Phase II Study of Bempegaldesleukin (NKTR-214) Together with Palliative Radiation and anti-PD-1 Checkpoint Blockade in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma (HNSCC)[1]

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IND Sponsor: Zachary Morris, MD, PhD

IND Number: 155886

NCT04936841

STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Council for Harmonization guidelines for Good Clinical Practice (GCP) (ICH E6) and the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments, and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines.

Principal Investigator or Clinical Site Investigator:

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LIST OF ABBREVIATIONS

AE	Adverse Event/Adverse Experience
ALT	Alanine aminotransferase
ANC	Absolute Neutrophil Count
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
CB	Clinical Benefit
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CMP	Comprehensive Metabolic Panel
CNS	Central Nervous System
CoC	Certificate of Confidentiality
CR	Complete Response
CRCO	Clinical Research Central Office
CTCAE	Common Terminology Criteria for Adverse Events
CTV	Clinical Target Volume
CVA	Cerebrovascular Accident
DCR	Disease Control Rate
DHHS	Department of Health and Human Services
DOAC	Direct Oral Anticoagulation
DOT	Disease Oriented Team
DSMC	Data and Safety Monitoring Committee
EBRT	External Beam Radiation Therapy
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EQD2	Equivalent Dose in 2 Gy Fractions
FDA	Food and Drug Administration
FFPE	Formalin Fixed Paraffin Embedded
FFR	Federal Financial Report
GCP	Good Clinical Practice
GTV	Gross Tumor Volume
Hgb	Hemoglobin
HHS	Health and Human Services
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus

HNSCC	Head and Neck Squamous Cell Carcinoma
HRQoL	Patient-reported Health-Related Quality of Life
IB	Investigator's Brochure
ICH	International Council for Harmonization
IFN	Interferon
IME	Important Medical Event
IMRT	Intensity Modulated Radiation Therapy
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous
LMWH	Low Molecular Weicht Heparin
MHC	Major Histocompatibility Complex
MOS	months
MTD	Maximum Tolerated Dose
N	Number (typically refers to participants)
NKTR-214	Bempegaldesleukin
OHRP	Office for Human Research Protections
ORR	Overall Response Rate
OS	Overall Survival
PBMC	Peripheral Blood Mononuclear Cells
PD	Progressive Disease
PD-1	Programmed death one
Anti-PD1	Anti-program death one
PEG	Polyethylene glycol
PFS	Progression-free Survival
PHI	Protected Health Information
PI	Principal Investigator
PR	Partial Response
PRC	Pharmaceutical Research Center
PSR	Protocol Summary Reports
PTV	Planning Target Volume
RECIST	Response Evaluation Criteria in Solid Tumors
RT	Radiation Therapy
SAE	Serious Adverse Event/Serious Adverse Experience
SD	Stable Disease

SOC	Standard of Care
SOP	Standard Operating Procedure
ULN	Upper Limit of Normal
UP	Unanticipated Problem
UW	University of Wisconsin
UWCCC	University of Wisconsin Carbone Cancer Center
WBC	White Blood Cell
WOCBP	Women of Childbearing Potential

PROTOCOL SUMMARY

Title: *Phase II Study of Bempegaldesleukin (NKTR-214) Together with Palliative Radiation and anti-PD-1 Checkpoint Blockade in Patients with Recurrent or Metastatic Head and Neck Squamous Cell Carcinoma*

Précis: This is a Phase II study of NKTR-214 in combination with palliative radiation and anti-PD-1 checkpoint blockade in patients with recurrent or metastatic head and neck cancer. For all enrolled participants, cycle 1 consists of anti-PD-1 therapy and NKTR-214, followed by palliative radiation combined with anti-PD-1 therapy and NKTR-214 in cycle 2. In subsequent cycles participants will receive NKTR-214 and anti-PD-1. Participants who have one or more sites in need of palliative radiation therapy who have not received previous PD-1 directed therapy are eligible. The phase II study will enroll 24 subjects with a primary endpoint of overall response rate.

Objectives:

Primary Objective:

- Evaluate the objective response rate (ORR) to NKTR-214 in combination with anti-PD-1 therapy and palliative radiation in the efficacy-evaluable population.
    - *Outcome measure:* ORR will include confirmed complete response (CR) + confirmed partial response (PR) and will be determined as per RECIST1.1, by investigator assessment.

Secondary Objectives:

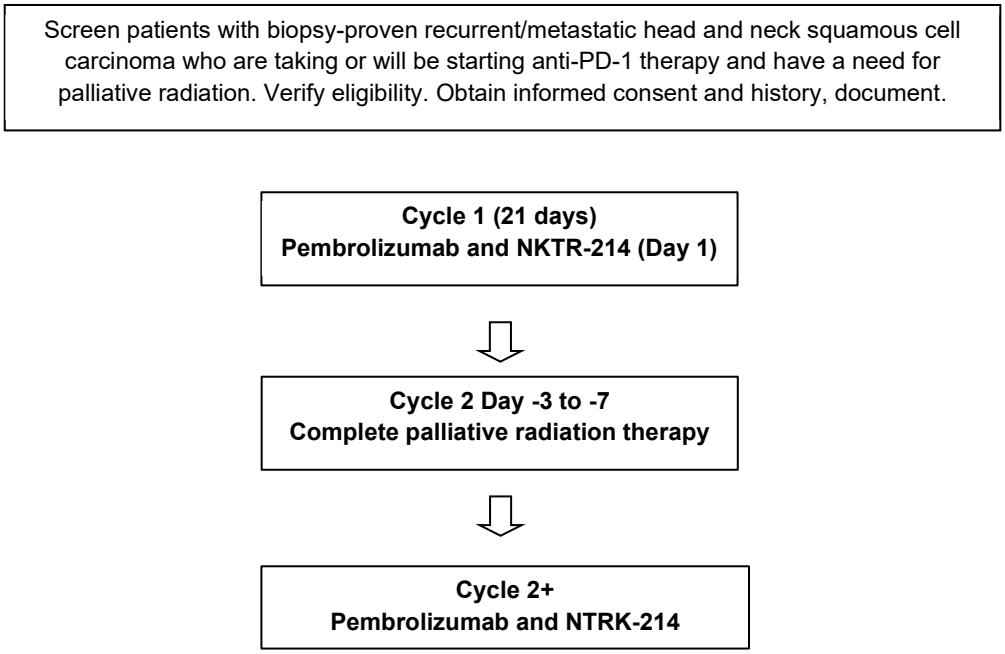
- Determine the safety, as well as, the progression free survival (PFS), overall survival (OS), clinical benefit (CB, defined as CR + PR + stable disease at ≥ 6 months (SD)), and duration of response with NKTR-214, anti-PD-1, and palliative radiation in the efficacy-evaluable population
- *Outcome measures*:
    - Toxicities ≥ Grade 3 is defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Toxicities not "unrelated" to treatment, will be considered treatment-related.
    - PFS is defined as the time from D1 of treatment until the criteria for disease progression is met as defined by RECIST1.1 or death as a result of any cause.
    - OS is defined as time from D1 of treatment until death as a result of any cause.
    - CB will include confirmed complete response (CR) + confirmed partial response (PR) + stable disease at ≥ 6 months (SD) and will be determined as per RECIST1.1.
    - Duration of response is the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented.

- Determine the impact of NKTR-214, palliative RT, and anti-PD-1 therapy on patient-reported health-related quality of life (HRQoL)
    - *Outcome measures:* Patient-reported HRQoL will be monitored to evaluate participant tolerance of treatment using EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D. These will be administered at baseline; 7 days after cycle 1 and cycle 2; then every 12 weeks to the end of treatment + once more at 30 days post treatment. HRQoL will be analyzed in pts who received ≥ 1 dose of study drug and have ≥ 1 HRQoL assessment.

	Exploratory Objectives: • Evaluate each subject's tumor expression of PD-L1 by histology (using anti-PD-L1 clone 22c3 – standard in UW Surgical Pathology) and determine whether this predicts response to NKTR-214, palliative RT, and anti-PD-1 therapy • Evaluate the immunologic activation induced by NKTR-214, palliative RT, and anti-PD-1 using serologic and flow cytometry immune assays and T cell receptor sequencing • Evaluate for histological evidence of antitumor activity based on the cellular phenotype of infiltrate
Population:	24 adult patients of any gender, race or ethnicity, age ≥ 18 with Eastern Cooperative Oncology Group (ECOG) Performance Status 0-2 and a biopsy-proven recurrent/metastatic head and neck squamous cell carcinoma who are taking or will be starting anti-PD-1 therapy and have a need for palliative radiation will be eligible for this study.
Phase:	Phase II
Number of Sites:	1
Description of Intervention:	Following an informed consent process, the subjects will receive anti-PD-1 therapy with 200 mg of pembrolizumab and NKTR-214 at 0.006 mg/ml. Palliative radiation therapy will then be delivered to tumor sites causing or felt by the treating physician to have a high potential for causing symptoms with either 8 Gy X 3 or 4 Gy X 5 completed 3 to 7 days prior to cycle 2 of anti-PD1 and NKTR-214. Combined anti-PD-1 and NKTR-214 will then be delivered each subsequent cycle. This trial will evaluate safety and efficacy of the combination of anti-PD1, NKTR-214, and palliative radiation therapy in patients with recurrent or metastatic squamous cell carcinoma of the head and neck. Twenty-four participants will be enrolled to evaluate the efficacy of this combination. Efficacy will be measured by ORR, PFS, OS, CB, and duration of response with ORR the primary outcome being compared to historical control data. Toxicity will be evaluated prior to administration of each cycle, while receiving NKTR-214 followed by every four months after the participant is off trial. Health related quality of life questionnaires will be completed with cycle 1 and 2 and then every 4 cycles thereafter.
Study Duration:	36 months
Estimated Mean Duration of Subject Participation:	9 months

Estimated Time to Complete Enrollment:	27 months

Schematic of Study Design:



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1. INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

1.1. Background Information

1.1.1. Recurrent/Metastatic Head and Neck Squamous Cell Carcinoma

Concurrent or induction chemotherapy used with radiation therapy (RT) has the potential to cure some patients diagnosed with locoregional head and neck squamous cell carcinoma (HNSCC). However, many patients will relapse with locoregional recurrent disease or metastatic spread. The median survival for patients with recurrent or metastatic HNSCC is 6-12 months (1). Some of these patients are candidates for salvage therapy with intent to cure using surgery or re-irradiation. Most, however, will ultimately require systemic palliative therapy.

1.1.2. Checkpoint Inhibitor Immunotherapy in Metastatic Head and Neck Cancer

Prior to publication of Keynote-048, anti-PD-1 checkpoint inhibition was reserved for patients with recurrent or metastatic disease that was refractory to first line platinum agents. Keynote-048 demonstrated non-inferiority of anti-PD-1 monotherapy to the previous standard of care cetuximab, platinum, and 5-FU in the overall study population and demonstrated a 17 % ORR to pembrolizumab alone in patients with metastatic or recurrent HNSCC (2). This has resulted in approval of anti-PD-1 monotherapy with pembrolizumab for patients with combined positive score for PD-L1 of greater than or equal to one. Both nivolumab and pembrolizumab are approved following progression on platinum containing chemotherapy. Nivolumab and pembrolizumab are checkpoint inhibitors that bind PD-1 surface molecules on immune cells and antagonize the interactions of PD-1 with PD-L1. In healthy individuals, this PD-1/PD-L1 interaction suppresses the immune system, thereby preventing autoimmune disease. HNSCC and other tumor types utilize PD-L1 expression as a means to evade immune surveillance and turn off an anti-tumor immune response. Nivolumab and pembrolizumab block the PD-1/PD-L1 interaction in the tumor microenvironment, effectively “taking the breaks off” the immune system.

1.1.3. NKTR-214 in Combination with Anti-PD-1 Following Palliative Radiation

Preclinical and clinical studies demonstrate a cooperative interaction between radiation and anti-PD-1 checkpoint blockade (3). In this context, radiation can function as a method of in situ tumor vaccination resulting in enhanced dendritic cell maturation, antigen cross-presentation, and diversification of the anti-tumor T cell response. A Phase II clinical trial (MSKCC 15-253) delivered combined anti-PD-1 checkpoint blockade together with radiation in patients with recurrent/metastatic HNSCC. Early results did not indicate any excess toxicity with this combination (11 % incidence of treatment related toxicity ≥ Grade 3). That study demonstrated an overall response rate of 22 % and median PFS of 2.4 mos with radiation and anti-PD-1 therapy in patients with metastatic or recurrent HNSCC.

Bempegaldesleukin (NKTR-214), a novel cytokine with enhanced immune system activation, has the potential to be an important advancement for the treatment of patients with cancer. NKTR-214 consists of IL2, which has the same amino acid sequence as aldesleukin, conjugated at a defined region within the protein to releasable polyethylene glycol (PEG) chains. The PEG chains render the molecule inactive. After administration in vivo, the PEG chains are slowly hydrolyzed to generate active cytokine conjugates. This affords a superior safety profile for NKTR-214 compared to IL2, allowing for outpatient administration and a longer duration of action requiring less frequent dosing. The most active IL2 conjugates are 2-PEG-IL2 and

1-PEG-IL2. The location of the PEG chains on the active conjugated-IL2 reduces its affinity to the IL2 receptor alpha subunit (IL2Ra), responsible for activating undesirable Treg cells to a greater extent than affinity to the IL2-receptor beta subunit (IL2Rb) (4, 5). In the tumor, NKTR-214 preferentially activates CD8+ T cells and natural killer (NK) cells over Treg cells and provides sustained exposure to active 1-PEG and 2-PEG-IL2 (6).

Preclinical data from our group and others suggests a synergistic interaction between NKTR-214 and radiation (7). In this combination, radiation acts as a “spark” by inducing neoantigen presentation by tumor cells on MHC-I, increased IFN-γ production, and improved antigen presentation (8). NKTR-214 helps to exploit these immunologic changes at the tumor by increasing tumor infiltrating lymphocytes (mainly CD4 and CD8 T cells) and NK cells (5). The combination has repeatedly been shown to be effective in preclinical syngeneic murine tumor models where neither treatment alone is sufficient to decrease tumor burden, but combined radiation and NKTR-214 result in decreased tumor burden and ~80 % of the mice become disease free.

In a recent clinical study (PIVOT-02), NKTR-214 demonstrated safety in combination with anti-PD-1 checkpoint blockade. Grade 3 or 4 treatment-related adverse events (AEs) were observed in 5.7 % of patients receiving NKTR-214 dose at or below 0.006 mg/kg plus anti-PD-1 checkpoint blockade. At a higher NKTR-214 dose 0.009mg/kg with anti-PD-1 blockade, two patients experienced dose limiting toxicity in the form of hypotension and metabolic acidosis. There were no patient discontinuations due to treatment-related AEs and no treatment-related deaths. Based off the PIVOT-02 toxicity results, we have decided to forgo a traditional 3+3 dose escalation study exploring the toxicity of NKTR-214 in combination with anti-PD-1 following palliative radiation. Instead, we propose to test the safety and efficacy of the MTD dose of the PIVOT-02 trial (0.006 mg/kg NKTR-214) in combination with palliative radiation and anti-PD-1 therapy.

The PIVOT-02 trial also demonstrated NTKR-214 in combination with anti-PD-1 is effective in mounting an anti-tumor immune response. This combination (0.006 mg/kg NKTR-214 + 360 mg Nivolumab q3w) has shown efficacy in patients with Stage IV melanoma [ORR 50 %, disease control rate (DCR) 71 %], Stage IV renal cell carcinoma (ORR 46 %, DCR 77 %), and Stage IV non-small cell lung carcinoma (ORR 75 %, DCR 75 %) (9, 10).

1.2. Rationale

Based on the available clinical data and preclinical data, we hypothesize that the combination of palliative radiation, NKTR-214, and anti-PD-1 checkpoint blockade will improve the ORR compared to a 22 % estimated ORR (based on historical data outlined above) for pembrolizumab alone or pembrolizumab plus palliative radiotherapy in patients with metastatic or recurrent HNSCC. Given the non-redundant and potentially synergistic immunologic effects of radiation, NKTR-214, and anti-PD-1 checkpoint blockade, our primary hypothesis is that this combination will be effective in generating an anti-tumor immune response against recurrent/metastatic HNSCC resulting in ≥ 44 % ORR. We further anticipate a rate of ≤ 25 % unexpected grade 3 toxicity with good patient-reported HRQoL and with correlative evidence demonstrating a more diversified and activated adaptive anti-tumor immune response. Because many side effects related to IL2 based therapies are predictable, transient, and manageable, they should not limit the evaluation of overall safety or therapeutic efficacy.

1.3. Potential Risks and Benefits

1.3.1. Potential Risks

NKTR-214

The potential AEs of NKTR-214 have been assessed in recent clinical studies and commonly include: fatigue, flu-like symptoms, rash, fever, pruritus, hypotension, decreased appetite, arthralgia, and cough. Flu-like symptoms, rash and pruritus are assumed to be cytokine mediated and have occurred 3-4 days after treatment. These were mild to moderate in severity. Other possible risks include, anemia, periorbital edema, cerebrovascular accident, atrial fibrillation and tachycardia, abdominal pain, constipation, diarrhea, nausea, weight decrease, myalgia, dizziness, headache, syncope, anxiety, dyspnea, dysphonia, and pleural effusion.

SAEs of cerebrovascular accident (CVA), including one fatal event, have been observed in patients who have received NKTR 214 in the triplet combination with nivolumab and ipilimumab and in the doublet combination with nivolumab. A comprehensive search (data cutoff 21 June 2019) found 3 of 43 patients (7 %) who received triplet therapy in Study 16-214-02 (PIVOT-02) to have CVA events, all of which were considered by the investigator to be related to treatment with bempegaldesleukin, nivolumab, and ipilimumab. Additionally, 8 of 478 patients (1.7 %) who received doublet therapy (bempegaldesleukin and nivolumab) in Study 16-214-02 had CVA events, which were considered by the investigator to be related to treatment with bempegaldesleukin and nivolumab in 3 patients, to nivolumab in 1 patient, and unrelated to treatment in 4 patients. The relationship of these events to the triplet and doublet combinations is unclear. Based on these events and a comprehensive assessment of CVA across all NKTR-214 clinical studies, CVA has been escalated to an adverse event of special interest (AESI) and mitigations have been put in place to reduce the risk of CVA. These mitigations include implementation of a CVA AESI management algorithm (Appendix B) and updates to the exclusion criteria, renal function and hydration assessment, hydration guidelines, concomitant and prohibited medications, dose modification guidelines, and discontinuation criteria. Additional information on the clinical safety and risk of CVA is found in the NKTR-214 Investigator's Brochure (IB).

There is also the risk that previously unidentified AE could occur, as this is an investigational agent.

Anti- PD-1

The side effects of anti- PD-1 therapy are well described and are similar between nivolumab and pembrolizumab. The most common side effects reported in 20 % of patients were fatigue, pruritus, diarrhea, decreased appetite, rash, dyspnea, constipation, and nausea. Other serious but less common side effects were immune related pneumonitis, colitis, hepatitis, endocrinopathies (including hypophysitis thyroid disorders and type I diabetes mellitus), nephritis, infusion reactions, and embryonal toxicities.

Palliative radiation therapy

The side effects related to radiation therapy will vary by the site in need of palliative radiation therapy. They are well known but are listed here to distinguish between those related to NKTR-214. Within the head and neck region, common side effects include: mucositis, difficulty swallowing which may necessitate a feeding tube, dry mouth, change in taste and smell, reduced saliva production, hoarseness, radiation dermatitis, ear pain/infection, hearing loss, fatigue, weight loss, dehydration requiring IV fluids and electrolyte replacement, hair loss, tooth decay, decreased thyroid function. Rare and serious side effects include: breathing and swallowing issues that require a tracheotomy, nerve damage in the head and neck region, radiation necrosis of the jaw, damage to the larynx or nerves, damage to the skin, soft tissues or other parts of the head and neck that may require a surgery to correct and damage to the spinal cord which may cause permanent weakness.

Outside of the head and neck, side effects vary by body region. Within the thorax, common side effects include esophagitis, dry cough, and fatigue. Esophagitis may require gastrostomy tube placement. Rare but significant side effects include radiation pneumonitis, radiation fibrosis, and rib fracture. Within the abdominal and pelvic regions, common side effects include diarrhea, nausea, and fatigue. Rare but significant side effects include ulcer, hemorrhage, obstruction, liver failure, renal failure, radiation cystitis, radiation proctitis, and pelvic insufficiency fracture. At extremity and skin sites, common side effects include skin reaction and fatigue. Significant effects include lymphedema and rarely non-healing wound.

Other risks from research-related procedures

- Biopsy tissue collection: primary risks include temporary discomfort, bleeding, infection, and ulceration
    - There are some risks associated with a tissue biopsy and steps will be taken to minimize these. Standard laboratory tests will be done to assess bleeding risk before the procedure is done. The sample will be taken from an area of reduced risk of complications. Possible side effects of a biopsy include bleeding, infection, bruising, pain or discomfort at the biopsy site and possible side effects from the local anesthetic (pain or bruising at the site where anesthetic is given). The main discomfort associated with this test is pain when the bone or tissue is being withdrawn. In order to make the procedure more comfortable, subjects may get a local anesthetic such as lidocaine to numb the area, at the discretion of the physician performing the biopsy. Local anaesthesia is generally very safe, however potential risks include blurred vision, dizziness, vomiting, headache, muscle twitching, continuing numbness, weakness, tingling, and allergic reaction. It is recommended that subjects be observed for at least 2 hours after the biopsy.
- CT scans for biopsies: At the time of biopsy, a CT scan may be done to determine where the biopsy will be done. After the biopsy, a CT scan may be done over the biopsy site to look for any immediate complications. These scans will be performed in addition to the scans as part of normal cancer care. The scans involve exposure to radiation in the form of x-rays. The level of radiation used is kept to a minimum to prevent damage to body cells. Under some rare circumstances of prolonged, high-dose exposure, x-rays

can cause adverse health effects, such as skin reddening (erythema), skin tissue injury, hair loss, and cataracts. The amount of radiation from the additional scans in this study is not known to be associated with any serious health risks. The exposure related to this CT scan equals approximately one year of standard environmental background radiation.

- IV fluid bolus is generally very safe, however potential risks include injury to peripheral vein, bleeding, bruising, infection at infusion site, and development of peripheral or pulmonary edema.
- Blood draws for clinical laboratory testing risks include bruising, swelling at the injection site, dizziness and lightheadedness.
- Questionnaire risk loss of confidentiality, which is possible but not likely with data security safeguards in place.

1.3.2. Potential Benefits

There is no known benefit to subjects' participation in this study. While there is hope that a subject's cancer will respond to treatment with the combination of NKTR-214 with palliative radiation, anti-PD-1 checkpoint inhibitor, there is no proof of that at this stage. Pembrolizumab was shown to be non-inferior to EXTREME chemotherapy in patients with cancer positivity score 1 on Keynote-048. Anti- PD-1 is the standard of care for all patients after progression on platinum doublet. Thus, as this therapy adds to the standard of care, we expect it to be no less effective. The current ORR with anti-PD-1 therapy or anti-PD-1 therapy together with palliative radiation in this patient population is 20 % and PFS is approximately 5 months, demonstrating an unmet need. This study is likely to yield knowledge about the use of NKTR-214 in treating HNSCC when combined with palliative external beam radiation therapy and checkpoint inhibitors, which could help future patients.

2. OBJECTIVES AND OUTCOME MEASURES

2.1. Primary

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Evaluate ORR in patients receiving NKTR-214 in combination with palliative radiation, and pembrolizumab.	Response to anti-PD-1 therapy can be quite durable in patients with metastatic or recurrent HNSCC (~ 22 months); however, low ORR (~ 20 %) limits therapeutic benefit in this population as a whole. Improving ORR could result in a dramatic impact on survival of patients with metastatic or recurrent HNSCC.	ORR will include confirmed CR + confirmed PR and will be determined as per RECIST1.1. Progression of any radiated tumors will be considered in this evaluation but response of radiated tumor(s) will not be considered as evidence of response for the purpose of this study.	• Pre-treatment standard-of-care imaging • Standard-of-care imaging 3 to 6 months after Cycle 1

2.2. Secondary

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Evaluate the safety of NKTR-214 in combination with anti-PD-1 therapy and palliative radiation.	Grade 3 or grade 4 adverse event except those listed in 8.3.2 are anticipated to occur in < 25 % of patients based on the previous rate of 11 % with PD-1 inhibition and radiation. The safety of this combination must be established prior to evaluation of efficacy.	Toxicities ≥ Grade 3 will be defined by the NCI Common Terminology Criteria for Adverse Events (CTCAE) v5. Toxicities not determined to be "unrelated" to treatment, will be considered treatment-related (including those that are unlikely, possibly, probably, or definitely related).	• Study screening • Cycle 1, day 1, 8 • Cycle 2, day 1, 8 • Cycle 3+, day 1 • Every 4 months once off study without progression for 5 years, Every 6 months once off study with progression for 3 years

Objective	Brief Description/ Justification of Outcome Measure	Outcome Measured By	Time Frame
Determine CB, PFS, duration of response, and OS after treatment with NKTR-214, anti- PD-1, and palliative radiation.	PFS, OS, CB, and duration of response were chosen as efficacy outcomes based on prior immunotherapy trials. Duration of response is particularly important, as more durable responses are expected with immunotherapy.	• CB will include confirmed complete response (CR) + confirmed partial response (PR) + stable disease at ≥ 6 months (SD) and will be determined as per RECIST1.1. • PFS is defined as the time from D1 of treatment until the criteria for disease progression is met as defined by RECIST1.1 or death as a result of any cause. • OS is defined as time from D1 of treatment until death as a result of any cause. • Duration of response is the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented.	• D1 of treatment • Standard-of-care imaging follow-up ~3 and 6 months after Cycle 1 • Time of disease progression • Death
Determine the impact of NKTR-214, palliative RT, and anti-PD-1 therapy on patient-reported health-related quality of life (HRQoL)	In incurable diseases, patient reported outcomes and quality of life have great influence in a patients' choice of therapy.	• Patient-reported HRQoL will be monitored to evaluate patient tolerance of treatment using EORTC QLQ-C30, EORTC QLQ-H&N35, and EQ-5D. • HRQoL will be analyzed in subjects who received ≥ 1 dose of study drug and have ≥ 1 HRQoL assessment.	• Cycle 1, Day 1 pre-treatment • Cycle 1, Day 8 • Cycle 2, Day 8 • Cycle 3, day 1 and every day 1 every 4 cycles (Q12 weeks) to discontinuation of therapy (Sect 5.5) 30 days post treatment

2.3. Tertiary/Exploratory

Objective	Brief Description/Justification of Outcome Measure	Outcome Measured By	Time Frame
Evaluate each subject's tumor expression of PD-L1 by histology and determine whether this predicts response to NKTR-214, palliative RT, and anti-PD-1 therapy.	PD-L1 expression has been shown to predict response to immunotherapy regimens. If PD-L1 expression correlates with outcome, it could be used in the future to select patients who have greatest benefit from this regimen.	• Expression of PD-L1 by histology	• Baseline • Cycle 2, Day 8
Evaluate the immunologic activation induced by NKTR-214, palliative RT, and anti-PD-1 using serologic and flow cytometry immune assays and T cell receptor sequencing.	Evaluation of the *in vivo* immune response will help better define the mechanism of action of this combination therapy.	• Levels of IFN-γ expressing and CD122+ T cells in Peripheral Blood Mononuclear Cells (PBMC) • Diversity and clonality of the T cell receptor repertoire by deep sequencing of PBMC	• Cycle 1, 2, and 3, Day 1 prior to treatment infusion • Cycle 1, 2, and 3, Day 8 • 30 days post-treatment
Evaluate for histological evidence of antitumor activity based on the cellular phenotype of infiltrate.	Evaluation of the *in vivo* immune response will help better define the mechanism of action of this combination therapy.	• Levels of tumor infiltrating lymphocytes by histology	• Baseline • Cycle 2, Day 8

3. STUDY DESIGN

This is a Phase II study to characterize the efficacy of NKTR-214 in combination with palliative radiation, and anti-PD1 in metastatic head and neck cancer patients. These patients very frequently require palliation of local symptoms with radiation in combination with systemic therapies and currently have very limited systemic options, making this an ideal population for investigation of NKTR-214 combination therapy. The study has been designed as a phase II due to the results of PIVOT-02, which demonstrate safety of anti-PD1 and NKTR-214 at the doses utilized in this study. The palliative radiation therapy delivered is unlikely to significantly increase toxicity. We will conduct efficacy evaluation on 24 participants. Under the null hypothesis for ORR ≤ 0.22, based on one-sided one sample proportion test with type I error of 0.1, the expected power levels to detect alternative ORRs of 0.35, 0.4, and 0.45 are 55 %, 74 %, 87 % respectively. The null hypothesis will be rejected and superiority concluded if 8 or more responses are observed in 24 participants. This design yields a type I error rate of .04 and power of 0.8 when the true response rate is 44 %.

4. STUDY POPULATION

4.1. Participant Inclusion Criteria

To be eligible to participate in this study, an individual must meet all of the following criteria:

1. Written informed consent and HIPAA authorization for release of personal health information. NOTE: HIPAA authorization may be included in the informed consent or obtained separately
2. Qualify for anti-PD-1 therapy based on current guidelines at the time of registration. This includes the standard requirement for the participant's tumor to have been previously determined to express PD-L1 with a combined positive score ≥ 1, as determined by an FDA-approved test.
3. Age 18 years and older at the time of consent
4. ECOG Performance Status of 0-2 within 30 days prior to enrollment
5. Histologically proven diagnosis of head and neck squamous cell carcinoma that is metastatic or recurrent disease that is surgically incurable
6. Prior cancer treatment other than anti-PD-1 therapy must be completed at least 30 days prior to registration and the subject must have recovered from all reversible acute toxic effects of the regimen (other than alopecia) to ≤ Grade 1 or baseline. Patients may not undergo concurrent anti-cancer treatment during treatment with protocol therapies. This includes no treatment with growth factors, tyrosine kinase inhibitors, tumor-specific antibodies, or cytotoxic chemotherapies such as cisplatin. Patients who have previously or are currently taking an anti-PD-1 therapy are eligible for this study if they meet eligibility criteria 2. Patients who have previously taken any other immune checkpoint inhibitor are eligible as long as they have completed that treatment at least 30 days prior to registration and meet all other eligibility criteria.
7. Subjects with central nervous system (CNS) metastases are eligible if the CNS lesions are stable for at least 2 months and if tapered off treatment doses of systemic corticosteroids for at least 2 weeks prior to enrollment on the trial. Management with maintenance physiologic doses of corticosteroids (equivalent doses of prednisone ≤ 10 mg daily) is acceptable.
8. Subjects must have an "index" tumor that: 1) is deemed by the treating radiation oncologist to potentially benefit from palliative radiation 2) is amenable to biopsy, 3) is ≥ 1 cm in longest dimension.
9. Demonstrate adequate organ function as defined in the table below; all screening labs to be obtained within 30 days prior to enrollment

System	Laboratory Value
Hematological	
White blood cell (WBC)	≥ 3,000/mm^3
Absolute Neutrophil Count (ANC)	≥ 1,500/mm^3
Hemoglobin (Hgb)	≥ 9 g/dL
Platelets	≥ 100,000/mm^3
Renal	
Serum creatinine	≤ 2.0 mg/dL
Hepatic	

Total Bilirubin	≤ 2.0 × ULN (< 3.0 for subjects with Gilbert's Syndrome)
Aspartate aminotransferase (AST)	≤ 3 × ULN
Alanine aminotransferase (ALT)	≤ 3 × ULN

10. Females of childbearing potential must have a negative serum pregnancy test within 14 days prior to enrollment and must agree to use effective contraception during active treatment and for 5 months after last dose of pembrolizumab and/or NKTR-214. NOTE: Females are considered of childbearing potential unless they are surgically sterile (have undergone a hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or they are naturally postmenopausal for ≥ 12 consecutive months.
11. As determined by the enrolling physician or protocol designee, ability of the subject to understand and comply with study procedures for the entire length of the study

4.2. Participant Exclusion Criteria

An individual who meets any of the following criteria will be excluded from participation in this study:

1. Subjects with significant intercurrent illnesses per physician discretion
2. Subjects with active or acute infections or active peptic ulcers, unless these conditions are adequately corrected or controlled, in the opinion of the treating physician
3. Subjects with a diagnosed auto-immune disease (exceptions: subjects with controlled diabetes mellitus type I, thyroid disease, rheumatoid arthritis, vitiligo and alopecia areata not requiring treatment with immunosuppressants are eligible)
    - Subjects with a history of diabetes mellitus requiring systemic therapy within the past 3 months (i.e. either oral hypoglycemic agents or insulin) must have a documented Hemoglobin A1c < 8.0 % within 90 days of registration.
4. Subjects with known genetic conditions causing pre-disposition to RT toxicity (i.e.: Li-Fraumeni, ATM deficiency, active scleroderma, etc.)
5. Subjects with a prior diagnosis of CVA or transient ischemic attack (TIA)
6. Pregnant or breastfeeding (**NOTE:** breast milk cannot be stored for future use while the mother is being treated on study)
7. Known additional malignancy that is active and/or progressive requiring treatment; exceptions include basal cell or squamous cell skin cancer, in situ cervical or bladder cancer, or other cancer for which the subject has been disease-free for at least three years prior to enrollment
8. Prolonged Fridericia's corrected QT interval (QTcF) > 450 ms for men and > 470 ms for women at time of enrollment
9. Subjects with symptoms of ischemic cardiac disease, congestive heart failure, or myocardial infarction within 6 months of registration and/or uncontrolled cardiac rhythm disturbance
10. Subjects with a pulmonary embolism, deep vein thrombosis, or prior clinically significant venous or non-CVA/TIA arterial thromboembolic event (e.g., internal jugular vein thrombosis) within 3 months prior to enrollment
    - Patients with a history of a venous or arterial thromboembolic event must be asymptomatic prior to enrollment and must be receiving a stable regimen of

therapeutic anticoagulation (low molecular weight heparin [LMWH] or direct oral anticoagulation [DOAC]). Use of coumadin is permitted; however, therapeutic dosing should target a specific international normalized ratio (INR) stable for at least 4 weeks prior to enrollment. NKTR-214 has the potential to down-regulate metabolizing enzymes for coumadin for approximately 1 week after administration of each dose of NKTR-214. Due to the possibility of drug-drug interactions between coumadin and NKTR-214, frequent monitoring of INR and ongoing consideration of dose adjustments are warranted throughout the patient's participation on study.

11. Subjects with significant psychiatric disabilities or seizure disorders if considered unsafe in the opinion of the treating physician
12. Subjects with symptomatic pleural effusions or ascites
13. Subjects with organ allografts
14. Subjects who require, or are likely to require, systemic treatment doses of corticosteroids, or other immunosuppressive drugs, or have used them within 2 weeks of registration (clarification: subjects receiving physiologic maintenance or replacement doses of systemic steroids or inhaled steroids are eligible)
15. Subjects with known human immunodeficiency virus (HIV) infection, active or chronic hepatitis B or hepatitis C infection, or with clinical evidence of hepatitis
16. Subjects with known hypersensitivity to IL2 or those who experienced significant immune-related AEs requiring treatment with steroids or other immunosuppressant therapy during prior treatment with ipilimumab, or anti- PD-1/PD-L1 checkpoint blockade therapy
17. Subjects who cannot provide independent, legal, informed consent

4.3. Strategies for Recruitment and Retention

The methods used for recruitment of subjects in the study will be devoid of any procedures that may be construed as coercive. The recruitment process will not involve any restrictions on socio-demographic factors, including gender or ethnic characteristics, of the subject population. However, the composition of the study participant population will depend on patient sources available to the clinical site.

The trial will be managed by physicians at the University of Wisconsin Hospital and Clinics and will be conducted at the University of Wisconsin Hospital and Clinics. 24 eligible subjects will be recruited from the treating physicians' own clinical practice, through clinic contacts, and referring physicians.

4.4. Treatment Assignment Procedures

Patients who agree to participate in the clinical trial and have been deemed eligible to do so based upon inclusion/exclusion criteria will be enrolled after they provide written informed consent. The study coordinator will assign a case number and register the patient in the UWCCC OnCore database prior to study therapy. The following information will be recorded for the purpose of registration.

- Protocol number
- Subject's name
- Subject's medical record number
- Subject's demographic data such as:

  - Birth date
  - Race
  - Ethnicity
  - Gender
  - Insurance type
- Date of consent

4.5. Participant Withdrawal or Discontinuation from Study Procedures/Intervention

4.5.1. Reasons for Participant Withdrawal or Discontinuation from Study Procedures/Intervention

Subjects are free to withdraw from participation in the study at any time upon request.

Treatment may continue as specified in the above treatment modality sections or until one of the following criteria applies:

- disease progression;
- intercurrent illness that prevents further administration of treatment;
- unacceptable adverse event(s) (as determined by the subject or treating physician)
- subject decides to withdraw consent for participation in the study;
- subject refuses further treatment (without withdrawing consent for study participation);
- general or specific changes in the subject's condition render the subject unacceptable for further treatment in the judgment of the treating physician;
- new data related to the experimental agent which would suggest that continuing treatment on protocol would impose unwarranted potential risks beyond what was known at the time of treatment initiation;
- delay of any protocol therapy for > 15 weeks
- a female subject becomes pregnant;

Subjects will be removed from protocol therapy and the site investigator notified when any of the criteria listed above apply. The reason for discontinuation of protocol therapy will be documented on the electronic case report form (eCRF).

4.5.2. Handling of Participant Withdrawals from Study or Participant Discontinuation of Study Intervention

Subjects will be removed from protocol therapy and the site investigator notified when any of the criteria listed above apply. The reason for discontinuation of protocol therapy will be documented on the eCRF.

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete the final study assessments. The study team will attempt to contact the subject by telephone or through a clinic visit to determine the reason for the study withdrawal. If the reason for withdrawal is an adverse event, it will be recorded on the eCRF. The study team will make all efforts to undertake protocol-specified safety follow-up procedures to capture AEs, serious adverse events (SAEs), and unanticipated problems (UPs).

If a subject leaves the study prior to administration of NKTR-214, they will be replaced by an additional subject.

4.6. Premature Termination or Suspension of Study

This study may be suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to the UWCCC DSMC and regulatory authorities. The principal investigator will also promptly inform the institutional review board (IRB) and will provide the reason(s) for the termination or suspension.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Insufficient adherence to protocol requirements
- Poor enrollment (< 1 patient in any 18 month period)
- Request to discontinue the study from a regulatory authority
- Company business decision
- Data that are not sufficiently complete and/or evaluable

5. STUDY INTERVENTION

5.1. Pembrolizumab (Standard of Care)

5.1.1. Acquisition

Pembrolizumab is kept on formulary and would be administered as part of the standard of care for participants enrolled on this study.

5.1.2. Formulation, Packaging, Labeling, and Administration

Commercial supplies will be utilized. Formulation and labeling will be per package inserts. UW Health standard operating procedures will be followed for administration.

5.2. NKTR-214 (Research-related)

The study will utilize the UWCCC's Pharmaceutical Research Center (PRC). The PRC ensures that drug research protocols proceed optimally through UWCCC's established medication use system and in accordance with all federal, state, institutional and sponsor regulations governing clinical research.

5.2.1. Acquisition

NKTR-214 will be provided by Nektar Therapeutic's designated manufacturer and an estimated 3-4 month supply will be delivered directly to the institution based on anticipated rates of accrual.

5.2.2. Formulation, Packaging, and Labeling

NKTR-214 drug product is packaged as a sterile, single-use, lyophilized powder in 5 mL glass vials to be reconstituted and diluted for IV injection. Each vial of NKTR-214 drug product has a label claim of 1.0 mg rhIL2.

5.2.3. Product Storage and Stability

The product will be stored at -20 ºC +/- 5 ºC. Vials will be protected from light prior to reconstitution. After reconstitution, the solution does not need to be protected from light. The solution may be held at room temperature for up to 6 hours prior to infusion.

5.2.4. Dosage, Preparation and Administration of Study Product

NKTR-214 will be reconstituted in 1.1 mL water for injection by the PRC. The reason for reconstitution in 1.1 mL is a 0.1 mg overflow (total of 1.1 mg per vial) to ensure the full 1 mg of medication can be withdrawn for injection. The product should not be shaken to reconstitute but can be gently inverted. It should subsequently be diluted into 5 % dextrose or 0.9 % sodium chloride, USP. The final concentration for infusion should be 0.0024 mg/mL to 0.0675 mg/mL.

PRC will document release of NKTR-214 to research nurse/staff or physician. Each subject will receive NKTR-214 through a freely-running peripheral IV catheter in the D5W or NS as noted above. Dosage will be 0.006 mg/kg and can be decreased to 0.003 mg/kg for some participants according to rules in section 5.5 of this protocol. **AN IN-LINE FILTER INCLUDING IN-LINE FILTER EXTENSION SETS MUST NOT BE USED DUE TO DRUG LOSSES ON THE FILTER MEMBRANE.** If a filter must be used, only 15 µm pore size drip-chamber filters are acceptable. NKTR-214 infusion must be promptly followed by a flush of diluent to clear the line. Care must be taken to assure sterility of the prepared solution as the product does not contain any antimicrobial preservative or bacteriostatic agent. NKTR-214 infusions prepared in 0.9 % NaCl solution or 5 % Dextrose solutions are compatible with polyvinyl chloride or polyolefin containers and infusion sets, as well as closed-system transfer devices (CSTDs) when following specific instructions to ensure prepared dose accuracy. Please refer to the Pharmacy Manual/current Investigators Brochure for requirements regarding preparation and administration.

5.2.5. Premedication for Flu-like Symptoms

These recommendations have been developed to reduce the risk of flu-like symptoms during the first week of each treatment cycle. Investigator may modify these recommendations based on the needs of individual patient.

- Administer acetaminophen (eg, 650 mg every 6 hours) or NSAIDs (eg, ibuprofen 400 mg every 6 hours) a minimum of 30 minutes prior to treatment on Day 1 of each cycle.

- Administer acetaminophen or NSAIDs q6h on Day 2 to 5 of each cycle.

- Instruct patients on the signs and symptoms (fever over 100.4 °F or 38 °C, chills and sweats, muscle aches or join paint, fatigue and weakness), how to treat with acetaminophen or NSAIDs, and when to call their treating oncologist or present for medical care.

5.3. Accountability Procedures for the Study Product

A 3-4 month supply of NKTR-214 will be delivered from Nektar Therapeutics to the UWCCC Pharmaceutical Research Center (PRC) at the beginning of the study and will be replenished 3-4 times annually in an amount sufficient to meet the demands of anticipated study accrual. UWCCC PRC will maintain careful inventory of the study drug, per standard operating procedures. Any unused NKTR-214 remaining at the end of this study will be destroyed by the UWCCC PRC.

5.4. Assessment of Participant Compliance with Study Product Administration

All therapeutic medications will be administered at UW facilities via intravenous route and delivery will be documented in the UWHC electronic medical record system by research nurses or treating physicians. External beam radiation therapy delivery will be confirmed via the record and verify system.

5.5. Modification or Delay of Protocol Therapy

Participants experiencing Grade 4 toxicity with a probable or definite attribution to NKTR-214 will discontinue this treatment indefinitely. Participants experiencing Grade 4 toxicity with an unrelated, unlikely, or possible attribution to NKTR-214 will delay further therapy with this agent until this toxicity resolves to baseline or < Grade 2, or is deemed irreversible.

Participants with toxicities ≤ Grade 3 will remain eligible to continue or to resume NKTR-214, but may be required to take a treatment break according to the following rules:

> Participants experiencing Grade 3 toxicity with an unrelated, unlikely, or possible attribution to NKTR-214 or Grade 2-3 toxicity with a probable or definite attribution to NKTR-214 will delay further therapy with this agent until this toxicity resolves to baseline or < Grade 2, or is deemed irreversible. In participants who experience such a toxicity, if this toxicity resolves to baseline or < Grade 2 prior to the participant's next scheduled dose of NKTR-214 then no delay of therapy is required. Participants with any Grade 1 toxicity or Grade 2 toxicity with a unrelated, unlikely, or possible attribution to NKTR-214 will continue that therapy.

Participants who experience a treatment delay due to a Grade 3 toxicity with a possible, probable, or definite attribution to NKTR-214 or who experience a Grade 4 toxicity with a possible attribution to NKTR-214 will undergo a dose reduction to 0.003 mg/kg if resuming NKTR-214 dosing.

For all participants, protocol treatment may be delayed ≤ 1 week from the expected day of the next treatment for any reason. If protocol treatment is delayed > 1 week, subjects will proceed with protocol therapy once they are determined by the treating physician to be appropriate for further protocol therapy. Any dosing interruption will not impact the time interval or dose of subsequent treatment cycles for participants that remain on study. Missed doses of drug will not

be made up. Patients requiring systemic corticosteroids during a treatment break must be tapered off treatment doses of these prior to resuming protocol therapy. Patients delayed for > 15 weeks will be discontinued from protocol therapy.

Anti-PD-1 therapy and radiation therapy will be delivered and/or held per standard-of-care practice for all patients in this study, per the determination of the treating physician. Any patient for whom anti-PD-1 therapy is discontinued will also discontinue treatment with NKTR-214. Any patient for whom anti-PD-1 therapy is held will also have NKTR-214 held at least until the patient is determined by the treating physician to be eligible for anti-PD-1 therapy again, per standard-of-care practice. In that setting the above rules for discontinuing or holding NKTR-214 will still apply and a patient becoming eligible to resume anti-PD-1 therapy after a hold may resume NKTR-214 only if they also meet the above criteria for resuming NKTR-214. If NKTR-214 is held or discontinued, a patient may continue on anti-PD-1 therapy on this study if this is deemed to be within the standard-of-care for anti-PD-1 therapy administration, per the treating physician.

5.6. Concomitant Medications/Treatments

5.6.1. Allowed Concomitant Medications

All treatments the investigator considers necessary for a subject's welfare may be administered at the discretion of the investigator in keeping with the community standards of medical care provided they are not growth factors, steroids, or myelosuppressive anti-neoplastic drugs.

5.6.2. Prohibited Concomitant Medications

Treatment with systemic treatment doses of corticosteroids will result in discontinuation of protocol therapy with NKTR-214 + anti-PD-1 (clarification: physiologic maintenance or replacement doses of systemic steroids and topical steroids are acceptable). If the use of systemic treatment doses of corticosteroids or other immunosuppressive drugs is considered unlikely or not related to NKTR-214 + anti-PD-1, the NKTR-214 + anti-PD-1 treatment may be resumed two weeks following discontinuation of systemic steroids with the subsequent cycle at the discretion of the responsible physician.

No other cancer chemotherapy, growth factors, or therapeutic doses of corticosteroids can be used unless required to manage immune-related toxicity. Management with maintenance physiologic doses of corticosteroids is acceptable (prednisone equivalent dose ≤ 10 mg daily).

5.7. Administration of Intervention

5.7.1. Pre-medication, Hydration, and Ancillary Medications

Hydration Guidelines - Adequate hydration mitigates the development of hypotension associated with NKTR-214 administration. Hydration and renal function must be assessed within 72 hours, or as soon as locally feasible, prior to NKTR-214 study drug administration (see Appendix C for the list of analytes that require collection and evaluation prior to NKTR-214 study drug administration). For participants who must delay study treatment due to creatinine increase, see additional information regarding criteria to delay (Sections 6.4), resume (Section 6.4), or permanently discontinue study treatment (Section 5.5). Underlying reasons for decreased oral intake (e.g., nausea) should be addressed and treatment (e.g., IV hydration)

should be provided. The Investigator may modify these recommendations based on the needs of the individual participant. Participants will also be provided a handout with hydration guidance.

Participants should be administered 1 liter of IV fluid on the day of each dosing of NKTR-214. In addition, consider administering 1 liter of normal saline IV when the Participants return for clinic visits (e.g., if the participant returns for PK draws on Days 3 and 5 of Cycle 1), anytime based on the participant's need, or as clinically indicated. Participants are to be instructed that for the next 3 days after administration of NKTR-214, they should 1) drink at least 2 liters per day of self-administered oral hydration and 2) avoid activity which may contribute to dehydration (including, but not limited to, strenuous activity, long hot showers, and saunas) for 3 days following treatment with NKTR-214.

Allergic reaction guidelines - Any subject showing allergic symptoms with NKTR-214+anti-PD-1 should receive diphenhydramine, acetaminophen, and an H2 blocker (e.g. ranitidine 150 mg PO) as premedication before all subsequent doses.

In the case of common symptoms related to NKTR-214+anti-PD-1: appropriate antibiotics, blood products, antiemetics, fluids, electrolytes, and general supportive care are to be used as necessary.

In the case of a severe allergic reaction (anaphylactic precautions should be taken): treatment can include:

- Dexamethasone 10 mg IV
- Diphenhydramine 50 mg IV
- Epinephrine 3-5 mL IV [1:10,000]; 0.5 mL SC [1:1000]
- Equipment for assisted ventilation
- A free flowing IV line must be established at all times.

5.7.2. Supportive Care

Treatment of any immune-related toxicities will be guided by the NCCN guidelines on this subject. Treatment of any radiation-related toxicities will be guided by the treating radiation oncologist. Any necessary supportive care is permitted, except as noted above.

5.7.3. NKTR-214+anti-PD-1 following palliative RT administration

Drug	Dose[1]	Route	Schedule[2]
Palliative RT	8 Gy x 3 fractions or 4 Gy x 5 fractions	External beam radiation (EBRT) with MV photons, MV electrons, or protons	Completed 3-7 days before the second dose of anti-PD-1. Delivered in person by UWCCC Radiation Therapists under the direction of the treating physician. Approximately 30 minute duration of each treatment fraction.
NKTR-214	0.006 mg/kg[3]	IV	Q3W. Administered in person by UWCCC staff

			under the direction of the treating physician, immediately prior to anti-PD-1 infusion. Approximately 1 hour infusion.
Anti-PD-1	200 mg pembrolizumab	IV	Pembrolizumab Q3W, administered in person by UWCCC staff under the direction of the treating physician, immediately following NKTR-214 infusion. Approximately 1 hour infusion.
[1] Based on subject's actual body weight. [2] A window of ± 7 days may be applied to all treatment visits and ± 7 days for all clinic visits to accommodate observed holidays, inclement weather, scheduling conflicts etc. Date and time of each drug administration should be clearly documented in subject's and eCRFs. [3] Dose of NKTR-214 may be reduced to 0.003 mg/kg according to rules defined in section 5.5 of this protocol.			

5.8. Palliative Radiation Therapy (RT)—Standard of Care

All procedures in Section 6.9 are considered standard of care and are described in detail to assure consistent treatment among study participants. In the study, subjects must be determined by the treating physician to have a need for palliative RT based on current or potential symptoms at a tumor site(s). These subjects will receive a course of palliative RT targeting any sites deemed to merit palliative RT treatment and will complete this RT on days -7 to -3 relative to the second doses of anti-PD-1 and NKTR-214.

Palliative radiation therapy on this study may be directed to tumor(s) at any location in the body, except those located in the brain/brainstem or in the spinal cord. Targets adjacent to but not directly involving these exception sites may be targeted. No limit is placed on the maximum size of a tumor that can be radiated, given the palliative intent of this treatment. Patients can have received previous radiation to the target site(s).

Following radiation therapy, acute and late AEs related to the RT will be assessed at all scheduled follow-ups where AEs are evaluated.

5.8.1. Selection of an Index Tumor Site

From the tumor site(s) receiving palliative RT, a targeted (index) tumor will be selected at the discretion of the attending physician based on need for palliative radiation, ease of being able to obtain post-treatment biopsies from that site, and size at least 1 cm in longest dimension. Whenever possible, the targeted region should not have received RT prior to enrollment in this study. Palliative RT may be delivered to other sites of disease if deemed necessary and safe.

5.8.2. Radiation Dose (SOC)

The treating physician will use his/her discretion to decide between a dose and fractionation schedule of 8 Gy x 3 or 4 Gy x 5. Radiation can be delivered either daily or every other day and is generally provided on weekdays only. The treating physician will also use his/her discretion if multiple sites of disease will be treated with RT. If multiple sites of disease are being treated, these treatments should conclude between days -7 to -3 relative to the second doses of anti-PD-1 and NKTR-214.

5.8.3. Radiotherapy Delivery (SOC)

RT delivery will follow standard practice for palliative RT treatment and will utilize megavoltage (MV) photons or electrons. Any number or arrangement of beams may be used at the discretion of the treating physician to achieve target coverage and conformality.

Treatment Simulation, Subject Positioning and Set-up

Subject will be positioned in a comfortable position. Any immobilization apparatus may be used at the discretion of the treating physician as long as it does not interfere with the proper functioning of any necessary treatment planning or image-guidance systems. A CT simulation will be performed for all patients to facilitate treatment planning, consistent with standard practice approaches for the planning of palliative RT. The planning CT scan may be done with intravenous contrast if this is beneficial for target or normal tissue segmentation. CT scan thickness will be ≤ 0.3 cm. Planning CT scan will be acquired with the subject in the same position and using the same immobilization device as for treatment. At a minimum, all tissues within 5 cm of the target volume will be included in the CT scan. For spinal lesions treated with 8 Gy x 3, a pre-treatment MRI is required to assess the extent of disease and position of the cord. This must be fused with the planning CT scan.

Treatment positioning and simulation techniques will follow standard approaches for palliative radiation. Examples are detailed below for specific body sites.

Head and neck

Immobilization will be performed using a thermoplastic head mask. A head and shoulder masks should be used if treatment includes cervical nodes to help immobilize the shoulders. Head only masks can be used if lesion does not extend to the neck. Patients will be planned in the supine position with their arms at their sides, ensuring the shoulders are situated as far inferior as possible to avoid entry and exit through the shoulders. Additional immobilization devices such as a bite block are permitted.

Thoracic

The patient will typically be positioned supine and a vac lock mold or a wingboard with arms overhead may be used for immobilization. Body fix is not required unless an 8Gy X 3 plan is utilized to a target site located within 1 cm of the spinal canal. The CT will include the entire volume of both lungs. Both 4D-CT and use of respiratory gating are permissible but not required.

Abdomen and pelvis

The patient will typically be simulated supine with arms on chest or overhead. Immobilization with vac lock body fix can be utilized and a 4DCT or respiratory gating are permissible but not required. If the tumor is adjacent to the bladder, bladder filling instructions will be provided to the patient, and the patient should be treated with the same bladder filling as simulation.

Tumor Localization and Target and Normal Tissue Volumes

CT will be the primary image platform for treatment planning. Treatment planning and dosimetry will be performed to confirm adequate target coverage. Tumor localization will be performed by the treating physician. This can be done clinically by visual demarcation for electron treatment and can be aided by placing a wire or other marker at the time of CT simulation. The Gross Tumor Volume (GTV) will be defined by the treating physician using a combination of clinical assessment, available diagnostic imaging, and the planning CT scan. The GTV should encompass the entirety of the tumor volume. This volume will be expanded to generate a clinical target volume (CTV). The CTV will typically be an expansion of the GTV by 3-5 mm, however in certain instances, the treating physician may elect a 0 mm expansion of GTV to CTV in some or all directions due to proximity of adjacent critical structures or anatomic barriers to microscopic spread of disease. The CTV will be confined by an external skin contour. The CTV may include any contiguous areas that the treating physician deems likely to harbor microscopic disease. The CTV will be expanded to define a planning target volume (PTV) that accounts for potential variations in positioning and set-up, as well as isodose convergence at depth in the case of electron therapy. PTV will be 2-3 mm in the neck, 5 mm in the lung with 4DCT per institutional standards, customized if respiratory gating is used (based on calculated uncertainty from 5 repeat scans), and 2-10 mm in the abdomen and pelvis depending on location (i.e. spine may be 2-3 mm, while a soft tissue lesion will require larger margins).

Organs at risk that are visible in the planning CT scan will be contoured. Any organs at risk will be contoured and considered as solid structures. Structures not deemed to be at risk due to their distance from the target area need not be contoured. If the targeted lesion is within 10 cm of the following organs it is anticipated they will be contoured: spinal cord, kidneys, bowel, stomach, liver, heart, lungs, esophagus, bladder, rectum, brain, eyes, lenses, cochlea, brainstem, larynx, oral cavity, gonads, genitalia. Contouring of these organs at risk should be done following the region-specific contouring atlas guidelines of the NRG, found here: *https://www.nrgoncology.org/ciro-contouring-atlases-templates-and-tools*.

Radiation Treatment Planning and Dosimetry

3D-conformal RT planning will be utilized to determine target coverage and to evaluate the dose delivered to other organs at risk. For all patients, image artifacts on the CT simulation scan such as streaks near metal, dental implants, fillings, surgical shunts, clips or other high or low density objects should be overridden with appropriate Hounsfield Units. Intensity modulated radiation therapy (IMRT) planning and delivery may be utilized, if deemed necessary by the treating physician for the purpose of achieving target coverage, conformality, or other dosimetric parameters. The treating physician will use his or her discretion to determine the appropriate dose, fractionation, and treatment planning/delivery approach for any treatment site, working within the parameters set forth in this protocol. Dose conformality should be maximized, when feasible. The point of maximum dose should be placed within the GTV when practical.

The goal for target coverage will be for 95% of the PTV to receive 95% of the prescription dose. This is consistent with standard practice for a palliative radiotherapy plan. Also consistent with a palliative plan, it is understood that in some cases this will not be possible due to normal tissue

constraints. In those cases, lower coverage is acceptable for the purpose of achieving normal tissue constraints and there is not minimal acceptable dose coverage for this reason. The maximum acceptable dose to 0.03 cc in any treatment plan is 150% of the prescription dose within the GTV and 115% of the prescription dose outside of the GTV.

We will use the collapsed-cone superposition-convolution calculation algorithm in the RayStation for treatment planning software for treatments using Tomotherapy or Varian linear accelerators with photon plans. For electron plans, we will use Monte Carlo calculations in Raystation. For ViewRay we will use Monte Carlo algorithm for treatment planning. The grid size is <=3 mm for all plans.

Treatment planning will be carried out respecting all normal tissue constraints. Dose constraints for three- and five-fraction radiotherapy treatments will be those specified in table 3 of the report of the AAPM Task Group 101 on stereotactic body radiation therapy: *https://aapm.onlinelibrary.wiley.com/doi/full/10.1118/1.3438081*. Each of these constraints will take priority over GTV, CTV, and PTV coverage because of the palliative nature of the standard of care radiotherapy being used in this study.

For patients who have received prior radiotherapy to a target site, an EQD2 composite plan will be generated to account for the hypofractionated approach utilized in this study. All attempts will be made to limit the dose to 0.03 cc to the spinal cord to < 60 Gy in the composite; however, a dose of 65 Gy will be the absolute limit in this circumstance. The brainstem will be constrained to 70 Gy in the composite. Mandible will be constrained to a maximum dose of 105Gy in the composite. The uninvolved larynx will be limited to an EQD2 composite mean dose of 35 Gy. 20 Gy in 5 fractions will be used for any tumor sites that have previously been treated to an EQD2 of ≥ 60 Gy.

Every radiotherapy treatment plan will be approved by the attending physician and a quality assurance check will be performed, per standard of care, by a medical physicist. All 8 Gy X 3 radiotherapy treatment plans will be reviewed, per standard practice, at the weekly UW Radiation Oncology Chart Rounds.

Treatment Verification

After the subject is setup on the treatment table, standard imaging approaches (orthogonal x-rays, CT, MRI, and/or light field clinical set-up) will be used to align the subject with the treatment machine geometry based on the treatment plan. After initial alignment, shifts or rotations will be made as necessary using couch motion to achieve precise replication of the planned positioning. After initial localization is performed, all effort should be made to initiate the treatment delivery as quickly as possible. If reproducible positioning is not achieved treatment re-planning will be allowed as deemed necessary by the treating physician.

Sequencing of Radiation with Other Treatments

Following RT, subjects will receive cycle two of anti-PD-1 + NKTR-214. A minimum of 3 days should separate completion of RT from the second NKTR-214 dose and second anti-PD-1 dose. A maximum of 7 days should separate completion of RT from the second NKTR-214 dose and second anti-PD-1 dose.

Radiotherapy dose modifications, interruptions, or discontinuation

Because radiation therapy is delivered as a standard-of-care on this study the dose will not be modified once that treatment has commenced. If radiotherapy is interrupted for any reason including participant missing an appointment or a treatment machine being temporarily out-of-

service, that treatment can be resumed after interruption so long as radiotherapy is completed greater than 3 days prior to cycle 2 of NKTR-214 and anti-PD-1. Notably, as specified in section 5.5, delivery of NKTR-214 and anti-PD-1 therapy can be delayed by ≤ 1 week if needed for any reason and this includes for allowing time to complete radiotherapy. Radiotherapy will not be interrupted electively by the treating physician. The treating physician may discontinue a course of radiotherapy for a participant for any Grade 3 or greater toxicity that develops after initiating radiation or for any situation in which the treating physician determines that standard-of-care practice or patient safety would deem it necessary to discontinue radiation therapy. Any participant receiving at least one fraction of radiotherapy and subsequently discontinuing radiotherapy will remain eligible to proceed on study and receive planned cycles of NKTR-214 and anti-PD-1 therapy. Any participant deciding to discontinue radiotherapy prior to receiving any radiotherapy will be discontinued from the study.

Additional Radiation Treatments

For subjects who meet criteria for continuing on trial after completion of cycle 3 of NKTR-214+anti-PD-1 injections, additional courses of palliative RT may be delivered if deemed clinically necessary for palliative purposes by the treating radiation oncologist. Whenever possible, a dose of 8 Gy x 3 or 4 Gy x 5 will be used for these additional course(s) of palliative RT. RT in these courses may target any tumor sites that become currently or imminently symptomatic.

6. STUDY SCHEDULE

Cycle = 21 days

6.1. Screening (Day -28)

Screening/Baseline Visit (Day -28 to -1)

- Obtain demographics, medical and smoking history (SOC)
- Confirm diagnosis and staging (SOC)
- Confirm histologically proven recurrence (SOC)
- Perform physical exam (SOC)
- Collect vital signs, ECOG Performance status (SOC)
- Obtain and review concomitant medications (SOC)
- Obtain EKG and confirm no QT prolongation [Research Related (RR)]
- Review trial awareness, obtain, and document informed consent (one copy to be provided to subject) (RR)
- Collect laboratory assessments (SOC):
    - Complete blood count with diff (CBC w/diff)
    - Comprehensive Metabolic Profile (CMP)
    - Amylase and lipase
    - PT/INR and PTT
    - Thyroid function (TSH, T4)
    - Pregnancy test (serum or urine) for women of child bearing potential (WOCBP)

- Perform disease assessments (SOC)
    - CT of neck
    - PET scan and/or CT of Chest ± CT of Abdomen/Pelvis
- Confirm eligibility based on inclusion/exclusion criteria (RR)
- Collect health-related quality of life (HRQoL) questionnaires (RR)
- Specimen Collection
    - Archival tumor tissue (SOC)
        - Unstained fixed formalin, paraffin embedded (FFPE) slides (if available)

6.2. Cycle one

6.2.1. Cycle one, day 1 (C1D1)

- Perform physical exam (SOC)
- Collect vital signs and ECOG performance status (SOC)
- Perform Laboratory Assessments (SOC)
    - CBC w/diff (if within 7 days of screening labs, no need to repeat)
    - CMP (if within 7 days of screening labs, no need to repeat)
    - Amylase and Lipase (if within 7 days of screening labs, no need to repeat)
- Collect blood for serum and PMBC prior to infusion of anti-PD-1 or NKTR-214 (RR)
- Document AEs (RR for NKTR-214, SOC for anti-PD-1) and review concomitant medications (SOC)
- Administer anti-PD-1 (SOC)
- Administer NKTR-214 (RR)

6.2.2. Cycle one, day 8 (C1D8) ± 5 days

- Collect HRQoL questionnaires (RR)
- Document AEs (RR for NKTR-214, SOC for anti-PD-1) and review concomitant medications (SOC)
- Collect blood for serum and PMBC (RR)

6.3. Palliative Radiation Therapy (to be completed between C2D-7 to C2D-3 or C1D15 to C1D19)

- Administer palliative RT to index tumor (SOC)

6.4. Cycle two

6.4.1. Cycle two, day 1 (C2D1 or C1D22) ± 5 days

- Perform physical exam (SOC)
- Collect vital signs and ECOG performance status (SOC)
- Collect blood for serum and PBMC prior to infusion of anti-PD-1 or NKTR-214 (RR)
- Document AEs (RR for NKTR-214, SOC for anti-PD-1 and RT) and review concomitant medications (SOC)

- Perform Laboratory Assessments (SOC)
    - CBC w/diff
    - CMP
    - Amylase and Lipase
    - TSH and T4
- Administer anti-PD-1 (SOC)
- Administer NKTR-214 (RR)

6.4.2. Cycle two, day 8 (C2D8) ± 5 days

- Collect HR-QoL questionnaires (RR)
- Document AEs (RR for NKTR-214, SOC for anti-PD-1 and RT) and concomitant medications (SOC)
- Collect biopsy of index tumor (RR)
- Collect blood for serum and PBMC (RR)

6.5. Cycle three and thereafter

6.5.1. Cycle three and thereafter, day 1 (C3+D1) ± 7 days

- Collect HRQoL questionnaires (RR) (Q4 cycles)
- Document AEs (RR for NKTR-214, SOC for anti-PD-1 and RT) and concomitant medications (SOC)
- Perform physical exam (SOC)
- Collect vital signs and ECOG performance status (SOC)
- Perform Laboratory Assessments (SOC)
    - CBC w/diff
    - CMP
    - Amylase and Lipase
    - TSH, T4 (prior to even cycles)
- Perform imaging assessment (SOC)
    - CT neck (Q4 cycles)
    - CT chest, abdomen, and/or pelvis of all known sites of disease OR PET/CT (Q4 cycles)
- Collect blood for serum and PMBC prior to infusion of anti-PD-1 or NKTR-214 (cycle three only, RR)
- Administer anti-PD-1 (SOC)
- Administer NKTR-214

6.5.2. Cycle three only, day 8 (C3D8) ± 7 days

- Document AEs (RR for NKTR-214, SOC for anti-PD-1 and RT) and review concomitant medications (SOC)
- Collect blood for serum and PBMC (RR)

6.6. Long term follow-up (Every 4 months +/- 30 days if no progression, every 6 months +/- 6 months after progression)

If the subject discontinues therapy for reasons other than progression, the participant will be followed per SOC, typically every 3-6 months for a total of 5 years follow-up. If the subject develops progression, they will enter SOC follow-up every 3-6 months for a total of 3 years.

- CT neck (SOC)
- CT chest, abdomen, and/or pelvis of all know sites of disease OR PET/CT (SOC)
- Documentation of survival status and subsequent therapy (SOC)
- Document AE > grade 3 with attribution of possibly, probably and definitely related to study treatment (RR for NKTR-214, SOC for anti-PD-1 and RT)

6.7. Safety Follow-up (30 days after therapy completion +/- 14 days)

This visit will be performed per standard of care, 30 days after the last dose of study therapy. This can be due to disease progression or due to other reasons for discontinuation as noted above.

- Document AEs (RR for NKTR-214, SOC for anti-PD-1 and RT) and concomitant medications (SOC)
- Collect HR-QoL questionnaire at 30 days after study discontinuation (RR)
- Perform physical exam (SOC)
- Collect vital signs and ECOG performance status (SOC)
- Collect blood for serum and PBMC (RR)
- Perform Laboratory Assessments (SOC)
    - CBC w/diff
    - CMP
    - TSH and free T4

6.8. Final Study Visit or Withdrawal Visit

If the participant decides they no longer wish to participate in study follow-up, that visit will constitute the final study visit. Otherwise, the final study visit will occur at the completion of long-term follow-up, as noted above.

- Record AEs as reported by participant or observed by investigator (RR for NKTR-214, SOC for anti-PD-1 and RT)
- Collect HRQoL questionnaire (RR)
- Perform physical examination (SOC)

7. STUDY PROCEDURES/EVALUATIONS

7.1. Study Procedures/Evaluations

7.1.1. Demographics (SOC)

Birth date, gender, race, and ethnicity will be collected at screening (recorded for the study from medical records maintained as part of standard clinical care).

7.1.2. Medical History (SOC)

A thorough review of the subject's medical history, taking into account all recent and pertinent medical conditions including prior cancer treatment, will be performed at screening. This will be recorded for the study from medical records maintained as part of standard clinical care.

7.1.3. Physical Exam (SOC)

A physical exam will be completed at the time of screening, C1D1, and D1 of each subsequent cycle, safety follow-up, withdrawal visit, and final visit. This will be recorded for the study from medical records maintained as part of standard clinical care

7.1.4. Vital Signs (SOC)

Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be recorded at screening, C1D1, and D1 of each subsequent cycle, and safety follow-up. This will be recorded for the study from medical records maintained as part of standard clinical care.

7.1.5. Adverse events (RR/SOC) and concomitant medications (SOC)

AEs will be recorded at screening and each clinic and research visit, and at the safety follow-up. All of these recordings will be performed as part of the standard of care. AEs will be assessed as described in Section 9. Concomitant medications will also be assessed at this time point.

7.1.6. Weight (SOC)

Weight will be recorded at screening, C1D1, and D1 of each subsequent cycle. This will be recorded for the study from medical records maintained as part of standard clinical care.

7.1.7. Diagnostic biopsy (SOC)

An SOC biopsy is required to prove metastatic or recurrent disease. When available in excess of what is required for Surgical Pathology diagnosis, archival FFPE tissue (up to 20 slides of 5um tissue) will be provided to the biological correlates study team.

7.1.8. Index tumor biopsy (RR)

A research-related biopsy will be performed by core needle, punch, or incisional technique at the discretion of the surgeon/interventional radiologist on day 8 (+/- 5 days) of cycle 2.

7.1.9. Blood draw (RR)

Blood will be collected (10 mL each in separate tubes for PBMC and serum) and sent on ice immediately to the UW H&N SPORE Pathology Core facility or the Morris lab for processing and storage prior to treatment infusion on Day 1 of C1, C2, and C3, at Day 8 of C1, C2, and C3, and at the safety follow-up.

7.1.10. ECOG Performance Status (SOC)

Determination of the subject's performance scale based on the ECOG rating scale (Appendix D) will be made at the time of screening, C1D1, D1 of each subsequent cycle, and safety follow-up. This will be recorded for the study from medical records maintained as part of standard clinical care. KPS scores will be converted to ECOG ratings using a conversion table (Appendix E).

7.1.11. Quality of Life Measures (RR)

Quality of life (HRQoL) surveys will be collected at screening/baseline, C1D8, C2C8, C3+D1 (every 4 cycles), at safety follow-up, and at long-term follow-up or withdrawal. The surveys are anticipated to take ~ 10 minutes to complete.

- EORTC QLQ-C30
- EORTC QLQ-H&N35
- EQ-5D

The completion of HRQoL surveys is a research procedure.

Validated health outcome surveys will be used to assess subject perception of mental and physical health, HRQoL, and cancer-related H&N functioning (11).

Each subject will serve as his or her own control with complete HRQoL evaluation prior to and following treatment. Current phase III NRG trials evaluating quality of life have not defined a minimally important difference using the above selected quality of life metrics, and further work is needed for this to be robustly defined. However, the EORTC QLC-C30 has been shown to be robust across trials and will allow for comparison of QOL to prior studies. This will take into account various baseline dysfunctions that may be present due to metastatic head and neck cancer.

Perception of general health and HRQoL will be evaluated using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) and EQ-5D (12) (13, 14). The EORTC QLQ-C30 was chosen for its sensitivity to cancer-related quality of life and symptomatology, such as nausea/vomiting, fatigue and pain, and because it was identified previously as being well-developed, reliable, valid, and responsive (15). The EQ-5D was chosen due to its wide use in assessing generic health status. It assesses five dimensions of health status: mobility, self-care, usual abilities, pain/discomfort, and anxiety/depression (16).

Specific cancer-related H&N functioning will be assessed with the EORTC QOL Questionnaire H&N35 (EORTC QLQ-H&N35) (17, 18). This validated instrument incorporates items related to swallowing, eating, dry mouth, and saliva production and is sensitive to cancer site and stage (17). The EORTC QLQ-C30 and QLQ-H&N35 will be administered together and will yield a global health status score.

7.1.12. Diagnostic Imaging (SOC)

Diagnostic imaging will be performed at screening, prior to cycle 3, and then every four cycles. Imaging studies can be obtained at any time if clinically indicated by the treating physician.

Imaging studies shall consist of a CT neck to evaluate locoregional disease status and a PET/CT or CT of the chest, abdomen, and pelvis to evaluate known systemic disease status.

Imaging studies are standard clinical care procedures being done within routine care guidelines.

7.2. Laboratory Procedures/Evaluations

Laboratory testing will be completed by CLIA-certified labs.

7.2.1. Clinical Laboratory Evaluations

Complete Blood Count with Differential (SOC)

Blood will be drawn for CBC with differential at screening, and prior to treatment infusion on C1D1, D1 of each subsequent cycle, and at safety follow-up. This is part of the standard of care for anti-PD-1 therapy.

The CBC will include red blood cell count, hemoglobin, hematocrit, WBC count with differential including % neutrophils, lymphocytes, monocytes, eosinophils and basophils, absolute neutrophil count, and platelet count.

Serum Chemistries (SOC)

Blood will be drawn for serum chemistries at screening, C1D1, D1 of each subsequent cycle, and at safety follow-up. This is part of the standard of care for anti-PD-1 therapy.

The serum chemistries will include sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, total bilirubin, calcium, protein, albumin, phosphorus, amylase, and lipase.

Pregnancy Test (SOC)

A urine pregnancy test will be completed within 7 days of registration and within 7 days C1D1. Women who are postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) are not considered to be of childbearing potential.

Pregnancy testing is being done as part of standard clinical care.

Thyroid Function Tests (SOC)

Blood will be drawn for serum analysis of TSH and free T4 at screening, prior to even cycles, and at safety follow-up. This is a standard clinical procedure performed within routine guidelines for participants receiving anti- PD-1 therapy.

Electrocardiogram (EKG) (RR)

A standard 12-lead EKG will be obtained at screening to evaluate for QT prolongation.

7.2.2. Specimen Preparation, Handling, and Storage

Index tumor biopsy will be obtained day 8 (+/-5) of cycle 2. Blood will be drawn for PBMC and serum prior to treatment infusion on Day 1 of Cycle 1, 2, and 3, on Day 8 of Cycle 1, 2, and 3, and at the safety follow-up after treatment discontinuation.

Source and Timing of Biospecimen Collections

Standard biopsy is required to prove metastatic or recurrent disease and archival tissue will be obtained from that biopsy whenever possible.

Whole blood specimens (10 mL each for PBMC and Serum, in separate tubes) will be collected and sent on ice immediately to the UW H&N SPORE Pathology Core facility or the Morris lab for processing and storage.

Index tumor biopsies (research biopsy) will be performed by core needle, punch, or incisional technique at the discretion of the surgeon/interventional radiologist. Tissue from these biopsy specimens will be used, in order of availability, for formalin-fixed paraffin embedded histology and flash frozen in an Eppendorf tube. Surplus tissue should be flash frozen.

Banking of Leftover Biospecimens

Subject consent will be obtained to bank any leftover samples that were collected for study-specific correlative research. The UW H&N SPORE Pathology Core facility and/or the Morris lab will manage the banked samples.

Confidentiality of Biospecimens

Samples will be identified by a subject's study number assigned at the time of registration to the trial. Any material issued to collaborating researchers will be anonymized and only identified by the subject's study number and specimen description.

8. ASSESSMENT OF SAFETY

8.1. Specification of Safety Parameters

The Investigator should elicit information regarding the occurrence of AEs through open-ended questioning of the subject, physical examination, and review of laboratory results. AE data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of participants enrolled in the studies as well as those who will enroll in future studies using similar agents. AEs are reported in a routine manner at scheduled times during a trial. Additionally, certain AEs must be reported in an expedited manner to allow for optimal monitoring of participant safety and care. The first step is to identify the event using the NCI CTCAE version 5.0. The CTCAE document provides descriptive terminology for adverse event reporting. A grading (severity) scale is provided for each AE term.

All AEs, whether serious or not, will be described in the source documents and the AE page of the eCRF. All new events, as well as those that worsen in intensity or frequency relative to baseline, that occur after administration of study drug through the period of protocol-specified follow-up must be captured.

Specific anticipated AEs are described in section 2.3.

Information to be reported in the description of each AE includes but is not limited to:

- Medical diagnosis of the event. (If a medical diagnosis cannot be determined, a description of each sign or symptom characterizing the event should be recorded.)
- The date of onset of the event
- The date of resolution of the event
- Whether the event is serious or not
- Action taken

- Outcome
- Relatedness to the study drug and expectedness (see below)
- Subject's condition is intermittent or continuing
- The grade of the event based on the CTCAE v5.0

8.1.1. Unanticipated Problems (UPs)

The Office for Human Research Protections (OHRP) considers UPs involving risks to subjects or others to include, in general, any incident, experience, or outcome that meets **all** of the following criteria:

- unexpected in terms of nature, severity, or frequency given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied;
- related or possibly related to participation in the research ("possibly related" means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

8.1.2. Adverse Events (AEs)

An AE is any untoward medical occurrence whether or not considered related to the study drug that appears to change in intensity during the course of the study. The following are examples of AEs:

- Unintended or unfavorable sign or symptom
- A disease temporally associated with participation in the protocol
- An intercurrent illness or injury that impairs the well-being of the subject

Abnormal laboratory values or diagnostic test results constitute AEs only if they induce clinical signs or symptoms or require treatment or further diagnostic tests.

Hospitalization for elective surgery or routine clinical procedures that are not the result of an AE (e.g., surgical insertion of central line) should not be recorded as an AE.

Disease progression should not be recorded as an AE, unless it is attributable to the study regimen by the site investigator.

8.1.3. Serious Adverse Events (SAEs)

A serious adverse event is defined as any adverse event that meets one or more of the following criteria:

- Results in death; OR
- Is life-threatening; OR
- Requires hospitalization or prolongs existing hospitalization; OR
- Results in significant or persistent disability or incapacity; OR
- Results in a congenital anomaly/birth

Planned hospitalizations for disease-related surgery, routine procedures, non–disease-related procedures, and grade 3 toxicities listed in section 2.6.1.2 are not considered SAEs.

8.1.4. Adverse Event of Special Interest (AESI)

Based on the results of prior studies, CVA has been defined as an AESI. Any CVA will be reported as an AESI.

8.2. Time Period and Frequency for Event Assessment and Follow-Up

At each study visit, the investigator will inquire about the occurrence of AE/SAEs since the last visit. Events will be followed for outcome information until resolution or stabilization.

- UP will be recorded in the data collection system throughout the study.
- AEs with start dates occurring any time after informed consent until 30 days after end of treatment.
- SAEs with start dates occurring any time after informed consent until 90 days after end of treatment or until a new anti-cancer therapy begins.
- After 90 days post completion of therapy, only SAEs with the attribution of possibly, probably or definitely will be recorded.

8.2.1. Safety Follow-up Evaluations

A safety follow-up visit should occur when subjects permanently stop study treatment for whatever reason (toxicity, progression, or at discretion of site investigator) and should be performed 30 days (±7 days) after the last dose of treatment. Subjects who have an ongoing ≥ grade 2 or serious AE (SAE) at this visit will continue to be followed until the AE resolves to ≤ Grade 1 or baseline, is deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever is earlier.

8.2.2. Long Term Follow-up Evaluations

All subjects will be followed until documented disease progression. Subjects who discontinue treatment for any reason without documented disease progression will be followed for disease progression every 4 months for 5 years.

Once disease progression is documented, subjects will enter a survival follow up period every 4 months for 3 years from the time of documented progression. Follow up may be accomplished via clinic visit, phone call, or other avenues as appropriate.

8.3. Characteristics of an Adverse Event

Each event will be recorded on an appropriate case report form that includes assessment of the characteristics defined below. These characteristics, along with the frequency of an event's occurrence, will be considered in determining if the event is a UP.

8.3.1. Relationship to Study Intervention

AEs will be categorized according to the likelihood that they are related to the study drug(s). Specifically, they will be categorized using the following terms:

Unrelated	The Adverse Event is ***not related*** to the drug(s)

Unlikely	The Adverse Event is ***doubtfully related*** to the drug(s)
Possible	The Adverse Event ***may be related*** to the drug(s)
Probable	The Adverse Event is ***likely related*** to the drug(s)
Definite	The Adverse Event is ***clearly related*** to the drug(s)

8.3.2. Expectedness

For this study, an AE is considered unexpected when it varies in nature, intensity or frequency from information provided in the current IB, package insert, or when it is not included in the informed consent document as a potential risk. Unexpected also refers to AEs that are mentioned in the IB as occurring with a class of drugs or are anticipated from the pharmacological properties of the drug, but are not specifically mentioned as occurring with the particular drug under investigation.

The Study PI and/or study-appointed, clinically/medically responsible individual will determine whether an AE is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the intervention.

There are expected significant toxicities and AEs associated with SOC EBRT. These toxicities include Grade 3 radiation mucositis and Grade 3 radiation dermatitis.

IL2 based therapies have been utilized for over 2 decades. Many of the side effects are predictable, transient, and well controlled clinically. The list below delineates some of the toxicities and AEs that are expected for NKTR-214:

a) Grade 3 pain, requiring intravenous narcotics, provided that the narcotics are controlling the pain, and that IV narcotics for pain are not required > 96 hours after completion of NKTR-214 during any cycle;

b) Grade 3 nausea, vomiting, or diarrhea that resolves within 96 hours after completion of NKTR-214 during any cycle;

c) Grade 3 fever (i.e.: T > 40° C) lasting < 6 hours and controllable with antipyretics;

d) Grade 3 transient hypotension that resolves with hydration;

e) Grade 3 systemic skin toxicity (rash, erythema) that does not require management with steroids and improves with non-steroidal treatment (e.g., IV diphenhydramine) within 24 hours;

f) Grade 3 metabolic/laboratory toxicity of hyponatremia, hyperglycemia, or hypophosphatemia, in the absence of CNS symptoms and/or sequelae, that improve with or without treatment within 48 hours;

g) Grade 3 hematologic toxicity (or grade 4 lymphopenia – a known transient marker of immune activation by IL2) which improves to at least Grade 2 or pre-therapy baseline values before the subsequent NKTR-214 treatment cycle;

h) Grade 3 infusion reactions lasting less than 24 h, readily controlled with supportive (non-steroidal) treatments (i.e., Benadryl or subcutaneous epinephrine);

i) Grade 3 fatigue or decrease of ECOG performance status to an ECOG performance status of 3 that resolves to pre-treatment, baseline values in < 1 week;

j) Grade 3 infection that resolves in < 1 week either with or without antibiotic therapy;

8.3.3. Severity of Event

AEs will be documented and recorded at each visit using NCI CTCAE v5.0.

8.4. Reporting Procedures

8.4.1. Unanticipated Problem (UP) Reporting

Incidents or events that meet the OHRP criteria for UPs require the creation and completion of an UP report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an UP to the IRB:

- appropriate identifying information for the research protocol, such as the title, investigator's name, and the IRB project number;
- a detailed description of the adverse event, incident, experience, or outcome;
- an explanation of the basis for determining that the adverse event, incident, experience, or outcome represents an UP;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the UP.

To satisfy the requirement for prompt reporting, UPs will be reported using the following timeline:

- UP that are SAE will be reported to the IRB per Table 1 timeline.
- Any other UP will be reported to the IRB per Table 2 timeline.
- All UPs should be reported to appropriate institutional officials (as required by an institution's written reporting procedures), the supporting agency head (or designee), and OHRP within one month of the IRB's receipt of the report of the problem from the investigator.

8.4.2. Serious Adverse Event Reporting

Depending on the nature, severity, and attribution of the serious adverse event an SAE report will be phoned in, submitted in writing, or both according to Table 1 below. All SAEs must also be reported to the UWCCC DSMC. All SAEs must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

Determine the reporting timeline for the SAE in question by using the following table.

Table 1: FDA Reporting Requirements.

Phase 1 and Early Phase 2 Studies: Expedited Reporting Requirements for Adverse Events that Occur on Studies under an IND/IDE within 30 Days of the Last Administration of the Investigational Agent/Intervention 1,2 FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)

NOTE: Investigators **MUST** immediately report to the UWCCC DSMC, Nektar Therapeutics, and the IRB (if applicable) and any other parties outlined in the protocol ANY SAE, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).

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

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

ALL SAE that meet the above criteria **MUST** be immediately reported to the UWCCC DSMC and Nektar within the timeframes detailed in the table below:

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

***Planned hospitalizations for disease-related surgery, routine procedures (such as G-tube placement), non–disease-related procedures, and grade 3 toxicities listed in section 2.6.1.2 will be exempt from SAE reporting as they are not dose limiting toxicities.**

Expedited AE reporting timelines are defined as:

• **24-Hour; 5 Calendar Days** – The AE must initially be reported within 24 hours of learning of the AE, followed by a complete expedited report within 5 calendar days of the initial 24-hour report. • **10 Calendar Days** – A complete expedited report on the AE must be submitted within 10 calendar days of learning of the AE.
Serious adverse events that occur more than 90 days post completion of therapy, only SAEs with the attribution of possibly, probably or definitely will require reporting as follows: **Expedited 24-hour notification followed by complete report within 5 calendar days for:** • All Grade 3, 4, and 5 AEs **Expedited 10 calendar day reports for:** • Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

Serious Adverse Event – Reported Within 24 Hours

Serious Adverse Events requiring reporting within 24 hours (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to *saenotify@uwcarbone.wisc.edu* within one business day. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). The DSMC Chair will review the information and determine if immediate action is required. Within 10 working days, all available subsequent SAE documentation must be submitted electronically along with a 24 hour follow-up SAE Details Report and a completed UWCCC SAE Routing Form to *saenotify@uwcarbone.wisc.edu*. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

See Section *[II]* for detailed instructions on SAE reporting.

a) Serious Adverse Event – Reported within 10 Days

Serious Adverse Events requiring reporting within 10 days (as described in the protocol) must also be reported to the Data and Safety Monitoring Committee (DSMC) Chair via an email to *saenotify@uwcarbone.wisc.edu*. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (NCI AdEERS form or FDA Medwatch Form #3500 and/or any other documentation available at the time of initial reporting). The DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, the sponsor, and the funding agency and provides documentation of these notifications to the DSMC.

If the SAE occurs on a clinical trial in which the UW PI serves as the sponsor-investigator, the PI reviews the event to determine whether the SAE requires reporting to the FDA and other participating investigators.

For a multiple-institutional clinical trial the PI is responsible for ensuring SAEs are reported to the FDA as well as to all participating investigators.

See Section *[II]* for detailed instructions on SAE reporting.

c) Sponsor-Investigator Responsibilities for SAE Review

In the event the UWCCC Principal Investigator is acting as the Sponsor-Investigator (i.e., the PI holds the IND), the PI assumes responsibilities of the study sponsor in accordance with FDA 21 CFR 312.32. In this capacity, the UWCCC PI reviews all reports of serious adverse events occurring on the study at the UWCCC and participating external sites and makes a determination of 1) **suspectedness** (i.e., whether there is a reasonable possibility that the drug caused the AE); and 2) **unexpectedness** (the event is not listed in the Investigator's Brochure or is not listed at the specificity or severity that has been observed) in the context of this study. SAE with suspected causality to study drug and deemed unexpected are reported as IND Safety Reports by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within 15 calendar days. All fatal or life-threatening SAE that are unexpected and have suspected causality to the study drug will be reported by the UWCCC PI to the FDA, all participating investigators on the study, and the external global sponsor (if applicable) within 7 calendar days.

Report to the UWCCC and Nektar

Reference the **SAE SOP** (Standard Operating Procedure) and the **SAE Reporting Workflow for DOTs** on the UWCCC website (http://kb.wisc.edu/uwccc) for specific instructions on how and what to report to the UWCCC for [24] hour initial and follow-up reports**. A follow-up report is required to be submitted within 10 days of the initial [24] hour report.**

For this protocol, the following entities are required to be notified:

a. *saenotify@uwcarbone.wisc.edu*
b. Study Chairs: Zachary Morris, MD, PhD and Paul Harari, MD
c. UWCCC PIs: Justine Yang Bruce, MD and Adam Burr, MD, PhD
d. UWCCC PM: Diana Trask
e. Nektar Therapeutics (Pharmacovigilance@nektar.com)
f. Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

Report to the IRB

Consult the UW-IRB website for reporting guidelines.

Reported within 10 Calendar Days

SAE requiring reporting within 10 calendar days (as described above) must also be reported to the DSMC Chair via an email to saenotify@uwcarbone.wisc.edu. SAEs will also be reported to Nektar in the same timeframe. The SAE Details Report must be submitted along with other report materials as appropriate. The UWCCC DSMC Chair will review the information and determine if further action is required. All information is entered and tracked in the UWCCC database.

The Principal Investigator notifies all investigators involved with the study at the UWCCC, the IRB, Nektar, and provides documentation of these notifications to the DSMC.

For this protocol, the following entities are required to be notified:

a. *saenotify@uwcarbone.wisc.edu*
b. Study Chairs: Zachary Morris, MD, PhD and Paul Harari, MD
c. UWCCC PIs: Justine Yang Bruce, MD and Adam Burr, MD, PhD
d. UWCCC PM: Diana Trask
e. Nektar Therapeutics (Pharmacovigilance@nektar.com)
f. Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

Report to the IRB

Consult the UW-IRB website for reporting guidelines.

Table 2. Other Reportable Events Timeframe

Event	Definition	Reporting
Breach of confidentiality	The exposure of any study information or communications directly related to a study subject to anyone not named as study staff or the release of a study subject's identifiable information to study staff who were not specified to receive such information in the protocol or IRB application.	Within 14 business days of knowledge of event
Protocol deviation	A deviation is an incident involving a departure from the IRB-approved protocol in the actual conduct of the study. Deviations may result from the action of the participant, investigator, or staff.	See details below

Event	Definition	Reporting
Major deviations	Deviations are considered major when the unapproved change(s) in previously approved research activities, implemented without IRB approval, may potentially adversely affect subjects' rights, safety, welfare, or willingness to continue participation, or affect the scientific design of the study and/or the integrity of the resultant data.	Within 14 business days of knowledge of event
Minor deviations	Deviations are considered minor when the unapproved change(s) in previously approved research activities, implemented without IRB approval, do not adversely affect subjects or the integrity of the study data.	Cumulative minor deviations are reported at the time of continuing review.
Protocol violation	An incident involving an intentional deviation from the IRB-approved protocol that was not implemented in response to an emergency situation and that may impact a subject's rights, safety, and/or welfare, makes a substantial alteration to risks to subjects, or affects the scientific design of the study and/or the integrity of the resultant data. Violations may also be repeated deviations (major or minor) of the same nature. Violations can represent serious or continuing non-compliance with the federal regulations and guidelines for ethical conduct of human subject research.	Within 14 business days of knowledge of event
Protocol Exceptions	A protocol exception is an IRB-approved deviation for a single subject or a small group of subjects but is not a permanent revision to the research protocol.	Protocol exceptions must be approved by local IRB prior to implementation.

Report to the IRB:

Consult the UW-IRB website for reporting guidelines.

8.4.3. Reporting of Safety Events to FDA

As the University of Wisconsin will hold the IND for this study, they will assume responsibility for reporting all events in accordance with FDA 21 CFR 312.32.

9. STUDY OVERSIGHT

The UWCCC Data and Safety Monitoring Committee (DSMC) is responsible for the regular review and monitoring of all ongoing clinical research in the UWCCC. A summary of DSMC activities are as follows:

- Reviews all clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Reviews all Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for all clinical trials conducted at the UWCCC, and studies conducted at external sites for which the UWCCC acts as an oversight body.
- Reviews all reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports).
- Notifies the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Notifies the CRC of DSMC decisions and any correspondence from the DSMC to the protocol Principal Investigator.
- Works in conjunction with the UW Health Sciences IRB in the review of relevant safety information as well as protocol deviations, non-compliance, and unanticipated problems reported by the UWCCC research staff.
- Ensures that notification of SAEs requiring expedited reporting is provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

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9.1. Monitoring and Reporting Guidelines

UWCCC quality assurance and monitoring activities are determined by study sponsorship and risk level of the protocol as determined by the PRMC. All protocols (including Intervention Trials, Non-Intervention Trials, Behavioral and Nutritional Studies, and trials conducted under a Training Grant) are evaluated by the PRMC at the time of committee review. UWCCC monitoring requirements for trials without an acceptable external DSMC are as follows:

Protocols subject to intermediate monitoring generally include UW Institutional Phase I/II and Phase II Trials. These protocols undergo review of subject safety at regularly scheduled DOT meetings where the results of each subject's treatment are discussed and the discussion is documented in the DOT meeting minutes. The discussion includes the number of subjects enrolled, significant toxicities, dose adjustments, and responses observed. Protocol Summary Reports are submitted on a quarterly basis by the study team for review by the DSMC.

9.1.1. Review and Oversight Requirements

- Study Progress Review
  - Protocol Summary Reports (PSR) are required to be submitted to the UWCCC DSMC quarterly. The PSR provides a cumulative report of SAEs, as well as instances of noncompliance, protocol deviations, and UPs, toxicities and responses that have occurred on the protocol in the timeframe specified. PSRs for those protocols scheduled for review are reviewed at each DSMC meeting.
  - Protocol Summary Reports enable DSMC committee members to assess whether significant benefits or risks are occurring that would warrant study suspension or closure. This information is evaluated by the DSMC in conjunction with other reports of quality assurance activities (e.g., reports from Internal Audits, Quality Assurance Reviews, etc.) occurring since the prior review of the protocol by the DSMC.

In the event that there is significant risk warranting study suspension or closure the UWCCC DSMC will notify the PI of the findings and ensure the appropriate action is taken for the protocol (e.g., suspension or closure). The DSMC ensures that the PI reports any temporary or permanent suspension of a clinical trial to the appropriate agencies. Any UWCCC DSMC findings and requirements for follow-up action are submitted to the UWCCC CRC.

Study Monitoring

Per UWCCC policy, the Clinical Research Central Office (CRCO) monitoring team monitors clinical trials by conducting a Quality Assurance Review (QAR) within 6 months of when the first subject is accrued to the study. Aspects of study conduct reviewed during a QAR include, but are not limited to, documentation of the informed consent process, subject eligibility, subject registration documentation, overall adherence to the protocol by the study team, and regulatory documentation.

Internal Audits are completed by the CRCO monitoring team on an approximately annual basis. Aspects of study conduct reviewed during an internal audit include, but are not limited to, documentation of the informed consent process, subject eligibility, response and toxicity (if applicable), investigational drug accountability records, regulatory files, and overall adherence to the protocol.

The CRCO monitoring team provides written reports to the PI, UWCCC DSMC, and IRB following the reviews described above.

10. IND APPLICATION MANAGEMENT

In compliance with FDA regulations, the sponsor-investigator manages the IND through its lifecycle, including the initial application, submission of amendments, new information, safety and annual reports.

The sponsor-investigator may seek guidance on the FDA IND submission process with the *ICTR IND/IDE Consultation Service (I3CS)*.

10.1. Initial Submission

The sponsor-investigator and/or study team members (as applicable) prepare and submit the initial application to the FDA, and maintain copies of all communications and correspondence between the FDA and sponsor-investigator. The FDA acknowledgment letter lists the assigned IND number and a statement that the IND will become active if the sponsor-investigator does not hear back from the FDA within 30 days of the date of receipt.

- The date of the acknowledgement letter is used as the IND activation date if further correspondence from the FDA is not received.
- If further communication is required, and all issues have been resolved, the FDA will send a letter stating that the clinical investigation may begin, including the IND activation date.

The sponsor-investigator maintains all FDA documentation, specifically the IND activation date, in the regulatory files.

10.2. Amendments

When necessary, the sponsor-investigator and/or study team members (as applicable) prepare and submit protocol amendments. Once submitted to the FDA, the FDA will not respond unless requested.

10.3. Safety Reports

The sponsor-investigator and/or study team members (as applicable) prepare and submit any serious, unexpected and related adverse events to the FDA, and all participating investigators, in an IND safety report.

Adverse Events that are:	Notify:
• **Serious** • **Suspected/Related** • **Unexpected**	**FDA** and all participating institutions as soon as possible, but no later than 15 *calendar* days after learning of the event
• **Serious** ○ **Life-threatening or Fatal** • **Suspected/Related** • **Unexpected**	**FDA** and all participating institutions within 7 *calendar* days after learning of the event

10.4. Annual Reports

Within 60 days of the anniversary date that the IND application went into effect, the sponsor-investigator and/or study team members (as applicable) prepare and submit the annual report. Once submitted to the FDA, the FDA will not respond unless requested.

11. STATISTICAL CONSIDERATIONS

11.1. Study Hypotheses

We hypothesize that the combination of radiation, NKTR-214, and anti-PD-1 checkpoint blockade will improve efficacy compared to the pembrolizumab arm of Keynote 048. Given the non-redundant immune modulatory roles of radiation, NKTR-214, and anti-PD-1 checkpoint blockade, our secondary hypotheses are that this combination will be effective in generating an anti-tumor immune response against recurrent/metastatic head and neck squamous cell carcinoma resulting in an ORR ≥ 44 % with good patient reported quality of life and with correlative evidence demonstrating a more diversified and activated adaptive anti-tumor immune response.

11.2. Sample Size Considerations

This study will enroll 24 participants to test the hypothesis that the combination of NKTR-214 with palliative radiation and anti-PD-1 therapy results in an ORR ≥ 44 %. Under the null hypothesis for ORR ≤ 0.22, based on one-sided one sample proportion test with type I error of 0.1, the expected power levels to detect alternative ORRs of 0.35, 0.4, and 0.45 are 55 %, 74 %, 87 % respectively. The null hypothesis will be rejected and superiority concluded if 8 or more responses are observed in 24 participants. This design yields a type I error rate of .04 and power of .8 when the true response rate is 44 %.

11.3. Final Analysis Plan

Any subject who receives at least one dose of NKTR-214 on this protocol will be evaluable for ORR. All subjects with measurable disease who have received at least one cycle of treatment and have their disease re-evaluated will be evaluable for assessment of objective response.

11.3.1. Analysis Plans for Primary Objective

ORR will include confirmed complete response (CR) + confirmed partial response (PR) and will be assessed based on RECIST 1.1 criteria. ORR will be reported with the 95 % confidence interval (CI). Progression of any radiated tumors will be considered in this evaluation but response of radiated tumor(s) will not be considered as evidence of response for the purpose of this study unless all tumor sites are radiated.

11.3.2. Analysis Plans for Secondary Objectives

Treatment-related AE will be reported in tabular format, and AE rates, including the proportion of participants experiencing Grade 3+ treatment-related toxicities, will be reported with the 95 % CI.

PFS will be analyzed using the Kaplan-Meier method, and median PFS will be computed with the associated 95 % CI. Subjects who have not progressed and are still alive will be right-censored at the date of the last disease evaluation. Kaplan-Meier curves will be plotted.

OS will be analyzed using the Kaplan-Meier method, and median OS will be computed with the associated 95 % CI. Subjects who have not died will be right-censored at the date of the last follow-up, and Kaplan-Meier curves will be plotted.

Clinical benefit rate (defined as CR + PR + SD at ≥ 6 months) will be reported via waterfall plot, and the 95 % CI for the clinical benefit rate will be computed.

Duration of response, duration of overall complete response and time to progression will be evaluated using the Kaplan-Meier method. Medians will be computed with the associated 95 % CI, and Kaplan-Meier curves will be plotted.

Patient-reported health-related quality of life will be evaluated using summary statistics and generalized linear mixed-effects models for measurements over time.

11.3.3. Analysis Plans for Exploratory Objectives

For the exploratory objectives, descriptive statistics will be used to summarize the levels of anti-tumor response, IFN-γ expressing T cells in peripheral blood, T cell receptor repertoire diversity and clonality, and tumor infiltrating lymphocytes and expression of PD-L1 as determined by immunohistochemistry.

11.3.4. Subgroup Analyses

Subgroup analyses for ORR will be performed on the basis of high versus low tumor mutation burden, high versus low PD-L1 expression on cycle 1 index tumor biopsy, HPV/EBV status, metastatic versus locally recurrent disease, and tobacco smoking history.

12. CRITERIA FOR DISEASE EVALUATION

The following sections describe the recommended method to track disease response per the RECIST1.1 (see Eisenhauer EA et al. *New response evaluation criteria in solid tumors: revised RECIST guideline (version 1.1).* Eur J Can, 2009.45:p.228-247). Progression of any radiated tumors will be considered in this evaluation but response of radiated tumor(s) will not be considered as evidence of response for the purpose of this study.

Refer to the RECIST1.1 publication for complete details on these criteria.

12.1. Measurable Disease

Measurable disease is defined as the presence of at least one measurable lesion. 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 using standard clinical measurements, such as calipers or single use measuring paper by clinical exam. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

12.1.1. 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.

12.2. 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/pulmonitis, 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 subject, these are preferred for selection as target lesions.

12.3. Target Lesions

All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion that can be measured reproducibly should be selected. 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. Target lesions will not include radiated tumor sites for this study unless all tumor sites have been radiated.

12.4. Non-target Lesions

All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as non-target lesions and should also be recorded at baseline. 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.

12.5. Evaluation of Target Lesions

NOTE: In addition to the information below, also see section 4.3.2 in the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) Committee, version 1.1 (Eur J Cancer 45;2009:228-247) for special notes on the assessment of target lesions.

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

12.6. Evaluation of Non-target Lesions

Complete Response (CR)	Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (< 10 mm short axis) Note: If tumor markers are initially above the upper normal limit, they must normalize for a subject to be considered in complete clinical response.
Non-CR/ Non-PD	Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits
Progressive Disease (PD)	Appearance of one or more new lesions and/or unequivocal progression of existing non-target 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 site investigator should prevail in such circumstances, and the progression status should be confirmed at a later time by the sponsor investigator.

12.7. Evaluation of Best Overall Response

Target Lesions	**Non-Target Lesions**	**New Lesions**	**Overall Response**
CR	CR	No	CR
CR	Non-CR/ Non-PD	No	PR
CR	Not evaluated	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	Non-evaluable
PD	Any	Yes or No	PD
Any	PD*	Yes or No	PD
Any	Any	Yes	PD
*In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.			

Subjects with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be classified as having “symptomatic deterioration”. Every effort should be made to document the objective progression even after discontinuation of treatment.

In some circumstances it may be difficult to distinguish residual disease from normal tissue. When the evaluation of complete response depends on this determination, it is recommended that the residual lesion be investigated (fine needle aspirate/biopsy) to confirm the complete response status.

12.8. Definitions for Response Evaluation – RECIST 1.1

12.8.1. Objective Response Rate

The objective response rate is the proportion of all subjects with confirmed PR or CR according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

12.8.2. Clinical Benefit Rate

The Clinical Benefit rate is the proportion of all subjects with stable disease (SD) at ≥ 6 months from cycle 1 day 1, or partial response (PR), or complete response (CR) according to RECIST 1.1, from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the start of treatment).

12.8.3. Progression Free Survival

A measurement from study treatment day 1until the criteria for disease progression is met as defined by RECIST 1.1 or death occurs. Subjects who have not progressed will be right-censored at the date of the last disease evaluation.

12.8.4. Overall Survival

Overall survival is defined by the date of study treatment day 1 to date of death from any cause.

12.8.5. Duration of Response

Duration of overall response—the period measured from the time that measurement criteria are met for complete or partial response (whichever status is recorded first) until the date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since treatment started).

13. SOURCE DOCUMENTS AND ACCESS TO SOURCE DATA/DOCUMENTS

Study staff will maintain appropriate medical and research records for this study, in compliance with ICH E6, Section 4.9 and regulatory and institutional requirements for the protection of confidentiality of participants. Study staff will permit authorized representatives of regulatory agencies to examine (and when required by applicable law, to copy) research records for the purposes of quality assurance reviews, audits, and evaluation of the study safety, progress, and data validity.

Source documents will include all records within the HealthLink Electronic Medical Records system such as hospital records, clinical and office charts, laboratory notes, memoranda, pharmacy dispensing records, copies or transcriptions certified after verification as being accurate and complete, photographs or digital photo files, x-rays, and subject files and records kept at the pharmacy, at the laboratories, and medico-technical departments involved in the clinical trial. In addition, protocol specific forms will be designed which require treating physician signature to serve as source documents. This may include forms such as toxicity forms with grading and attribution and tumor measurement forms.

14. ETHICS/PROTECTION OF HUMAN SUBJECTS

14.1. Ethical Standard

The investigator will ensure that this study is conducted in full conformity with the principles set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research, as drafted by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (April 18, 1979) and codified in 45 CFR Part 46 and/or the ICH E6.

14.2. Institutional Review Board (IRB)

The final study protocol and the final version of the informed consent form must be approved in writing by the University of Wisconsin Health Sciences IRB.

The site investigator is responsible for informing the IRB of any amendment to the protocol in accordance with local requirements. In addition, the IRB must approve all advertising used to recruit subjects for the study. The protocol must be re-approved by the IRB as local regulations require.

Progress reports and notifications of AEs will be provided to the IRB according to local regulations and guidelines.

14.3. Informed Consent Process

The subject's signed and dated informed consent must be obtained before conducting any procedure specifically for the study. The site investigator must store the original, signed informed consent form. A copy of the signed informed consent form must be given to the subject. A consent form describing in detail the study procedures and risks will be given to the participant. Consent forms will be IRB-approved, and the participant is required to read and review the document or have the document read to him or her.

The investigator or designee will explain the research study to the participant and answer any questions that may arise. The participant will sign the informed consent document prior to any research-only assessments or procedures. Participants will be given the opportunity to discuss the study with their surrogates or think about it prior to agreeing to participate. They may withdraw consent at any time throughout the course of the study. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their clinical care will not be adversely affected if they decline to participate in this study.

The consent process will be documented in the clinical or research record.

14.4. Exclusion of Children (Special Populations)

Adults of any gender or racial/ethnic group may participate. Since children do not make up a significant portion of the subjects with recurrent metastatic head and neck squamous cell carcinoma, children are excluded from this study.

14.5. Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the study sponsor(s) and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to any study information relating to participants.

The study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the study sponsor.

The study shall be conducted in full compliance with (i) all applicable laws, regulations, and guidance of Regulatory Authorities relating to human clinical research of the type described in the Protocol, including the United States Federal Food, Drug and Cosmetic Act ("FDC Act") and the relevant provisions of Title 21 of the United States Code of Federal Regulations; (ii) generally accepted standards of Good Clinical Practice ("GCP"), including ICH E6 Good Clinical Practice: Consolidated Guidance (April 1996) as adopted by the FDA; and (iii) all applicable laws relating to the collection, use, storage and disclosure of individually-identifiable patient medical information, records and data, including but not limited to the Health Insurance Portability and Accountability Act of 1996 as amended by the Health Information Technology for Economic and Clinical Health Act of 2009 and similar state, local and foreign laws (collectively "Privacy and Security Regulations").

Regulatory Authorities will have access to any and all of the following as may be required by applicable law and regulations or guidances of Regulatory Authorities: (i) the Principal Investigator, any other Investigator, or other personnel involved with the Study; (ii) Study facilities; and (iii) books, accounts, Study Drug records, patient records, case report forms, source data (as that term is defined and used in ICH E6 Good Clinical Practice: Consolidated Guidance (April 1996)), and other records, documents, materials and sources of information related to the Study ("Records").

AEs will be reported to Regulatory Authorities promptly in compliance with applicable law. In addition, any Serious Adverse Event ("SAE") will be reported to Nektar within 24 hours from the time it is determined by study personnel that such an event or reaction has occurred, or immediately if the event or reaction is fatal or life-threatening.

14.5.1. Certificate of Confidentiality

To further protect the privacy of study participants, the Secretary of Health and Human Services (HHS), has issued a Certificate of Confidentiality (CoC) to all researchers engaged in biomedical, behavioral, clinical, or other human subjects research funded wholly or in part by the federal government. Recipients of NIH funding for human subjects research are required to protect identifiable research information from forced disclosure per the terms of the NIH Policy (*https://humansubjects.nih.gov/coc/index*). As set forth in 45 CFR Part 75.303(a) and NIHGPS Chapter 8.3, recipients conducting NIH-supported research covered by this Policy are required to establish and maintain effective internal controls (e.g., policies and procedures) that provide reasonable assurance that the award is managed in compliance with Federal statutes, regulations, and the terms and conditions of award. It is the NIH policy that investigators and others who have access to research records will not disclose identifying information except when the participant consents or in certain instances when federal, state, or local law or regulation requires disclosure. NIH expects investigators to inform research participants of the protections and the limits to protections provided by a Certificate issued by this Policy.

14.5.2. NIH Data Sharing Policies

For this study, the correlative objectives are funded in part, through the NIH. As described in section 17, it is NIH policy that the results and accomplishments of the activities that it funds should be made available to the public (see *https://grants.nih.gov/policy/sharing.htm*). PIs and funding recipient institutions will ensure that all mechanisms used to share data include proper

plans and safeguards to protect the rights and privacy of individuals who participate in NIH-sponsored research. This will apply to the results of the correlative outcomes analysis.

14.6. Future Use of Stored Specimens and Other Identifiable Data

Subject consent will be obtained to bank any leftover samples that were collected for study-specific correlative research. The UW H&N SPORE Pathology Core facility and/or the Morris lab will manage the banked samples. All patient health information with the sole exception of sample date will be removed. The sample date will be available to the study team only to facilitate database structure. Any samples provided to collaborators; however, will be stripped of all PHI, including the date. Instead, samples will be coded with research sample ID and time point description.

15. DATA HANDLING AND RECORD KEEPING

This study will report clinical data using the UWCCC OnCore data management system and RedCap utilizing study specific case report forms. Key study personnel are trained on the use of case report forms and will comply with protocol specific instructions for data collection.

Subject demographics, subject-specific study treatment calendars, AEs and other information will be maintained UW Department of Human Oncology REDCap database.

Participant data will be collected using protocol specific eCRFs. The eCRFs will be approved by the study's Principal Investigator and the study biostatistician prior to release for use. The Study Coordinator or designee will be responsible for registering the subject into the data management system at time of study entry, completing eCRFs based on the subject specific calendar, and updating the subject record until subject death or end of required study participation.

To protect the confidentiality of subjects in this study the blood and tissue samples will be coded, using a limited data set. The only PHI will be the sample date, restricted to the study team members. The coded samples may be labeled with any subset of the following: sample number, subject ID number, date of biopsy/blood draw, biopsy location (if applicable), and study number. The key will be saved in computer files that are protected via passwords and access rights. The research data will also be saved in secure computer files and in the OnCore database, all of which are only accessible via username, password, and access rights. When not in use paper files will be stored in the research offices that are locked when not occupied, or in locked closets or cabinets associated with the Morris lab. Research samples will be stored in the Morris lab, or a collaborating laboratory at the University of Wisconsin - Madison.

Identifiers and information to be collected for this study

Name
Medical record number
Date of birth

Gender, Race and Ethnicity
Address, telephone & fax numbers
E-mail address
Health Insurance Information
Tumor characteristics & genetic information
Medical history including dates of treatments and procedures
Information generated from participation in the study

15.1. Management of Banked Samples

The table below outlines the data to be maintained for samples banked for future research. Information listed will be available to lab staff for use in selecting samples for potential future research projects. All future research projects using coded samples would be IRB approved before use of the samples.

Data to be maintained with samples banked for future research

Study number & study subject ID number (eg: UW20###_1)
Lab sample ID number
Diagnosis
Stage of disease
Therapeutic response
Types and timing of treatments received
Time points/sequence of sample collection
Biopsy locations
Results of lab analysis completed for the study

If the results of the study are published, participants' identity will remain confidential.

15.2. Data Management Responsibilities

Data collection and accurate documentation are the responsibility of the study staff under the supervision of the investigator. All source documents and laboratory reports must be reviewed

by the study team and data entry staff, who will ensure that they are accurate and complete. UPs and AEs must be reviewed by the investigator or designee.

UWCCC Radiotherapy will serve as the Clinical Research Office for this trial.

15.3. Data Capture Methods

Data will be collected through the web-based clinical research platform REDCap which is HIPAA compliant. UWCCC personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into the appropropriate database by study site personnel. We will utilize REDCap for Biospecimen-related data, REDCap for clinical data. Registration and demographic information from OnCore. The data available to the correlative research labs will be coded in REDCap, and a limited data set, with only the sample date as a subject identifier will be available to the correlative research team. Any collaborative researchers will be provided coded research only—stripped of all PHI.

15.4. Types of Data

Subject demographics, subject medical history, subject specific study treatment calendars, AEs, laboratory/pathology reports obtained during the course of treatment and afterwards, e.g., blood tests, biopsy results), findings from physical exams, and imaging scan reports/outcomes will be maintained within EPIC Healthlink, with research specific data being recorded in REDCap, and OnCore. There is potential for HNC-related genomic studies to be performed on future banked samples.

15.5. Schedule and Content of Reports

The UWCCC Protocol Review and Monitoring Committee (PRMC) determines the level of risk, thus the appropriate timelines for review of study documents, conduct and accrual. Protocol Safety Reports are run, reviewed and signed off by the study PI per the determined schedule. PSRs are then sent for review to the DSMC. Protocol Safety Reports include information such as accrual, AEs, SAEs, and UPs. Annual review by the UW Health Sciences IRB will review accrual, reportable events, and study progress.

15.6. Study Records Retention

Shadow research charts with original consent forms and documents specifically created for this study will be maintained in the Department of Human Oncology until the study is terminated. The records will then be sent to Wisconsin State Records Archiving facility for long-term storage (10 years) and re-archived as needed. Study records will be maintained for at least three years from the date that the grant federal financial report (FFR) is submitted to the NIH.

15.7. Protocol Deviations

Except in the case of a medical emergency, no protocol deviation is authorized. Changes to the protocol will be established by amendments by the Principal Investigator approved by the UW HS IRB. Protocol deviations may affect the conduct of the study from legal and ethical points of view and may influence the statistical analysis and pertinence of the study. Medical emergencies have to be handled in the subjects' best interest. The investigator has to contact the IND Sponsor to clarify if a subject may continue in the study when a protocol violation out of medical reasons has occurred. Protocol deviations that are not identifiable from the eCRF have to be recorded in a protocol deviation form. Protocol deviations will be evaluated at the data review meeting before database lock and will be described in the statistical analysis plan.

All deviations must be addressed in study source documents and reported to the UW HS IRB per their policies using *Table 1* as a guideline. The Principal Investigator is responsible for knowing and adhering to the reviewing IRB requirements.

16. PUBLICATION/DATA SHARING

The NIH funds a portion of the correlative research on biospecimens from this study. Therefore, data resulting from the correlative research will be subject to the *NIH Public Access Policy*, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

The clinical trial will be registered on *ClinicalTrials.gov*, which is sponsored by the National Library of Medicine.

At least thirty (30) days prior to any public dissemination of the results of the study, results will be provided to Nektar for review. The materials to be disseminated shall be forwarded to the Nektar Medical Contact. During the Review Period, Nektar may provide written suggestions or comments to Sponsor which Sponsor may incorporate in its own discretion. In the event that Nektar identifies any Confidential Information during its review, the PIs agree to remove the Nektar Confidential Information if requested by Nektar in writing prior to public dissemination. If during the Review Period, Nektar notifies the PIs that Nektar desires patent applications to be filed on any Nektar Inventions disclosed or contained in the disclosures, PIs will defer publication or other public disclosure for a period, not to exceed an additional sixty (60) days, sufficient to permit Nektar or any Nektar Nominee to file any desired patent applications.

Unless otherwise required by the journal in which a publication is to appear, or the forum in which a poster or presentation is to be made, PIs will comply with recognized ethical standards concerning publications and authorship, including the Uniform Requirements for Manuscripts Submitted to Biomedical Journals established by the International Committee of Medical Journal Editors. The support of Nektar will be acknowledged in any publication or presentation related to the Study, unless Nektar notifies Sponsor in writing in advance that Nektar declines to be so acknowledged.

In the event either the PIs or Nektar desire to issue any press release or other publicity materials relating to the study, then a draft of the proposed release or other materials shall be submitted to the other party at least ten (10) business days in advance of public disclosure for the other party's review and comment. The submission to the other party shall state the proposed date on which the submitting party plans to make the public release.

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APPENDIX A: SCHEDULE OF EVENTS

Cycle = 21 days	Screen	Cycle 1[1,2]		Radiation C1D15 – C1D19	Cycle 2[2] (C1D22)		Cycle 3+ [2]		Safety follow up[2]	Long-term Follow up[5]
	-28 days[1]	Day 1	Day 8		Day 1	Day 8	Day 1	Day 8[3]	30 days post Tx[2,4]	
REQUIRED ASSESSMENTS										
Medical history, smoking history, trial awareness[7]	X									
Diagnosis and Staging[6]	X									
Physical exam	X	X			X		X		X	
Weight	X	X			X		X			
Vital signs, ECOG Performance status[8]	X	X			X		X		X	
Health-related quality of life questionnaire	X		X			X	Q4 cycles		X	X
AEs & concomitant medications	X	X	X		X	X	X		X	X[5]
LABORATORY ASSESSMENTS										
Complete Blood Cell Count with diff (CBC)	X	X[1]			X		X		X	
Comprehensive Metabolic Profile (CMP)[9]	X	X[1]			X		X		X	
Amylase and Lipase	X	X[1]			X		X			
PT/INR and PTT	X									
Thyroid Function (TSH, T4)[10]	X								X	
Electrocardiogram (EKG)	X									
Pregnancy test (serum or urine) WOCBP[11]	X									
DISEASE ASSESSMENT[11]										
CT of neck	X						Q4 cycles[12]			X
PET Scan and/or CT Chest +/-CT Abdomen/Pelvis [12]	X						Q4 cycles[12]			X
TREATMENT EXPOSURE										
Anti-PD-1 (pembrolizumab[13])		X			X		X			
Palliative radiation to index tumor				X						
NKTR-214		X			X		X			
CORRELATIVE STUDIES (SPECIMEN COLLECTION)										
Archival tumor tissue[14]	X									
Biopsy of index tumor[15]						X				
BANKING SAMPLES (SPECIMEN COLLECTION)										
PBMC[16]		X	X		X	X	X[3]	X[3]	X	
Unstained Slides and Biopsy Specimens[17]	X					X				
Serum[16]		X	X		X	X	X[3]	X[3]	X	
FOLLOW-UP										
Survival status, subsequent therapy										X

[1]If screening (baseline) labs were performed within 7 days of D1 of treatment, these do not need to be repeated.

[2]A window of 5 days will be applied to all treatment study visits for cycle 1 and 2, a window of 7 days will be applied to all treatment study visits for cycle 3 and thereafter, and for the safety follow-up visit and tumor imaging, a 14-day window will apply.

[3]These events apply only to cycle 3.

[4]A safety follow-up visit will occur 30 days (±14 days) after the last dose of treatment. [SAEs will be collected for 90 days after the end of treatment, and Q4 mos for 12 mos after treatment for SAEs thought to be at least possibly related to study therapy, See Section 9.]

[5]Subjects without documented disease progression will be followed for disease progression every 4 months +/- 30 days for 5 years. Once disease progression is documented, subjects will enter a survival follow up period every 6 months +/- 6 months for 3 years from the time of documented progression.

[6]Diagnosis and staging to include pathology report and AJCC 8th Ed staging. Standard biopsy to prove metastatic or recurrent disease should be available prior to registration

[7]Medical history to include smoking history and trial awareness question.

[8]Vital signs to include blood pressure, weight, and height (screening only) and ECOG performance status

[9]CMP to include sodium, potassium, chloride, creatinine, blood urea nitrogen; liver function tests (LFTs) to include AST, ALT, total bilirubin, alkaline phosphatase

[10]Prior to even cycles of drug.

[11]For WOCBP: urine or serum βhCG, within 7 days prior to study registration. If a urine test is positive or cannot be confirmed as negative, a serum pregnancy test will be required.

[12]Tumor response assessment will be performed using standard-of-care imaging of all known sites of disease every 4th cycle starting with cycle 3; tumor imaging to be done at treatment discontinuation at discretion of investigator.

[13]Per standard of care, Pembrolizumab infusions will be given every 3 weeks and NKTR-214 administered on the same day each cycle.

[14]Fixed paraffin-embedded and/or frozen blocks/slides will be requested from the standard biopsy taken to prove metastatic or recurrent disease.

[15]Biopsy of the index tumor will be obtained by core, punch, or incisional biopsy on day 8 (+/- 5) of cycle 2.

[16]Serial blood samples for PBMC and serum will be collected prior to anti-PD-1 or NKTR-214 on Day 1 of Cycle 1, 2, and 3, on Day 8 of Cycle 1, 2, and 3, and at safety follow-up.

[17]Submission of unstained slides/blocks/frozen specimens for banking (if available).

APPENDIX B: CEREBROVASCULAR ACCIDENT ADVERSE EVENT MANAGEMENT ALGORITHM FOR THE COMBINATION OF BEMPEGALDESLEUKIN WITH CHECKPOINT INHIBITORS

The table below provides a management algorithm for possible signs of CVA and follow-up of CVA for patients treated with the combination of NKTR-214 with any checkpoint inhibitor. This general guideline constitutes guidance to the Investigator and may be supplemented by discussions with the Medical Monitor representing the Sponsor.

For unexplained neurological symptoms (such as hemiparesis, confusion, dysarthria, or visual disturbances) that may be associated with CVA: **perform neurological imaging with MRI including diffusion-weighted imaging (DWI) as soon as feasible after initial presentation of symptoms (preferably within 24 hours).** DWI MRI is preferred, but if contraindicated, alternative imaging modalities may be used. If imaging is consistent with a CVA, proceed to the following:	
1	For any new CVA events confirmed by imaging (DWI MRI preferred unless contraindicated), regardless of neurological symptoms (e.g., cryptogenic CVA): • Discontinue study treatment for patients receiving NKTR-214 in combination with a checkpoint inhibitor For suspected TIA without clear alternative etiology: • Study treatment for patients receiving NKTR-214 in combination with a checkpoint inhibitor may be continued only after careful risk-benefit assessment by the Investigator
2	Obtain a neurology consultation
3	Perform laboratory assessments (Assessments include coagulation studies including D-dimer, complete blood count with differential, serum blood urea nitrogen, and creatinine. Additionally, collect an exploratory biomarker test if a baseline exploratory biomarker test was collected).
4	Consider cardiac echocardiogram (trans-esophageal as appropriate) to evaluate for potential source of emboli.

CVA = cerebrovascular accident; DWI = diffusion-weighted imaging; MRI = magnetic resonance imaging; TIA = transient ischemic attack.

APPENDIX C: HYDRATION GUIDELINES

Adequate hydration mitigates the development of hypotension. Hydration and renal function should be assessed within 24 hours prior to study drug administration as specified in individual protocols, or as soon as locally feasible. Unless otherwise stipulated in the protocol, patients should be given at least one liter of IV fluids at each dosing of bempegaldesleukin (Day 1). For the next 3 days (Days 2- 4) after bempegaldesleukin administration, instruct patients to drink at least 2 liters per day of self-administered oral hydration. Advise patients to restrain from activity that may contribute to dehydration (including, but not limited to, strenuous activity, long hot showers, and saunas) for Days 1 to 4 following each bempegaldesleukin administration. Following bempegaldesleukin administration, patients should be contacted to ensure compliance with hydration guidelines as specified in the individual protocols. Per clinical judgment, IV fluids may be administered at any time in any cycle. The Investigator may decide to forego administering IV fluids to a patient if this is deemed in the best interest of the patient (e.g., evidence of fluid overload).

APPENDIX D: ECOG RATING SCALE

ECOG RATING	ECOG Status
0	Fully active, able to carry on all pre-disease performance without restriction
0	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
1	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
2	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
3	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair
5	Dead

APPENDIX E: ECOG AND KPS CONVERSION TABLE

The table below is derived from data available on the ESMO Oncology PRO website: http://oncologypro.esmo.org/Guidelines-Practice/Practice-Tools/Performance-Scales

Karnofsky Grade	ECOG Grade
100	0
90	1
80	1
70	2
60	2
50	3
40	3
30	4
20	4
10	4
0	5