reviewed before commencing an infusion. Creatinine clearance, gamma glutamyltransferase, magnesium, and uric acid testing are to be performed at screening, on Day 1 (unless screening laboratory assessments are performed within 3 days prior to Day 1), and if clinically indicated.
k. Blood and Saliva for correlatives will be collected before each of the first five cycles of immunotherapy and before the first quad-shot treatment. Saliva and blood samples will only need to be collected on the first day of Quadshot treatment. For patients treated with subsequent radiotherapy cycles (between ICI cycles 6-7 or 7-8 +/- cycles 11-12 or 12-13) to be collected before the quad-shot treatment and before each ICI cycle administered before and after the quad-shot treatment (ICI cycles 6 and 7 or cycles 7 and 8 +/- before cycles 11 and 12 or 12 and 13)
l. The PRO-CTCAE
m. ECOG performance status needs to be collected only on one of the two days of quadshot treatment – either day 1 or day 2.

6.2 Schedule of study procedures: follow-up for subjects who have completed treatment or have discontinued treatment due to toxicity

Evaluation[a]	**Month 1**	**Month 2**
Physical examination	X	X
Vital signs (temperature, respiratory rate, blood pressure, pulse)	X	X
Weight	X	X
Urine hCG or serum βhCG	X	X
AE/SAE assessment	X	X
Concomitant medications	X	X
ECOG performance status	X	X
Subsequent anti-cancer therapy		X
Hematology	X	X
Serum chemistry	X	X
Thyroid function tests (TSH, and fT3 and fT4)[b]	X	X

[a] A follow up visit for evaluation is preferred and will be scheduled monthly for 2 mo after the last administration of pembrolizumab whenever possible. Alternatively, available data will be collected from medical records and phone evaluation will be attempted as well.

[b] Free T3 and free T4 will only be measured if TSH is abnormal. They should also be measured if there is clinical suspicion of an adverse event related to the endocrine system.

6.3 Treatment Administration

Systemic therapy (ICI) and radiotherapy will be administered according to the standard of care, according to the treating medical oncologist and radiation oncologist, respectively. Adverse events will be reported according to Section 8 and logged in the AE log.

Medications considered necessary for the patient's well-being may be given at the discretion of the treating physician, i.e., chronic treatments for concomitant medical conditions, as well as agents required for life-threatening medical problems, etc.

6.4 Duration of Therapy

In the absence of treatment delays due to adverse events, treatment may continue one of the following criteria applies:

- Disease progression (not amendable to local therapy),
- Intercurrent illness that prevents further administration of treatment,
- Unacceptable adverse event(s),
- Patient decides to withdraw from the study, or
- General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator.

6.5 Duration of Follow Up

Patients will be followed for a minimum of 2 times every 30 days after the last study drug is administered for adverse events monitoring. Follow-up for serious adverse events and mortality after the last study dose is administered will take place during the routine clinic visits that the patient will have during the 60-day follow-up window (Also referenced in Appendix D). If no visit occurs during this window, a phone call confirmation should be made to the patient to determine vital status and whether any adverse events and in particular, Grade 4 unexpected adverse events occurred during that window of time and recorded on Appendix F.

Patients will be followed according to the treating physician after removal from study or until death, whichever occurs first. Patients removed from study for unacceptable adverse events will be followed until resolution or stabilization of the adverse event.

Patients will be followed until death for monitoring survival study endpoints. Frequency of visits will be established by the treating physician and will be done in person or over the phone. Tumor imaging will be also performed at the discretion of the treating physician and results will be collected from the medical records. Alternatively, if the patient stops visiting with our clinic, tumor status and survival information will be collected by phone from the patient and from any other oncology office.

6.6 Criteria for Removal from Study

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

- Patient withdrawal of consent or loss to follow-up.
- Adverse event that, in the opinion of the investigator or the sponsor, contraindicates further dosing.
- Subject is determined to have met one or more of the exclusion criteria for study participation at study entry and continuing investigational therapy might constitute a safety risk.
- Pregnancy or intent to become pregnant
- Grade ≥ 3 infusion reaction.
- Subject noncompliance that, in the opinion of the investigator or sponsor, warrants withdrawal; eg, refusal to adhere to scheduled visits.
- Initiation of alternative anticancer therapy including another investigational agent.
- Confirmation of PD and investigator determination that the subject is no longer benefiting from protocol treatment.
- Death.

Subjects who are permanently discontinued from further receipt of investigational product, regardless of the reason (withdrawal of consent, due to an AE, other), will be identified as having permanently discontinued treatment.

Subjects who are removed from study prior to completing at least 2 cycles of ICI followed by at least 1 cycle of quad-shot radiotherapy followed by at least 2 cycles of ICI will be discontinued from the study and replaced.

Subjects who are permanently discontinued from receiving investigational product will be followed for safety until follow-up criteria are met in Section 6.4. Subjects who decline to return to the site for evaluations will be offered follow-up by phone for at least 60 days as an alternative.

Withdrawal of Consent
Patients are free to withdraw from the study at any time without prejudice to further treatment.

Patients who withdraw consent for further participation in the study will not receive any further study drug or radiotherapy or further study observation. Patient will be asked for permission to use collected specimens if deemed useful by the investigator.

A patient who withdraws consent will always be asked about the reason(s) for withdrawal and the presence of any AE. The Investigator will follow up AEs outside of the clinical study.

7.0 Measurement of Effect

7.1 Antitumor Effect – Solid Tumors

In accordance with the standard of care, after a baseline scans obtained prior to study registration, patients will be reevaluated for response after 5 cycles of immunotherapy. Patients who continue to receive ICI at the discretion of the medical oncologist will be evaluated again after 10 cycles of ICI.

Response and progression will be evaluated in this study using the Response Evaluation Criteria in Solid Tumors (RECIST) criteria 1.1.(40) 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.

7.1.1 Definitions

- **Evaluable for toxicity:**

Only those patients who have received at least 1 fraction of radiotherapy and at least 1 cycle of ICI will be evaluable for toxicity from the time of their first fraction of radiotherapy.

- **Evaluable for objective response:**

Only those patients who received at least one cycle of quad-shot radiotherapy (given after at least 2 cycles of ICI), and have had their target disease re-evaluated will be evaluable. These patients will have their response classified according to the definitions stated below.

Note: Per Section 6.6, subjects who are removed from study prior to completing at least 2 cycles of ICI followed by at least 1 cycle of quad-shot radiotherapy followed by at least 2 cycles of ICI will be discontinued from the study and replaced.

- **Evaluable Non-Target Disease Response**.

Patients who have lesions present at baseline that are evaluable but do not meet the definitions of target disease, have received at least one cycle of quad-shot radiotherapy, and have had their disease re-evaluated will be considered evaluable for non-target disease. The response assessment is based on the presence, absence, or unequivocal progression of the lesions.

- **Measurable disease / measurable lesions**

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as ≥20 mm by chest x-ray, as ≥10 mm with CT scan, or ≥10 mm with calipers by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

- **Malignant lymph nodes.**

To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

- **Non-measurable disease / non-measurable lesions**:

All other lesions (or sites of disease), including small lesions (longest diameter <10 mm or pathological lymph nodes with ≥ 10 to <15 mm short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pneumonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

Note: Cystic lesions that meet the criteria for radiographically defined simple cysts should not be considered as malignant lesions (neither measurable nor non-measurable) since they are, by definition, simple cysts.

'Cystic lesions' thought to represent cystic metastases can be considered as measurable lesions, if they meet the definition of measurability described above. However, if non-cystic lesions are present in the same patient, these are preferred for selection as target lesions.

- **Target lesions**

The lesions (up to a maximum of 2) identified by the treating radiation oncologist as target for quad-shot radiotherapy should be identified as **target lesions** and recorded and measured at baseline. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters.

If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

If measurements are not able to be accurately made on target lesions either at baseline or in follow-up, that target lesion will be excluded from the sum diameters.

- **Non-target lesions**

All measurable lesions up to a maximum of 2 lesions per organ and 4 lesions in total not treated with quad-shot radiotherapy (i.e. not identified as a target lesion) should be identified as **non-target lesions** and should also be recorded at baseline. The number of non-target lesions will not exceed 5. Measurements of these lesions are not required, but the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

7.1.2 Methods for Evaluation of Measurable Disease

- **Method(s) for obtaining measurements:**
  All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and not more than 30 days before registration.

  The same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination unless the lesion(s) being followed cannot be imaged but are assessable by clinical exam.

  Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes) and ≥10 mm diameter as assessed using calipers (e.g., skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

- **Use of imaging techniques (e.g., x-ray, CT, MRI, PET) for measuring disease**

  Imaging (CT, MRI, or PET/CT) will be obtained routinely as per clinical practice for patients being treated with immunotherapy. Either modality will be suitable for obtaining

measurements. When possible, efforts should be made to obtain the same imaging modality used for baseline imaging for all follow-up response assessments.

7.1.3 Response Criteria

- **Definition of complete response (CR)** for target and non-target lesions, as appropriate
  - Target Lesions:
    - Disappearance (or decrease to the point at which measurement is not possible) of all target lesions. **Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm** (the sum may not be "0" if there are target nodes)
  - Non-target lesions:
    - Disappearance (or decrease to the point at which measurement is not possible) of all non-target lesions. **All lymph nodes must be non-pathological in size (< 10 mm short axis)**

- **Definition of partial response (PR)** for target and non-target lesions, as appropriate
  - Target lesions:
    - At least a 30% decrease in the sum of diameters of target lesions, taking as reference the baseline sum of diameters
  - Non-target lesions
    - **Non-CR/Non-PD:** Persistence of 1 or more **non-target lesion(s).**

- **Definition of progressive disease (PD)** for target and non-target lesions, as appropriate
  - Target Lesions:
    - > 20% increase in the sum of the longest diameters (SLD) taking as reference the smallest SLD recorded since the treatment started (nadir) **and minimum 5 mm increase over the nadir**
    - When sum becomes very small, increases within measurement error (2-3 mm) can lead to 20% increase
    - (Note: the appearance of one or more new lesions is also considered progressions)
  - Non-target lesions:
    - *Unequivocal progression* of existing non-target lesions. The appearance of one or more new lesions.
    - *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase
    - Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or Principal Investigator).

- **Definition of stable disease (SD)** for target and non-target lesions, as appropriate
  - Target lesions:
    - Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study

- **Definition and evaluation of best overall response**, if applicable
  The best overall response is the best response recorded from the start of the treatment across all time points.

Criteria for Determination of Best Overall Response

Target Lesion	Non-Target Lesion	New Lesions	Overall Response
CR	CR	No	CR
CR	Non-CR/Non-PD	No	PR
CR	NE	No	PR
PR	Non-PD or not all evaluated	No	PR
SD	Non-PD or not all evaluated	No	SD
Not all evaluated	Non-PD	No	NE
PD	Any	Yes or No	PD
Any	PD	Yes or No	PD
Any	Any	Yes	PD

7.1.4 Duration of Response

Duration of overall response: The duration of overall response is measured from the time measurement criteria are met for CR or PR (whichever is first recorded) until the first date that recurrent or progressive disease is objectively documented by clinical, radiographic, or pathologic findings (taking as reference for progressive disease the smallest measurements recorded since the treatment started).

The duration of overall CR is measured from the time measurement criteria are first met for CR until the first date that progressive disease is objectively documented.

7.1.5 Survival Outcomes

Progression-Free Survival is defined as the duration of time from registration to the time of progression, death, or date of last contact; those lost to follow-up will be censored.

Overall Survival is defined as the duration of time from registration to date of death or date of last contact; those lost to follow-up will be censored.

7.1.6 Response Review

Response will be assessed by the principal investigator(s) during the course of the study.

Following study completion, responses may be reviewed by independent expert neuroradiologist(s). Simultaneous review of the patients' files and radiological images is the best approach.

8.0 Adverse Events List and Reporting Requirements

The Principal Investigator is responsible for ensuring that all staff involved in the study is familiar with the content of this section.

8.1 Safety Parameters

Definition of adverse events:
The International Conference on Harmonization (ICH) Guideline for Good Clinical Practice (GCP) E6(R1) defines an AE as:

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

An AE includes but is not limited to any clinically significant worsening of a subject's pre-existing condition. An abnormal laboratory finding (including ECG finding) that requires an action or intervention by the investigator, or a finding judged by the investigator to represent a change beyond the range of normal physiologic fluctuation, should be reported as an AE.

Adverse events may be treatment emergent (ie, occurring after initial receipt of investigational product) or nontreatment emergent. A nontreatment-emergent AE is any new sign or symptom, disease, or other untoward medical event that begins after written informed consent has been obtained but before the subject has received investigational product.

Elective treatment or surgery or preplanned treatment or surgery (that was scheduled prior to the subject being enrolled into the study) for a documented pre-existing condition, that did not worsen from baseline, is not considered an AE (serious or nonserious). An untoward medical event occurring during the prescheduled elective procedure or routinely scheduled treatment should be recorded as an AE or SAE.

The term AE is used to include both serious and non-serious AEs.

Definition of serious adverse events
A serious adverse event is an AE occurring during any study phase (i.e., screening, run-in, treatment, wash-out, follow-up), at any dose of the study drugs that fulfils one or more of the following criteria:

- Results in death
- Is immediately life-threatening
- Requires in-patient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability or incapacity

- Is a congenital abnormality or birth defect in offspring of the subject
- Is an important medical event that may jeopardize the patient or may require medical intervention to prevent one of the outcomes listed above.
- Medical or scientific judgment should be exercised in deciding whether expedited reporting is appropriate in this situation. Examples of medically important events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in fatality

The causality of SAEs (their relationship to all study treatment/procedures) will be assessed by the investigator(s).

Definition of adverse events of special interest (AESI)
An adverse event of special interest (AESI) is one of scientific and medical interest specific to understanding of the Investigational Product and may require close monitoring. An AESI may be serious or non-serious.

AESIs for pembrolizumab include but are not limited to events with a potential inflammatory or immune-mediated mechanism and which may require more frequent monitoring and/or interventions such as steroids, immunosuppressants and/or hormone replacement therapy. These AESIs are being closely monitored in clinical studies with pembrolizumab monotherapy and combination therapy. An immune-related adverse event (irAE) is defined as an adverse event that is associated with drug exposure and is consistent with an immune-mediated mechanism of action and where there is no clear alternate aetiology. Serologic, immunologic, and histologic (biopsy) data, as appropriate, should be used to support an irAE diagnosis. Appropriate efforts should be made to rule out neoplastic, infectious, metabolic, toxin, or other etiologic causes of the irAE.

AESIs observed with pembrolizumab include:

- Colitis
- Pneumonitis
- ALT/AST increases / hepatitis / hepatotoxicity
- Neuropathy / neuromuscular toxicity (i.e. events of encephalitis, peripheral motor and sensory neuropathies, Guillain-Barré, and myasthenia gravis)
- Endocrinopathy (i.e. events of hypophysitis, adrenal insufficiency, and hyper- and hypothyroidism)
- Dermatitis
- Nephritis
- Pancreatitis (or labs suggestive of pancreatitis - increased serum lipase , increased serum amylase)

Patients should be thoroughly evaluated to rule out any alternative etiology (e.g., disease progression, infections etc.)

Steroids should be considered in the absence of clear alternative etiology even for low grade events (Grade 2), in order to prevent potential progression to higher grade event.

Severe and Fatal Immune-Mediated Adverse Reactions
Immune-mediated adverse reactions, which may be severe or fatal, can occur in any organ system or tissue and usually occur during treatment; however, they can also occur after discontinuation. Early identification and management are essential to ensuring safe use of PD-1–blocking antibodies. Monitor for symptoms and signs of immune-mediated adverse reactions. Evaluate clinical chemistries, including liver tests and thyroid function tests, at baseline and periodically during treatment. Institute medical management promptly to include specialty consultation as appropriate.

In general, withhold pembrolizumab for Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions. Permanently discontinue pembrolizumab for Grade 4 and certain Grade 3 immune-mediated adverse reactions. For Grade 3 or 4 and certain Grade 2 immune-mediated adverse reactions, administer corticosteroids (1 to 2 mg/kg/day prednisone or equivalent) or other appropriate therapy until improvement to Grade 1 or less followed by a corticosteroid taper over 1 month. Consider administration of other systemic immunosuppressants in patients whose immune-mediated adverse reaction is not controlled with corticosteroids. Institute hormone replacement therapy for endocrinopathies as warranted.

Immune-mediated pneumonitis: Immune-mediated pneumonitis occurred in about 2.5% of the patients treated with immune checkpoint inhibitors and leads to permanent discontinuation of the drug in about half of the patients. Systemic corticosteroids are required in all patients with pneumonitis. Withhold pembrolizumab for Grade 2, and permanently discontinue for Grade 3 or 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated colitis: Immune-mediated colitis occur in about 1% of patients receiving immune checkpoint inhibitors leading to permanent discontinuation pembrolizumab in a small percent of patients. Systemic corticosteroids are required in all patients with colitis. Withhold pembrolizumab for Grade 2 or 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated hepatitis: Immune-mediated hepatitis occurred in general in about 2% of patients receiving immune checkpoint inhibitors. Systemic corticosteroids are required in all patients with hepatitis. Withhold pembrolizumab if AST or ALT increases to more than 3 and up to 10 times the upper limit of normal (ULN) or if total bilirubin increases up to 3 times the ULN. Permanently discontinue pembrolizumab if AST or ALT increases to more than 10 times the ULN or total bilirubin increases to more than 3 times the ULN. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated endocrinopathies: Withhold pembrolizumab if clinically necessary for Grade 2, 3, or 4.

- **Adrenal insufficiency:** Adrenal insufficiency occurs in less than 1% of patients receiving immune checkpoint inhibitors
- **Hypophysitis:** Hypophysitis, which can result in hypopituitarism, occurs very rarely, around 0.2% of patients on immune checkpoint inhibitors
- **Hypothyroidism:** Hypothyroidism occurred in about 6% of patients receiving immune checkpoint inhibitors it is not necessary for the patients to discontinue hormone replacement therapy
- **Hyperthyroidism:** Hyperthyroidism occur in about 1.5% of patients receiving immune checkpoint inhibitors.
- **Type 1 diabetes mellitus:** Type 1 diabetes mellitus, which can present with diabetic ketoacidosis, occurred in less than 1% of patients undergoing immune checkpoint inhibitors and leads to permanent discontinuation of the drug in exceptional cases.

Immune-mediated nephritis with renal dysfunction: Immune-mediated nephritis occurs in about 0.5% of patients receiving immune checkpoint inhibitors and leads to permanent discontinuation of the drug in about half of the patients. Systemic corticosteroids are required in all patients with nephritis. Withhold pembrolizumab for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Immune-mediated dermatologic adverse reactions: Immune-mediated dermatologic reactions, including erythema multiforme and pemphigoid, occur in about 2% of patients receiving immune checkpoint inhibitors. In addition, SJS and TEN have been observed with immune checkpoint inhibitors. Systemic corticosteroids are required in all patients with dermatologic reactions. Withhold pembrolizumab for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

Other immune-mediated adverse reactions: The following clinically significant immune-mediated adverse reactions occur at an incidence of <1% of patients who receive immune checkpoint inhibitors. Severe or fatal cases have been reported for some of these adverse reactions. Withhold pembrolizumab for Grade 3, and permanently discontinue for Grade 4. Resume in patients with complete or partial resolution (Grade 0 to 1) after corticosteroid taper.

- **Neurological:** Meningitis, encephalitis, myelitis and demyelination, myasthenic syndrome/myasthenia gravis, Guillain-Barré syndrome, nerve paresis, and autoimmune neuropathy
- **Cardiovascular:** Myocarditis, pericarditis, and vasculitides
- **Ocular:** Uveitis, iritis, and other ocular inflammatory toxicities. Some cases can be associated with retinal detachment. Various Grades of visual impairment to include blindness can occur. If uveitis occurs in combination with other immune-mediated adverse reactions, consider a Vogt-Koyanagi-Harada–like syndrome, as this may require treatment with systemic corticosteroids to reduce the risk of permanent vision loss
- **Gastrointestinal:** Pancreatitis to include increases in serum amylase and lipase levels, gastritis, and duodenitis
- **Musculoskeletal and connective tissue:** Myositis, rhabdomyolysis, and associated sequelae, including renal failure, arthritis, and polymyalgia rheumatica
- **Hematological and immunological:** Hemolytic anemia, aplastic anemia, hemophagocytic lymphohistiocytosis, systemic inflammatory response syndrome, histiocytic necrotizing lymphadenitis (Kikuchi lymphadenitis), sarcoidosis, immune thrombocytopenic purpura, and solid organ transplant rejection

Infusion-related reactions
Severe infusion-related reactions (Grade 3) occur in about 0.2% of patients receiving checkpoint inhibitors. Monitor patients for signs and symptoms of infusion-related reactions. Interrupt or slow the rate of infusion for Grade 1 or 2, and permanently discontinue for Grade 3 or 4.

Embryo-fetal toxicity
Pembrolizumab can cause fetal harm when administered to a pregnant woman due to an increased risk of immune-mediated rejection of the developing fetus resulting in fetal death. Advise women of the potential risk to a fetus. Advise females of reproductive potential to use effective contraception during treatment with pembrolizumab and for at least 4 months after the last dose.

Adverse reactions

- Serious adverse reactions occurred in 28% of patients. Serious adverse reactions that occurred in ≥2% of patients were cellulitis, sepsis, pneumonia, pneumonitis, and urinary tract infection. The most common Grade 3-4 adverse reactions (≥2%) were cellulitis, sepsis, hypertension, pneumonia, musculoskeletal pain, skin infection, urinary tract infection, and fatigue
- pembrolizumab was permanently discontinued due to adverse reactions in 5% of patients; adverse reactions resulting in permanent discontinuation were pneumonitis, autoimmune myocarditis, hepatitis, aseptic meningitis, complex regional pain syndrome, cough, and muscular weakness
- The most common adverse reactions (incidence ≥20%) were fatigue, rash, and diarrhea

Assessment of safety parameters
Assessment of severity
Assessment of severity is one of the responsibilities of the investigator in the evaluation of AEs and SAEs. Severity will be graded according to the NCI CTCAE v 5.0.
The determination of severity for all other events not listed in the CTCAE should be made by the investigator based upon medical judgment and the severity categories of Grade 1 to 5 as defined below.

Grade 1 (mild) An event that is usually transient and may require only minimal treatment or therapeutic intervention. The event does not generally interfere with usual activities of daily living.

Grade 2 (moderate) An event that is usually alleviated with additional specific therapeutic intervention. The event interferes with usual activities of daily living, causing discomfort but poses no significant or permanent risk of harm to the subject.

Grade 3 (severe) An event that requires intensive therapeutic intervention. The event interrupts usual activities of daily living, or significantly affects the clinical status of the subject.

Grade 4 (life threatening) An event, and/or its immediate sequelae, that is associated with an imminent risk of death or with physical or mental disabilities that affect or limit the ability of the subject to perform activities of daily living (eating, ambulation, toileting, etc).

Grade 5 (fatal) Death (loss of life) as a result of an event.

It is important to distinguish between serious criteria and severity of an AE. Severity is a measure of intensity whereas seriousness is defined by the criteria in Section 10.1.2. A Grade 3 AE need not necessarily be considered an SAE. For example, a Grade 3 headache that persists for several hours may not meet the regulatory definition of an SAE and would be considered a nonserious event, whereas a Grade 2 seizure resulting in a hospital admission would be considered an SAE.

Assessment of relationship
The Investigator will assess the causal relationship between the IP and each AE and answer “yes” or “no” to the question “Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?”

For SAEs, causal relationship will also be assessed for other medications and study procedures. Note that, for SAEs that could be associated with any study procedure, the causal relationship is implied as “yes.”

When making an assessment of causality, consider the following factors when deciding if there is a "reasonable possibility" that an AE may have been caused by the drug.

- Time Course. Exposure to suspect drug. Has the patient actually received the suspect drug? Did the AE occur in a reasonable temporal relationship to the administration of the suspect drug?

- Consistency with known drug profile. Was the AE consistent with the previous knowledge of the suspect drug (pharmacology and toxicology) or drugs of the same pharmacological class? Or could the AE be anticipated from its pharmacological properties?

- De-challenge experience. Did the AE resolve or improve on stopping or reducing the dose of the suspect drug?

- No alternative cause. The AE cannot be reasonably explained by another etiology such as the underlying disease, other drugs, or other host or environmental factors.

- Laboratory tests. A specific laboratory investigation (if performed) has confirmed the relationship in difficult cases, other factors could be considered such as:
  - Is this a recognized feature of overdose of the drug?
  - Is there a known mechanism?

Causality of "related" is made if, following a review of the relevant data, there is evidence for a "reasonable possibility" of a causal relationship for the individual case. The expression "reasonable possibility" of a causal relationship is meant to convey, in general, that there are facts (evidence) or arguments to suggest a causal relationship. The causality assessment is performed based on the available data including enough information to make an informed judgment. With limited or insufficient information in the case, it is likely that the event(s) will be assessed as "not related." Causal relationship in cases where the disease under study has deteriorated due to lack of effect should be classified as no reasonable possibility.

8.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 5.0. A copy of the CTCAE version 5.0 can be downloaded from the CTEP web site (http://ctep.cancer.gov).

- **'Expectedness'**: AEs can be 'Unexpected' or 'Expected' (see Section 7.1 above) for expedited reporting purposes only.

- **Attribution** of the AE:

  - Definite – The AE **is clearly related** to the study treatment.
  - Probable – The AE **is likely related** to the study treatment.
  - Possible – The AE **may be related** to the study treatment.
  - Unlikely – The AE **is doubtfully related** to the study treatment.
  - Unrelated – The AE **is clearly NOT related** to the study treatment.

8.3 STRC SAE Reporting Requirements

The Data Safety Monitoring Committee (DSMC) is responsible for reviewing SAEs for WFBCCC Institutional studies as outlined in Appendix B. All Adverse Events that occur during protocol intervention and are coded as either 1) unexpected grade 4, 2) unplanned inpatient hospitalization ≥ 24 hours (regardless of grade), or grade 5 (death) must be reported to the DSMC using the using the SAE console in WISER.

All WFBCCC Clinical Protocol and Data Management (CPDM) staff members assisting a Principal Investigator in investigating, documenting and reporting an SAE qualifying for DSMC reporting are responsible for informing a clinical member of the DSMC as well as the entire committee via the email notification procedure of the occurrence of an SAE.

8.4 WFUHS IRB AE Reporting Requirements

Any unanticipated problems involving risks to subjects or others and adverse events shall be promptly reported to the IRB, according to institutional policy. Reporting to the IRB is required regardless of the funding source, study sponsor, or whether the event involves an investigational or marketed drug, biologic or device. Reportable events are not limited to physical injury, but include psychological, economic and social harm. Reportable events may arise as a result of drugs, biological agents, devices, procedures or other interventions, or as a result of questionnaires, surveys, observations or other interactions with research subjects.

All members of the research team are responsible for the appropriate reporting to the IRB and other applicable parties of unanticipated problems involving risk to subjects or others. The Principal Investigator, however, is ultimately responsible for ensuring the prompt reporting of unanticipated problems involving risk to subjects or others to the IRB. The Principal Investigator is also responsible for ensuring that all reported unanticipated risks to subjects and others which they receive are reviewed to determine whether the report represents a change in the risks and/or benefits to study participants, and whether any changes in the informed consent, protocol or other study-related documents are required.

Any unanticipated problems involving risks to subjects or others occurring at a site where the study has been approved by the WFUHS IRB (internal events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any unanticipated problems involving risks to subjects or others occurring at another site conducting the same study that has been approved by the WFUHS IRB (external events) must be reported to the WFUHS IRB within 7 calendar days of the investigator or other members of the study team becoming aware of the event.

Any event, incident, experience, or outcome that alters the risk versus potential benefit of the research and as a result warrants a substantive change in the research protocol or informed consent process/document in order to insure the safety, rights or welfare of research subjects.

9.0 Correlative/Special Studies

9.1 Laboratory Correlative Studies

Biological sampling procedures
Immunogenicity sampling and evaluation methods

- Saliva and blood for correlative studies will be collected as described in Section 4.2.
- Blood specimens will be drawn into EDTA tubes. Samples will be labelled and transported at room temperature within one hour to Dr. Furdui laboratory in Nutrition Building 2nd floor for isolation of plasma and exosomes, which will then be frozen in liq N2 for long-term storage until the completion of study.
- A portion of plasma will be submitted to Dr. Triozzi's lab for measurement of immune micro RNA.
- A portion of the blood sample will be submitted to Dr. Wei Zhang's lab for single cell RNA sequencing.

Saliva collection procedures

- We will target collection of 5 ml saliva from each patient.

Saliva Collection Recommendations

- Participants should not eat or brush their teeth within 4h prior to sample collection.
- Dental work should not be performed within 24 hours prior to sample collection.
- Saliva samples visibly contaminated with blood should be discarded and recollected. Contamination that is not visible is not of concern for this study.
- For saliva sample collection we will use 50 ml Falcon tube kept on ice. 5 mL of saliva will be collected.

Instructions for Collecting Saliva

1. Remove cap from tube. We will use laboratory tubes with large diameter.
2. Instruct participants to allow saliva to pool in the mouth. Some find it helpful to imagine eating their favorite food.
3. With head tilted forward, participants should drool through the SCA to collect saliva in the tube.
4. Replace cap onto tube.
5. Place label immediately.
6. Place tube in refrigerator and transport as soon as possible in an ice box.
7. Samples will be transported within one hour to Dr. Furdui's laboratory in Nutrition building. Saliva samples will be processed immediately after collection.

Proteomics

For global protein identification analysis, 10 µL of plasma will be purified by passing through a Pierce top-2 abundant protein depletion spin column before protein extraction. Protein will be reduced and alkylated by treatment with dithiothreitol (DTT) and iodoacetamide (IAM), and then will be precipitated by adding four times the sample volume of cold acetone with incubation at -20°C. 10 ug of protein extracted from the exosome fraction will be similarly processed. Protein pellet will be air-dried at room temperature and re-suspended in 50 mM ammonium bicarbonate. 5 – 25 µg of protein will be taken and digested with sequencing-grade modified trypsin. The peptide mixture will be acidified to quench enzyme activity and purified using a C18 desalting spin column. Peptides will be prepared in 5% (v/v)

ACN containing 1% (v/v) formic acid and analyzed on an Orbitrap Velos Pro Mass Spectrometer (Thermo Scientific, Waltham, MA) with a Dionex Ultimate-3000 nano-UPLC system (Thermo Scientific, Waltham, MA). The LC-MS/MS system will be equipped with an Acclaim PepMap 100 (C18, 5 µm, 100 Å, 100 µm x 2 cm) trap column and an Acclaim PepMap RSLC (C18, 2 µm, 100 Å, 75 µm x 50 cm) analytical column for peptide separation. MS spectra will be acquired by data dependent scans consisting of MS/MS scans of the ten most intense ions from the full MS scan with dynamic exclusion option. To identify proteins, spectra will be searched using Sequest HT algorithm within the Proteome Discoverer v2.2 (Thermo Scientific, Waltham, MA) in combination with the UniProt protein FASTA database. Search results will contain description of identified proteins or compounds with their peak areas which represent relative abundance. Data will be exported and finalized in Microsoft Excel spreadsheet format for further statistical analysis.

Metabolomics

For metabolomics analysis, 50 µL of plasma or exosome suspension spiked with an internal standard, 2-morpholinoethanesulfonic acid (MES) will be mixed with four times the sample volume of cold methanol. Supernatant will be obtained from centrifugation, which will be dried down and re-constituted in water for LC-MS/MS analysis. Sample will be analyzed on a Q Exactive HF hybrid quadrupole-Orbitrap mass spectrometer (Thermo Scientific, Waltham, MA) combined with a Vanquish UHPLC system (Thermo Scientific, Waltham, MA). Metabolites will be separated on an Ultra PFPP column (3 µm, 2.1 mm x 150 mm, Restek, Bellefonte, PA) using a linear gradient with 100% water (mobile phase A) and 90% acetonitrile (mobile phase B) both of which equally contain 0.1% formic acid and 10mM ammonium formate. Compound Discoverer v2.1 (Thermo Scientific, Waltham, MA) will be used for metabolite annotation and relative quantification. Search results will contain description of identified compounds with their peak areas which represent relative abundance. Data will be exported and finalized in Microsoft Excel spreadsheet format for further statistical analysis.

Untargeted proteomics and metabolomics data processing

We will utilize an integrated mixomics data processing pipeline to align and interpret proteomic and metabolomics profiles to identify drivers of response to immunotherapy with prior quad-shot treatment. Expression of the top five candidate biomarkers identified, as determined by predictive value and fold-expression, will be secondarily validated by Western blot or mass spectrometry-based targeted analysis using standard techniques.

Immune microRNA (miRs) measurements

Levels of immune-regulatory miRs will be quantified in plasma using PCR-based techniques.

miRs are important regulators of immune response miRs negatively regulate gene expression by base pairing with the 3′ untranslated region of their target mRNAs. Most cellular processes, both physiological and pathological, are affected. These include differentiation, development, metabolism, proliferation, death, viral infection, and malignant transformation. Recent studies have shown that miRs play a critical role in regulating the development of immune cells and in modulating innate and adaptive immune responses. Several miRs, referred to as “immunomiRs,” have been identified. miR-125b, 155, 181a, and miRs of the 17-92 complex play central roles in T-cell; miR 146a and 155, in NK cell; miR-155 and 146a, in dendritic cell; miR 125b, 146a, 155, and miRs of the 17-92 complex, in T regulatory cell; and miR-223, in myeloid derived suppressor cell development and function. Because of their low complexity (when compared to proteins), their stability, and highly sensitive detection methods, miRs are attractive biomarkers. Because of incorporation in microparticles and exosomes, miRs are stable and can be measured in blood and several other body fluids, including saliva.

Total RNA will be isolated from plasma and saliva using the miRNeasy Mini Kit (Qiagen). Reverse transcription reactions are performed using a TaqMan MicroRNA Reverse Transcription Kit (Applied Biosystems) according to the manufacturer's instructions. qRT-PCR will be performed using the reverse transcription reaction product, TaqMan MicroRNA Assay kits, and TaqMan Universal PCR Master Mix (Applied Biosystems. Data are normalized to a C. elegans synthetic miR sequence, cel miR-39 (Qiagen), which is spiked in as a control during RNA isolation.

Single cell RNA-sequencing in blood before and after treatment.
We propose to examine our blood samples collected before and after treatment with Pembrolizumab by single cell sequencing experiments at the Cancer Genomics Shared Resource and data analyzed by the Bioinformatics Shared Resources to determine the complex response in the immune cell populations. PBMCs from selected patients are thawed, assessed for > 70% viability, and then processed for single cell gene expression using the Next GEM Single Cell 3' GEM, Library & Gel Bead Kit v3.1 and 10X Genomics Chromium platform. Barcoded UMI-tagged libraries are sequenced on an Illumina NovaSeq 6000 targeting 4000 cells per sample at a median read depth of 50,000 reads per cell. Raw bcl and fastq data will be demultiplexed, normalized and post-processed using Cell Ranger mkfastq pipelines and QC algorithms (10X Genomics). The Cell Ranger mkfastq pipelines (10X Genomics) is used to process, QC and align sequencing reads and to optimize cell calling. Graph-based or K-means clustering algorithms implemented in Cell Ranger are applied to delineate populations of diverse immune cell lineages whose identities are frequently confirmed by the presence or absence of marker gene combinations informed by antibody-based cell sorting and identification methods, or published transcriptional signatures of FACS-sorted immune cells (42-44).
scRNAseq data processing. Transcript read counts will be normalized and statistically compared for differential expression between patients using DESeq2 [2] that applies the negative binomial model with independent dispersions. Differentially expressed genes (DEGs; FDR-corrected, $p<0.05$) will be analyzed by Ingenuity Pathway Analysis (IPA, www.ingenuity.com) and Gene Set Enrichment Analysis (GSEA) [3] to identify gene enrichment for biological processes or signaling pathways that underlie response.

Red Blood Cells (RBCs) that are left over after the isolation of plasma for metabolomics and miRNA measurement, and of PBMCs for the scRNA sequencing, instead of being discarded as per routine protocols, will be saved and utilized for testing the optimization of protocols designed to quench redox metabolism. Redox metabolism is tightly associated with all aspects of cancer pathophysiology, including response to immunotherapy and radiotherapy. However, redox metabolism remains inadequately studied and utilized in clinic due to the lack of appropriate biospecimen preservation technologies. RBC, a valuable source of redox components, will be washed and either used immediately for testing of redox preservation media or stored for future use.
Currently, simple banking of whole blood or its components fails to capture an accurate redox status of blood or tissues because of artifacts introduced by handling and the absence of redox preservation mechanism.

The research-dedicated blood samples are de-identified by the clinical study team such that a study research ID replaces any subject identifier (MRN, name). The clinical study team securely maintains the key for study IDs and patient information.

Remaining samples will be retained for future research after the study report has been finalized if agreed by patients in the ICF. Otherwise, it will be disposed.

Oral microbiota profiling will be performed using 16S rRNA gene sequencing to characterize the bacterial diversity and composition in the saliva collected from these patients at indicated time points before and during treatment.

PD-L1 Testing
To ensure comparability of data across all studies of pembrolizumab and to gain real world experience on the performance of this assay, it is strongly encouraged that all studies that include PD-L1 testing utilize the Dako 22C3 assay.
Estimate of volume of blood to be collected for research purposes

The total volume of blood that will be drawn from each subject in this study is as follows:

Volume of Blood to Be Drawn From Each Subject

Assessment	Sample volume (mL)	No. of samples	Total volume (mL)
Immune Studies	20	7	140
Additional Research Samples (with patient's consent per ICF)	20	7	140
Total: 280 ml			

Three additional samples of blood (120 ml) will be collected for each additional quad-shot treatment (blood collection before starting radiotherapy and before each cycle of pembrolizumab administered before and after the quad-shot treatment)

Withdrawal of informed consent for donated biological samples
If a subject withdraws consent to the use of donated samples, the samples will be disposed of/destroyed, and the action documented.

The Principal Investigator:
- Ensures that biological samples from that subject, if stored at the study site, are immediately identified, disposed of /destroyed, and the action documented.
- Ensures the laboratory(ies) holding the samples is/are informed about the withdrawn consent immediately and that samples are disposed/destroyed.
- Ensures that the subject is informed about the sample disposal.

10.0 Pharmaceutical Information

A list of the adverse events and potential risks associated with the investigational or commercial agents administered in this study can be found in Section 10.1.3.

Pharmaceutical Accountability

Drug accountability logs will be maintained for all [investigative (if appropriate)] agents used under this protocol. These logs shall record quantities of study drug received and quantities dispensed to patients, including lot number, date dispensed, patient identifier number, patient initials, protocol number, dose, quantity returned, balance remaining, and the initials of the person dispensing the medication.

11.0 Statistical Considerations

11.1 Analysis of Primary Objective

11.1.1 For this pilot study, the primary analytic objective is to measure the overall response rate measured according to RECIST criteria and determine the percent of patients with either a partial or complete response (PR or CR) and the corresponding 95% Clopper Pearson exact confidence interval. This estimate will provide useful information concerning the potential efficacy of this treatment for planning future studies.

11.2 Analysis of Secondary Objective

There are 6 secondary outcomes of interest for this pilot study. These are 1) response rate for the target lesion; 2) response rate for non-target lesions 3) duration of response for the target lesion 4) progression free survival (PFS) 5) overall survival (OS) and tolerability assessed using PRO-CTCAE. We now describe our analytic approach for each measure.

For the response rate measures we will estimate the percent of responders (PR or CR) and the corresponding 95% Clopper Pearson exact confidence intervals. For the duration of response, among responders we will estimate both the mean and median duration and the corresponding 95% confidence intervals for the mean and inter-quartile range for the median. For time to event measures (PFS and OS) we will estimate Kaplan Meier survival curves and estimate the median time to event times as well as the percent PFS and OS at 6 months and 1 year post treatment. For tolerability, we will estimate the percent of patients with different AEs assessed using the PRO-CTCAE and corresponding 95% Clopper Pearson exact confidence intervals.

11.3 Power and Sample Size

Since this is a pilot study there will be no formal hypothesis tests performed. With a sample size of 15 evaluable patients (patients must be evaluable for objective response as described in Section 7.1.1), the maximum width of a 95% Clopper Pearson exact confidence interval is 0.52 (since the interval may not be symmetric this corresponds to approximately +/- 0.26 (if the response rate is as high as 7/15). If the response rate is lower than this then the width of the confidence interval will be less. With this sample size we will be able to determine whether the response rate in this treatment is high enough to warrant future examination. Based on preliminary data presented in Table 1 the response rates from previous studies is between 13 and 36% thus we would anticipate that the response rate in this study will need to be at least this high to warrant future studies.

11.4 Estimated Accrual Rate

According to the TriNetX tool (live.trinetx.com), using the query as defined below, the Wake Forest Baptist Medical Center has seen an average of 2.6 historic arrivals per month over the past 3 years. Using the predicted arrivals tool, 3.5 arrivals per month are expected over the next 1 year. Considering ineligibility and patient declination, we expect to accrue 15 evaluable patients over the course of 2 years. This would correspond to approximately 0.7 patients per month being accrued (meaning 20% of the arrivals per month participating).

1547545	pembrolizumab	
OR		
1597876	nivolumab	670
AND		
C01	Malignant neoplasm of base of tongue	970
OR		
C02	Malignant neoplasm of other and unspecified parts of tongue	1,260
OR		
C03	Malignant neoplasm of gum	320
OR		
C04	Malignant neoplasm of floor of mouth	420
OR		
C05	Malignant neoplasm of palate	340
OR		
C06	Malignant neoplasm of other and unspecified parts of mouth	1,850
OR		
C09	Malignant neoplasm of tonsil	1,100
OR		
C10	Malignant neoplasm of oropharynx	1,020
OR		
C11	Malignant neoplasm of nasopharynx	490
OR		
C12	Malignant neoplasm of pyriform sinus	170
OR		
C13	Malignant neoplasm of hypopharynx	590
OR		
C14	Malignant neoplasm of other and ill-defined sites in the lip, oral cavity and pharynx	560

11.5 Estimated Study Length

We anticipate that accrual will be accomplished within 21 months and then follow-up for response can be finished within approximately 3 months, thus this study should be completed within approximately 24 months once accrual commences.

12.0 Ethical and regulatory requirements

12.1 Ethical conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice, and applicable regulatory requirements Subject data protection.

12.2 Ethics and regulatory review

Institutional Review Board (IRB) will approve the final study protocol, including the final version of the ICF and any other written information and/or materials to be provided to the patients. The Investigator will ensure the distribution of these documents to the IRB and to the study site staff.

The opinion of IRB should be given in writing.

The protocol should be re-approved by the IRB annually. Before enrollment of any patient into the study, the final study protocol, including the final version of the ICF, should be approved by the

national regulatory authority or a notification to the national regulatory authority should be approved, according to local regulations.

Principal Investigator is responsible for providing the IRB with reports of any serious and unexpected adverse drug reactions from any other study conducted with the IP.

12.3 Informed consent

The Principal Investigator will:

- Ensure that each patient is given full and adequate oral and written information about the nature, purpose, possible risk, and benefit of the study
- Ensure that each patient is notified that he or she is free to discontinue from the study at any time
- Ensure that each patient is given the opportunity to ask questions and allowed time to consider the information provided
- Ensure that each patient provides a signed and dated informed consent before conducting any procedure specifically for the study
- Ensure that the original, signed ICF(s) is/are stored in the Investigator's Study File
- Ensure that a copy of the signed ICF is given to the patient
- Ensure that any incentives for patients who participate in the study as well as any provisions for patients harmed as a consequence of study participation are described in the ICF that is approved by an EC/IRB.

Changes to the protocol and informed consent form
If there are any substantial changes to the study protocol, then these changes will be documented in a study protocol amendment and, where required, in a new version of the study protocol (revised clinical study protocol). The amendment is to be approved by the relevant IRB and, if applicable, the national regulatory authority, before implementation. Local requirements will be followed for revised protocols.

12.4 Audits and inspections

The CCCWFU, a regulatory authority, or IRB may perform audits or inspections at the center, including source data verification. The purpose of an audit or inspection is to systematically and independently examine all study-related activities and documents, to determine whether these

activities were conducted, and to determine if data were recorded, analyzed, and accurately reported according to the protocol, GCPs, ICH
guidelines, and any applicable regulatory requirements. The Investigator will contact AstraZeneca immediately if contacted by a regulatory agency about an inspection at the center.

13.0 Study Management

13.1 Training of study site personnel

The Principal Investigator will ensure that appropriate training relevant to the study is given to all of these staff and that any new information relevant to the performance of this study is forwarded to the staff involved.

13.2 Data Management

Informed consent document	EPIC
Protocol registration form	WISER/OnCore
Off Study, Off Treament,Survival	WISER/OnCore
Pre-toxicity	WISER/OnCore
Cycle Tracking	Redcap
Adverse Events Log	WISER/OnCore
Treatment Response Evaluation	Redcap
Evaluation of Best Overall Response	WISER/OnCore
Tumor Measurement	Redcap
PRO-CTCAE	Redcap
Comorbidites	Redcap
Specimen Tracking	Redcap
Tobacco Use	Redcap
Withdrawal of Consent for the Intervention	WISER/OnCore
Follow up post washout	WISER/OnCore
Demographics	Redcap
Medications	Redcap
ECOG Status	WISER/OnCore

13.3 Confidentiality and Privacy

Confidentiality will be protected by collecting only information needed to assess study outcomes, minimizing to the fullest extent possible the collection of any information that could directly identify subjects, and maintaining all study information in a secure manner. To help ensure subject privacy and confidentiality, only a unique study identifier will appear on the data collection form. Any collected patient identifying information corresponding to the unique study identifier will be maintained on a linkage file, store separately from the data. The linkage file will be kept secure, with access limited to

designated study personnel. Following data collection subject identifying information will be destroyed (state the anticipated time the data will be destroyed, e.g. three years after closure of the study, and the method of destruction), consistent with data validation and study design, producing an anonymous analytical data set. Data access will be limited to study staff. Data and records will be kept locked and secured, with any computer data password protected. No reference to any individual participant will appear in reports, presentations, or publications that may arise from the study.

13.4 Data Safety and Monitoring

The principal investigator will be responsible for the overall monitoring of the data and safety of study participants. The principal investigator will be assisted by other members of the study staff.

13.5 Reporting of Unanticipated Problems, Adverse Events or Deviations

Any unanticipated problems, serious and unexpected adverse events, deviations or protocol changes will be promptly reported by the principal investigator or designated member of the research team to the IRB and sponsor or appropriate government agency if appropriate.

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The following Appendices are required for all WFBCCC cancer treatment protocols.

Add additional appendices as needed.

***ALL** data collection forms must be included as protocol appendices at the time the protocol is submitted to the WFBCCC Protocol Review Committee (PRC) for review.*

Appendix A – Eligibility Checklist

IRB Protocol No.	**WFBCCC Protocol No.**
Study Title: Quad-Shot Radiotherapy in Combination with Immune Checkpoint Inhibition for Advanced/Recurrent Head and Neck Cancer	
Principal Investigator: Dr. Mercedes Porosnicu	

Inclusion Criteria (as outlined in study protocol)	**Criteria is met**	**Criteria is NOT met**	**Source Used to Confirm * (Please document dates and lab results)**
Advanced, recurrent or metastatic head and neck squamous cell carcinoma, as defined by clinical or pathological diagnosis of any of the following:			
Locally advanced head and neck squamous cell carcinoma not suitable for curative local treatment.	☐	☐	
Locally recurrent head and neck squamous cell carcinoma not suitable for curative local treatment within or outside a previously irradiated tissue.	☐	☐	
Metastatic head and neck squamous cell carcinoma.	☐	☐	
Target site in the head and neck region amenable to quad-shot palliative radiotherapy, as determined by the treating radiation oncologist.	☐	☐	
Age 18 years or greater at time of registration	☐	☐	
ECOG Performance Status of 0-2.	☐	☐	
Women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately.	☐	☐	
Ability to understand and the willingness to sign an IRB-approved informed consent document (either directly or via a legally authorized representative).	☐	☐	
Willingness to provide blood and saliva samples for exploratory research purposes	☐	☐	

Organ and Marrow Function as defined below:			
Absolute neutrophil count (ANC) ≥ 1.5 x 10^9/L	☐	☐	
Platelet count ≥ 100 x 10^9/L	☐	☐	
Hemoglobin ≥ 9.0 g/dL	☐	☐	
Serum bilirubin ≤ 1.5 x ULN (institutional upper limit of normal)	☐	☐	
AST and ALT ≤ 2.5 x ULN (institutional upper limit of normal)	☐	☐	
Serum creatinine CL>40 mL/min by the Cockcroft-Gault formula (Cockcroft and Gault 1976) or by 24-hour urine collection for determination of creatinine clearance: Males: Creatinine CL (mL/min) = Weight (kg) x (140 – Age) / 72 x serum creatinine (mg/dL) Females: Creatinine CL (mL/min) = Weight (kg) x (140 – Age) / 72 x serum creatinine (mg/dL) x 0.85	☐	☐	
Exclusion Criteria (as outlined in study protocol)	**Criteria NOT present**	**Criteria is present**	**Source Used to Confirm * (Please document dates and lab results)**
Radiation therapy to the head and neck region within 30 days of registration.	☐	☐	
Prior radiotherapy to the head and neck that precludes safe delivery of study radiotherapy, as determined by the treating radiation oncologist.	☐	☐	
Active medical conditions that are contraindications to study radiotherapy (i.e. scleroderma), as determined by the treating radiation oncologist.	☐	☐	
Pregnant or lactating women are excluded from this study because radiotherapy is contraindicated in pregnancy and because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with immunotherapy.	☐	☐	
Participation in another clinical study with an investigational product during the last 3 months.	☐	☐	

Any previous treatment with a PD1 or PD-L1 inhibitor	☐	☐	
Any anti-cancer therapy (chemotherapy, immunotherapy, endocrine therapy, targeted therapy, biologic therapy, tumor embolization, monoclonal antibodies, other investigational agent) within the last 30 days.	☐	☐	
Mean QT interval corrected for heart rate (QTc) ≥470 ms. except for patients with pacemaker who have a paced ventricular rhythm	☐	☐	
Current or prior use of immunosuppressive medication within 30 days, with exceptions of intranasal and inhaled corticosteroids or systemic corticosteroids at physiological doses, which are not to exceed 10 mg/day of prednisone, or an equivalent corticosteroid.and with the exception of a short course of prednisone that is prescribed for acute allergic situations or for prevention of an allergy to contrast substance utilized for imaging studies.	☐	☐	
Any unresolved toxicity (>CTCAE grade > 2) from previous anti-cancer therapy. Subjects with irreversible toxicity that is not reasonably expected to be exacerbated by the investigational product may be included (e.g., hearing loss, peripherally neuropathy).	☐	☐	
Any prior Grade ≥3 immune-related adverse event (irAE) while receiving any previous immunotherapy agent, or any unresolved irAE >Grade 1.	☐	☐	
Active or prior documented autoimmune disease within the past 2 years NOTE: Subjects with vitiligo, Grave's disease, or psoriasis not requiring systemic treatment (within the past 2 years) are not excluded.	☐	☐	
Active or prior documented inflammatory bowel disease (e.g., Crohn's disease, ulcerative colitis).	☐	☐	
History of primary immunodeficiency.	☐	☐	
History of primary immunodeficiency.	☐	☐	
History of hypersensitivity to any excipient in pembrolizumab.	☐	☐	
History of pneumonitis or interstitial lung disease.	☐	☐	
Subjects with uncontrolled seizures.	☐	☐	

Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection, symptomatic congestive heart failure, uncontrolled hypertension, unstable angina pectoris, uncontrolled cardiac arrhythmia, active peptic ulcer disease or gastritis, active bleeding diatheses, evidence of acute or chronic hepatitis B, hepatitis C or human immunodeficiency virus (HIV), or psychiatric illness/social situations that would limit compliance with study requirements or compromise the ability of the subject to give written informed consent.	☐	☐	
Known history of active tuberculosis.	☐	☐	
Receipt of live attenuated vaccination within 30 days prior to study entry or within 30 days of receiving pembrolizumab.	☐	☐	
Any condition that, in the opinion of the investigator, would interfere with evaluation of study treatment or interpretation of patient safety or study results.	☐	☐	

This subject is ☐ eligible / ☐ ineligible for participation in this study.

OnCore Assigned PID: ___ ___ ___ ___ ___ ___ ___ ___

Signature of research professional confirming eligibility: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Treating Physician: _____

Date: ___ ___ / ___ ___ / ___ ___

Signature of Principal Investigator**: _____

Date: ___ ___ / ___ ___ / ___ ___

* Examples of source documents include clinic note, pathology report, laboratory results, etc. When listing the source, specifically state which document in the medical record was used to assess eligibility. Also include the date on the document. Example: “Pathology report, 01/01/14” or “Clinic note, 01/01/14”

**Principal Investigator signature can be obtained following registration if needed

Appendix B – Protocol Registration Form

DEMOGRAPHICS

Patient: Last Name: _____ First Name: _____

MRN: ___ ___ ___ ___ ___ ___ ___ ___ DOB (mm/dd/yy): ___ ___ / ___ ___ / ___ ___

ZIPCODE: ___ ___ ___ ___ ___

SEX: ☐ Male ☐ Female Ethnicity (choose one): ☐ Hispanic

☐Non-Hispanic

Race (choose all that apply): ☐ WHITE ☐BLACK ☐ ASIAN ☐ PACIFIC ISLANDER ☐ NATIVE AMERICAN

Height: ___ ___.___ inches Weight: ___ ___ ___.___lbs.(actual)

Surface Area: ___ ___.___m^2

Primary Diagnosis: _____

Date of Diagnosis: ___ ___ /___ ___/___ ___

Performance Status: ___ ☐ ECOG

PROTOCOL INFORMATION

Date of Registration: ___ ___ / ___ ___ / ___ ___

MD Name (last) : _____

Date protocol treatment started: ___ ___ / ___ ___ / ___ ___

Informed written consent: ☐ YES ☐ NO

(consent must be signed prior to registration)

Date Consent Signed: ___ ___ / ___ ___ / ___ ___

PID # (to be assigned by OnCore): ___ ___ ___ ___ ___ ___ ___ ___

Protocol Registrar can be contact by calling [redacted] between 8:30 AM and 4:00 PM, Monday – Friday.

Compete the eligibility checklist in WISER and then give the completed Eligibility Checklist and Protocol Registration Form must be hand delivered, faxed or e-mailed to the registrar at [redacted] respectively.

Appendix C - Race & Ethnicity Verification Form

Thank you so much for helping us to verify your race and ethnicity to ensure the quality of our information. As a brief reminder, the information you provide today will be kept confidential.

1. Are you:
   - ☐ Hispanic or Latino/a
   - ☐ Not Hispanic or Latino/a

2. What is your race? One or more categories may be selected.
   - ☐ White or Caucasian
   - ☐ Black or African American
   - ☐ American Indian or Alaskan Native
   - ☐ Asian
   - ☐ Native Hawaiian or Other Pacific Islander
   - ☐ Other, Please Specify: _____

Internal use only:

Name: _____ MRN#: _____

Was the self-reported race and ethnicity of the participant verified at the time of consent?
☐ **Yes** ☐ **No**

Was a discrepancy found? **Yes** ☐ **No** ☐
If yes, please provide what is currently indicated in the EMR:
Ethnicity: _____ Race: _____

Additional comments: _____
_____
_____

Appendix D

Data and Safety Monitoring Committee (DSMC) Serious Adverse Event (SAE) Notification SOP	**Date: 02/11/2021**

Mandatory DSMC SAE Reporting Requirements in WISER

This document describes reporting requirements of adverse events from **WFBCCC Investigator Initiated interventional trials to the Data and Safety Monitoring Committee (DSMC).** A trial is considered a **WFBCCC Investigator Initiated interventional trial** if the following criteria are met:

1) The Principal Investigator (PI) of the trial is a member of a department at the Wake Forest University Baptist Medical Center.
2) WFBCCC is considered as the primary contributor to the design, implementation and/or monitoring of the trial.
3) The trial is designated as "Interventional" using the Clinical Research Categories definitions provided by the NCI in the Data Table 4 documentation. (https://cancercenters.cancer.gov/GrantsFunding/DataGuide#dt4)

There are two distinct types of WFBCCC Investigator Initiated interventional trials based on where patient enrollment occurs. These include:

1) Local WFBCCC Investigator Initiated interventional trials defined as trials where **all patients are enrolled from one of the WFBCCC sites.** These include the main outpatient Cancer Center clinics (located in Winston-Salem) as well as WFBCCC affiliate sites located in Bermuda Run (Davie Medical Center), Clemmons, Lexington, High Point, or Wilkesboro.
2) Multi-Center WFBCCC Investigator Initiated interventional trials defined as trials where patients are enrolled from other sites in addition to WFBCCC sites.
   There are three types of trials that are included in this category:
   a. Trials sponsored by the NCI Community Oncology Research Program (NCORP) that are conducted at multiple sites where the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   b. Trials sponsored by Industry that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.
   c. Trials sponsored by WFBCCC that are conducted at multiple sites and the PI is a member of a department at the Wake Forest University Baptist Medical Center.

All Adverse Events (AEs) and Serious Adverse Events (SAEs) that occur on any patients enrolled on WFBCCC Investigator Initiated Interventional trials must be entered into the WISER system. The only exception to this requirement is for patients enrolled on NCORP trials at non- WFBCCC sites. AEs and SAEs for NCORP patients enrolled at WFBCCC sites must be entered into the WISER system. Once these AEs and SAEs are entered in WISER, certain actions must be taken regarding the reporting of specific

Adverse Events to the DSMC.

All Adverse Events that occur during protocol intervention (defined below) and are coded as either 1) **unexpected grade 4,** 2) **unplanned inpatient hospitalization > 24 hours (regardless of grade)**, or **grade 5 (death)** must be reported to the DSMC using the using the SAE console in WISER.

A research nurse or clinical research coordinator when made aware that an adverse event meets one of the above criteria has occurred on a WFBCCC Investigator Initiated interventional trial, is responsible for informing a clinical member of the DSMC by phone (or in-person) about the adverse event. The nurse/coordinator should contact the treating physician prior to calling the DSMC clinical member to obtain all details of the SAE, as well as all associated toxicities to be recorded along with the SAE. In addition, this nurse or coordinator is responsible for entering the adverse event information into the SAE console in WISER. Once the adverse event has been entered into the SAE console an email informing the entire DSMC will be generated.

THESE REPORTING REQUIREMENTS APPLY TO any staff member on the study team for a WFBCCC Institutional Interventional trial. Ultimately, the protocol PI has the primary responsibility for AE identification, documentation, grading and assignment of attribution to the investigational agent/intervention. However, when an AE event as described above is observed, it is the responsibility of the person who observed the event to be sure that it is reported to the DSMC.

What is considered during protocol intervention?

During protocol intervention is considered to be the time period while a patient is on study treatment or during the time period within 30 days of last study treatment (even if patient begins a new (non-study) treatment during the 30 days). This window of 30 days should be the standard window to be used in all protocols unless a specific scientific rationale is presented to suggest that a shorter window can be used to identify events. If it is a trial sponsored by Industry and the sponsor requires a longer window for monitoring of SAEs, then the longer window of time specified by the sponsor should be followed.

What is considered as an Unexpected Grade 4 event?

Any grade 4 event that was not specifically listed as an expected adverse event in the protocol should be considered as unexpected. A grade 4 adverse event can be considered to be unexpected if it is an event that would not be expected based on the treatment being received or if it is unexpected based on the health of the patient. In either case, if there is any uncertainty about whether a grade 4 adverse event is expected or unexpected it should be reported to DSMC.

DSMC notification responsibilities of the person (e.g., nurse) handling the reporting/documenting of the SAE in WISER:

1. Make a phone call (or speak in person) to the appropriate clinical member of the DSMC according to the schedule as listed below (page if necessary).
2. Enter a new SAE into the SAE module that is located in the Subject>> CRA Console in WISER WITHIN 24 HOURS of first knowledge of the event. Information can be entered and saved, but the DSMC members will not be notified until a date is entered into the DSMC Notification Date

Field. This will ensure that all persons that need to be made aware of the event (i.e., PI, study team members and DSMC members) will be notified; remember to file a copy of the confirmation.

3. Document that the appropriate person(s) on the DSMC has been contacted. Indicate the name of the DSMC clinician that was contacted and the date and time contacted in the Event Narrative field in the SAE console of the particular subject.
4. Document whether or not the protocol should be suspended based on the discussion with the DSMC clinician. This is the major function of the email notification. Enter whether the protocol should be suspended in the Event Narrative Field.
5. Follow up/update the clinical member(s) of DSMC regarding any new developments or information obtained during the course of the SAE investigation and reporting process.

Elements needed to complete the SAE form in the Subject Console in WISER (see Screen Shot 3):

1. Event Date
2. Reported Date
3. Reported by
4. If Grade 5, enter Death Date
5. If Grade 5, enter Death occurred: within 30 days
6. Event Narrative: Brief description (include brief clinical history relevant to this event, including therapies believed related to event). Begin narrative with the DSMC clinician who was notified and Date/Time notified. In addition, state attribution by DSMC clinician as either "Unrelated", "Unlikely", "Possibly", "Probably", or "Definitely". Always include the following here:
    i. DSMC clinician name, date/time contacted and comments
    ii. Date of last dose before the event
    iii. Is suspension of the protocol needed? Y/N
7. Treating Physician comments
8. PI comments, if available
9. Protocol Attribution after discussion with DSMC clinician
10. Outcome (Fatal/Died, Intervention for AE Continues, Migrated AE, Not Recovered/Not Resolved, Recovered/Resolved with Sequelae, Recovered/Resolved without Sequelae, Recovering and Resolving)
11. Consent form Change Required? Y/N
12. SAE Classification ***This is required in order for the email notification to be sent***
13. Adverse Event Details – Enter all details for each AE associated with the SAE.
    a. Course start date
    b. Category
    c. AE Detail
    d. Comments
    e. Grade/Severity
    f. Unexpected Y/N
    g. DLT Y/N
    h. Attributions

i. Action
j. Therapy
k. Click ADD to attach the AE Detail to the SAE.

14. Enter Date Notified DSMC -- ***This is required for the email notification to be sent***
15. Click Submit. The auto-generated notification email will disseminate within 5 minutes. If you do not receive an email within 5 minutes, check that you have entered the "Date Notified DSMC" and the "SAE Classification". If these have been entered and the email still has not been received, take a screen shot of the SAE in WISER and immediately email it out to all of the DSMC members listed in this SOP. In the subject line, indicate that this is a manual transmission of the SAE in lieu of the auto-generated email. It is required that a notification goes to the DSMC members immediately so that their assessment can be obtained within the 24 hour period requirement. Contact the Cancer Center Programmer/Analyst to alert that there is an issue with the auto-generated email.

The Clinical Members of DSMC to Notify by Phone or Page:

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser
Hughes	Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes
Goodman	Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman
Reed	Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed
Porosnicu	Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu
Seegars	Lesser	Hughes	Goodman	Reed	Porosnicu	Seegars

Definition of Unavailable:

As a general guideline if the first clinician that is contacted does not respond to the phone call or page within 30 minutes, then initiate contact with the next DSMC clinician listed in the table above on the particular day the SAE is being reported. Allow up to 30 minutes for the new DSMC clinician to respond to a phone call or page before contacting the next member in the table. These times (30 minutes) are a general guideline. Best judgment as a clinical research professional should be used giving considerations of the time of day, severity of the SAE, and other circumstances as to when it is appropriate to contact backup clinicians. If the event occurs near the end of day, then leave messages (voice or email) as appropriate and proceed with submitting the DSMC notification form. It is important to take reasonable steps and to document that some type of contact has been initiated to one or more of the clinical members of DSMC.

DSMC CLINICAN RESPONSIBILITY:

It is the responsibility of the DSMC clinician to review all reported events, evaluate the events as they are reported; and communicate a response to the Investigator, event reporter and the members of DSMC. The review will include but not be limited to the information reported; there may be times when additional information is needed in order for an assessment to be made and further communication directly with the investigator may be warranted. DSMC reserves the right to disagree with the Investigator's assessment. If DSMC does not agree with the Investigator, DSMC reserves the right to suspend the trial pending further investigation. If there is any immediate danger or harm that could be present for a future patient based on the information provided in the DSMC report then an immediate suspension of enrollment should be considered.

AMENDMENTS TO PREVIOUS REPORTS

If all pertinent information is unavailable with the initial submission, once the additional information is available **do not submit a new report**. Rather, go to the original email that was sent to the DSMC and using that email "reply to all". Entitle this new email "**Amendment** for (list date of event and patient ID)" this will avoid duplications of the same event. List the additional information being reported. This information needs to be entered into WISER as well. To do this, go to the Subject console and click SAEs on the left column. Click on the appropriate SAE number that needs updating. Then click Update. This will allow additional information to be added.

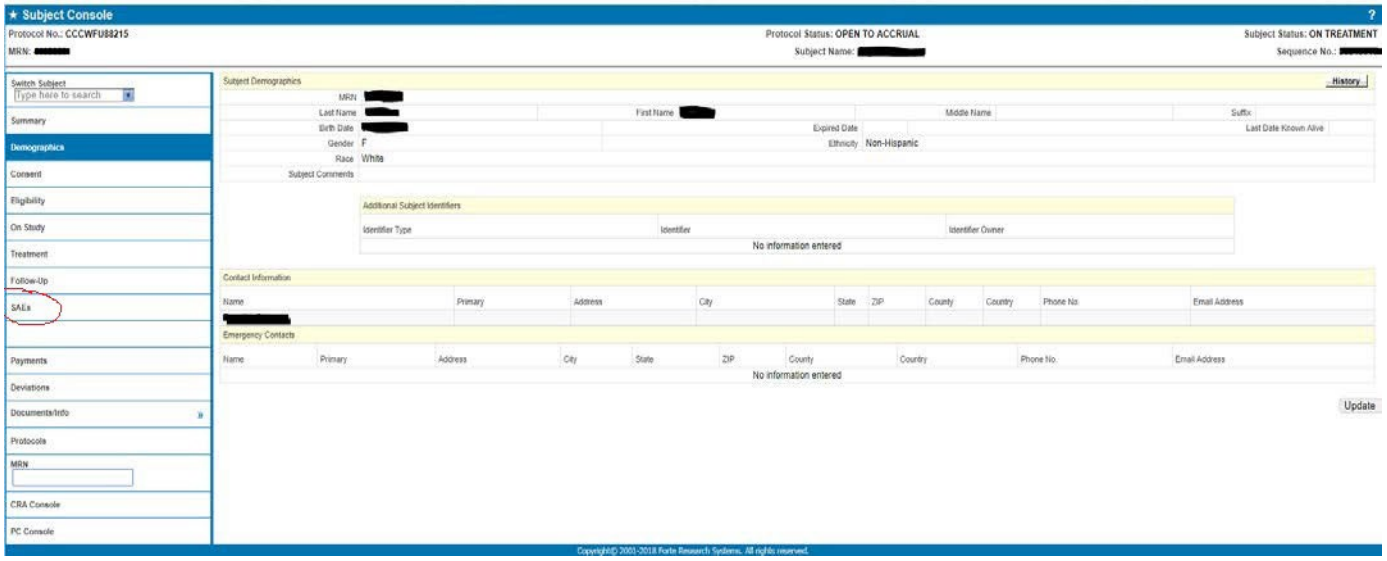
Acronyms

AE – Adverse Event
DSMC-Data and Safety Monitoring Committee
SAE-Serious Adverse Event
WFBCCC – Wake Forest Baptist Comprehensive Cancer Center
NCI-National Cancer Institute
WISER –Wake Integrated Solution for Enterprise Research

Screen Shots:

The following screen shots come from the SAE Console within the Subject Console in WISER.

Screen Shot 1:


★ Subject Console
Protocol No.: CCCWFU88215
Protocol Status: OPEN TO ACCRUAL
Subject Status: ON TREATMENT
Subject Name:
Switch Subject
Type here to search
Summary
Demographics
Consent
Eligibility
On Study
Treatment
Follow-Up
SAEs
Payments
Deviations
Documents/Info
Protocols
MRN
CRA Console
PC Console
Subject Demographics
History
MRN
Last Name
First Name
Middle Name
Suffix
Birth Date
Expired Date
Last Date Known Alive
Gender F
Ethnicity Non-Hispanic
Race White
Subject Comments
Additional Subject Identifiers
Identifier Type
Identifier
Identifier Owner
No information entered
Contact Information
Name
Primary
Address
City
State
ZIP
County
Country
Phone No.
Email Address
Emergency Contacts
Name
Primary
Address
City
State
ZIP
County
Country
Phone No.
Email Address
No information entered
Update
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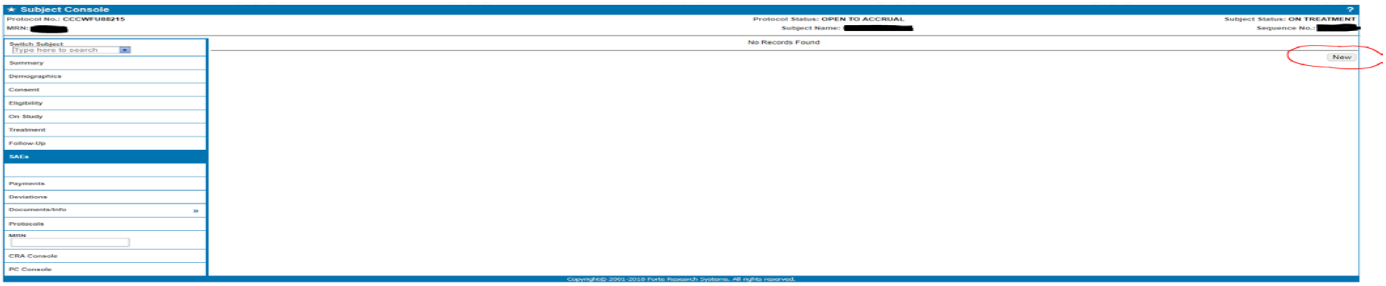
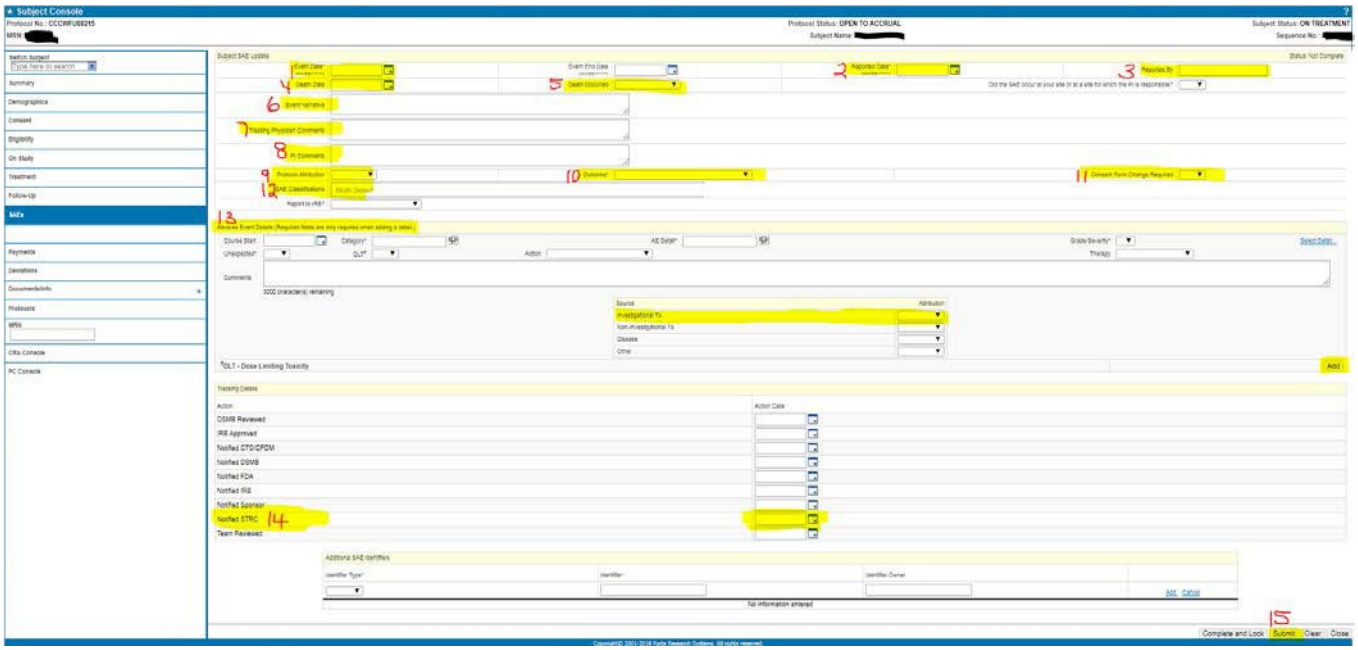
Screen Shot 2:



Screen Shot 3:



Screen Shot 4: