UW19041 Therapeutic Combination of CLR 131 with External Beam Radiation in Head and Neck Cancer

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IND#: 78434, Division of Oncology Projects 1

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STATEMENT OF COMPLIANCE

The study will be conducted in accordance with the International Council for Harmonisation guidelines for Good Clinical Practice (ICH E6), the Code of Federal Regulations on the Protection of Human Subjects (45 CFR Part 46). All personnel involved in the conduct of this study have completed human subjects protection training.

SIGNATURE PAGE

The signature below constitutes the approval of this protocol and the attachments and provides the necessary assurances that this trial 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 Investigators:

Signed: _____ Date: _____

Justine Yang Bruce, MD

Principal Investigator

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LIST OF ABBREVIATIONS

3D	Three dimensional
AE	Adverse Event/Adverse Experience
ALT	Alanine aminotransferase
ANC	Absolute neutrophil count
AST	Aspartate aminotransferase
BUN	Blood Urea Nitrogen
BSA	Body surface area
CBC	Complete blood count
CFR	Code of Federal Regulations
CLIA	Clinical Laboratory Improvement Amendments
CLR 124	18-(*p*-[^{124}I]-iodophenyl) octadecyl phosphocholine
CLR 131	18-(*p*-[^{131}I]-iodophenyl) octadecyl phosphocholine
CLR1404	18-(p-iodophenyl)octadecyl phosphocholine
CITI	Collaborative IRB Training Initiative
CoC	Certificate of Confidentiality
COPD	Chronic obstructive pulmonary disease
CRC	Clinical Regulatory Committee
CRF	Case Report Form
CT	Computed tomography
CTCAE	(NCI) Common Terminology Criteria for Adverse Events
CVA	Cerebrovascular event
DHHS	Department of Health and Human Services
DIGEST	Dynamic Imaging Grade of Swallowing Toxicity
DLT	Dose Limiting Toxicities
DOT	Disease Oriented Team
DSMC	Data and Safety Monitoring Committee
DSMS	Data and Safety Monitoring System
EAT-10	Eating Assessment Test-10
EBRT	External beam radiation therapy
ECOG	Eastern Oncology Cooperative Group
eCRF	Electronic Case Report Form

EKG	Electrocardiogram
EORTC	European Organisation for Research and Treatment of Cancer
FDA	Food and Drug Administration
FLC	Free Light Chain
FFR	Federal Financial Report
FOIS	Functional Oral Intake Scale
GCP	Good Clinical Practice
GSL	Glottic/supraglottic larynx
Gy	Gray
HNC	head and neck cancer
HNSCC	head and neck squamous cell carcinoma
HIV	Human immunodeficiency virus
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IDE	Investigational Device Exemption
IMRT	intensity modulated radiotherapy
IND	Investigational New Drug Application
IRB	Institutional Review Board
IUD	Intrauterine device
IV	Intravenous
KeV	kiloelectron volts
LINAC	linear accelerated-based
mCi	millicurie
MDADI	MD Anderson Dysphagia Inventory
MEP	Maximum expiratory pressure(s)
MM	Multiple myeloma
MRI	magnetic resonance imaging
MTD	Maximum tolerated dose
mTPI-2	modified toxicity probability interval
N	Number (typically refers to subjects)
OAR	Organs at risk
OHRP	Office for Human Research Protections
ORR	Overall response rate
OS	Overall survival

PJP	Pneumocystis jiroveci pneumonia
PD	Prescribed dose
PET	positron emission tomography
PFS	Progression-free survival
PLE	phospholipid ether
PI	Principal Investigator
PRMC	Protocol Review and Monitoring Committee
PS	Performance Status
PSS	Performance Status Scale
PSR	Protocol Summary Report
QLQ	Quality of Life Questionnaire
QOL	Quality of Life
rCTV	Recurrent clinical tumor volume
RECIST	Response evaluation criteria in solid tumors
rGTV	Recurrent gross tumor volume
RMS	Residual Mucosal Saliva
rPTV	Recurrent planning tumor volume
SAE	Serious Adverse Event/Serious Adverse Experience
SCC	Squamous cell carcinoma
SF-12	Medical Outcomes Trust Short Form 12
SOC	Standard of Care
SOP	Standard Operating Procedure
SPECT	Single photon-emission computed tomography
SSKI	Saturated solution of potassium iodide
TMJ	Temporal Mandibular Joint
TSH	Thyroid-stimulating hormone
T4	thyroxine
ULN	Upper limit of normal
UP	Unanticipated Problem
US	United States
USC	University of Southern California
USP	US Pharmacopeia
UW	University of Wisconsin
UWCCC	University of Wisconsin Carbone Cancer Center

WBC	White blood cell
WOCP	Women of childbearing potential
XeQoLS	Xerostomia-related Quality of life score

PROTOCOL SUMMARY

Title: **Therapeutic Combination of CLR 131 with External Beam Radiation in Head and Neck Cancer**

Précis: This is a Phase 1 study of the use of an investigational drug, CLR 131, in combination with external beam radiation therapy (EBRT) in subjects with locoregionally recurrent head and neck cancer. The trial will enroll up to 12 subjects at the Maximum Tolerated Dose (MTD) who are amenable to retreatment with radiation therapy. Subjects who also have distant metastatic disease may be enrolled on this clinical trial, but subjects must have evaluable disease that will be clinically treated with radiation therapy, as per standard of care. All subjects will receive a dosimetry test dose of CLR 131 to establish drug uptake by the tumor and enable Monte Carlo dose estimation based on CLR 131 SPECT/CT imaging evaluation. Subjects showing uptake will receive a cumulative tumor dose of 60-70 Gy using personalized dose calculation (via Monte Carlo methods) of CLR 131 combined with external beam radiation.

Objectives: Primary:

- To evaluate the safety and tolerability of CLR 131 in combination with external beam radiation therapy in subjects with recurrent cancers of the head and neck. *Outcome measure:* Incidence of adverse events assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Secondary:

- To perform dosimetric evaluation of CLR 131 in subjects with recurrent cancers of the head and neck. *Outcome measure: CLR 131 tumor uptake via SPECT/CT imaging and 3D dosimetric evaluations.*
- To assess tumor response following treatment with CLR 131 in combination with external beam radiation therapy. *Outcome measure: Overall response rate (ORR) defined as the proportion of subjects who experience either a partial response or complete response within 6 months post completion of EBRT as measured by standard of care imaging (e.g. CT, MR, PET-MR).*
- To evaluate changes in swallowing function before and after treatment with CLR 131 in combination with external beam radiation therapy. *Outcome measure: Swallow function assessed by Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) scale.*
- To evaluate changes in quality of life before and after treatment with CLR 131 in combination with external beam radiation therapy. *Outcome*

measure: Quality of life assessed by MD Anderson Dysphagia Inventory score (MDADI).

- To evaluate salivary flow rate before and after treatment with CLR 131 in combination with external beam radiation therapy. *Outcome measure: stimulated salivary flow.*

Population:	Up to twelve adult males and females of all races and ethnic groups with locoregionally recurrent head and neck cancer who may also have distant metastatic disease will be enrolled at the Maximum Tolerated Dose.
Phase:	I
Number of Sites:	1, University of Wisconsin Carbone Cancer Center
Description of Intervention:	Following informed consent, all subjects will receive a dosimetry test dose of 15 mCi CLR 131 to establish drug uptake by the tumor and enable Monte Carlo dose estimation based on CLR 131 SPECT/CT imaging evaluation. Subjects who have uptake of the CLR 131 dosimetry test dose at their disease site as determined by the study radiologist will be eligible to participate on the treatment portion of this clinical trial. Subjects showing uptake will receive a cumulative tumor dose of 60-70 Gy using personalized dose calculation of CLR 131 (via Monte Carlo) combined with external beam radiation. In this study, we are also studying a subset of up to 6 patients who do not uptake after the CLR 131 test dose, who will still proceed with treatment with CLR 131. This clinical trial involves two cohorts of subjects: (a) dose escalation and (b) dose expansion. In the dose escalation phase, an mTPI-2 design, an extension of modified toxicity probability interval (mTPI-2), will be used to identify the maximum tolerated dose (MTD) using cohorts of 4 subjects and up to 3 dose levels of CLR 131. Subjects in the dose escalation phase will receive 2 doses of CLR 131 with the first dose on day 1 followed by the second dose on day 8. Treatment with CLR 131 on the dose escalation cohort will begin at dose level 1 (15.6 mCi/m2). Subjects at dose level 1 will receive an intravenous infusion of CLR 131 at 15.6 mCi/m^2 on day 1 followed by a second dose on day 8. Subjects at dose level 2 will receive an intravenous infusion of CLR 131 at 18.75 mCi/m^2 on day 1 followed by a second dose on day 8. Once the MTD is determined by the dose escalation phase, participants will be enrolled on the dose expansion cohort. Participants on the dose expansion cohort will receive 2 doses of CLR 131 with the first dose on day 1 followed by

the second dose on day 8, with the dose determined by the dose escalation phase.

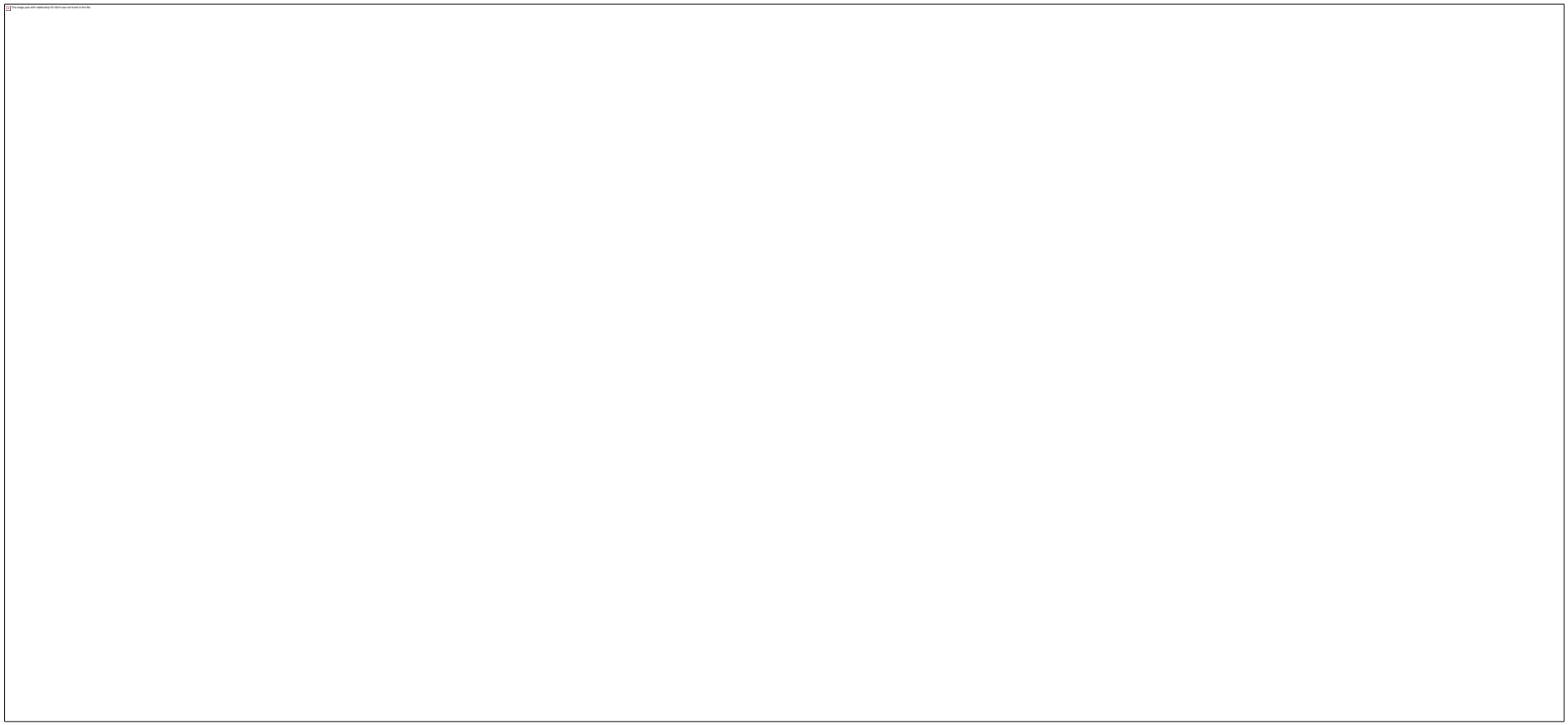
SPECT/CT imaging will be performed on days 2, 3, 4-6, and 7-8 of the treatment period to visualize and quantitate the biodistribution of CLR 131. Based on these SPECT/CT imaging scans, the Bednarz lab will utilize the Monte Carlo method to predict absorbed dose of CLR 131 to tumors and normal structures.

All subjects will start thyroid-protection medication the day prior to the CLR 131 dosimetry test dose and will continue to take thyroid protection medication for 14 days after the last CLR 131 dose.

Based on the calculated absorbed dose of CLR 131 to the specific targeted tissue, the subject will undergo external beam radiation therapy (EBRT) to complete the designated radiation dose outlined in the re-irradiation plan, as per standard of care. Prior to CLR 131 administration and at 3 and 6 months post EBRT, subjects will be assessed for changes to swallow function. Prior to CLR 131 administration and at 3, 6 and 12 months post EBRT, quality of life measures and salivary characteristics will be assessed. We anticipate the total study (baseline, CLR 131 administration, EBRT and 3, 6, 12 and 24 month follow up assessments) to take 27 months per participant.

Study Duration:	47 months
Subject Participation Duration:	27 months
Estimated Time to Complete Enrollment:	20 months
Date Accrual Goal Met / Study Closed to Accrual	April 18, 2022
Date DLT window completed by last participant	June 16, 2022

Schematic of Study Design:



***Approximately 6 safety labs will coincide with SOC EBRT visits, and 6 safety lab visits will fall outside of the SOC EBRT visits.**

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2 INTRODUCTION: BACKGROUND INFORMATION AND SCIENTIFIC RATIONALE

2.1 Background Information

2.1.1 Head and neck cancer

In 2018, it is estimated that 64,690 new cases of oral cavity, pharyngeal, and laryngeal cancers will occur, which accounts for approximately 3.7 % of new cancer cases in the United States (Siegel *et al.*, 2018). Head and neck cancer is a complex heterogeneous disease that arises from various sites including the oral cavity, pharynx, larynx, paranasal sinuses and salivary glands. Over 90 % of tumors that originate in the oropharyngolaryngeal axis are squamous cell carcinoma (SCC). Treatment for head and neck cancer patients includes surgery, radiation and chemotherapy in various combinations. Although the majority of patients can be cured from head and neck cancers, those patients with locally advanced and/or recurrent head and neck cancer have a 5 year overall survival rate of approximately 50-60% (Pulte & Brenner, 2010). Cure rates have improved only marginally over the last 30 years (Siegel *et al.*, 2015).

2.1.2 *Locoregional recurrence*

Approximately 50% of patients with head and neck cancer (HNC) manifest recurrence following initial treatment, and the majority of these recurrences are loco-regional (mouth, throat, neck) (Cognetti *et al.*, 2008; Forastiere *et al.*, 2001; Forastiere *et al.*, 2008; Peters *et al.*, 2010; Pignon *et al.*, 2009; Vokes *et al.*, 1993). Although a proportion of these patients remain potentially curable with further local treatment approaches (surgery, radiation, chemoradiation), retreatment is technically challenging and accompanied by a significant risk of irreversible damage to normal tissues.

Surgery is often limited by tumor adherence to critical structures (base of skull, neurovascular bundles), whereas radiation is often limited by normal tissue tolerance (spinal cord, bone, cartilage). Although retreatment of head and neck cancer (via surgical re-resection or re-irradiation of previously treated sites) is warranted in the attempt to provide disease control, these aggressive modalities can result in profound adverse effects on patient health-related quality of life (QOL) (A. M. Chen *et al.*, 2011; Dawson *et al.*, 2001; De Crevoisier *et al.*, 1998; Hehr *et al.*, 2005; Hoebers *et al.*, 2011; Kasperts *et al.*, 2005; Kramer *et al.*, 2005; Langer *et al.*, 2007; Mendenhall *et al.*, 2008; Nag *et al.*, 1998; Salama *et al.*, 2006; S. A. Spencer *et al.*, 2001; Stevens *et al.*, 1994). There is a compelling need to identify improved treatment approaches for patients with locoregionally recurrent head and neck cancer.

2.1.3 CLR 131

CLR 131 [18-(p-[131I]-iodophenyl)octadecyl phosphocholine] is an investigational, radio-iodinated cancer therapy that exploits the tumor-targeting properties of phospholipid ethers (PLEs) and PLE analogs by malignant cells (Mollinedo *et al.*, 2010; Weichert *et al.*, 2014). To produce CLR 131, the core PLE analog 18-(p-iodophenyl)octadecyl phosphocholine (referred to as CLR1404 or NM404) is radioiodinated with ^{131}I. ^{131}I was chosen as the radioactive constituent due to its 8-day physical half-life and well-established therapeutic capabilities in multiple cancer types such as

thyroid cancer, neuroblastoma, non-Hodgkin's lymphoma, and hepatocellular carcinoma (Hackshaw *et al.*, 2007; Macklis & Pohlman, 2006).

CLR 131 selectively delivers radiation to malignant tumor cells, thus minimizing radiation exposure to normal tissues; a scenario very difficult to achieve in HNC, even with the use of highly conformal radiation techniques. The mechanistic basis for the cancer-cell selective uptake involves interaction with lipid raft regions of the plasma membrane (Weichert *et al.*, 2014) In preclinical studies, CLR1404 radioiodinated with either ^{124}I for imaging purposes or ^{131}I for radiotherapeutic purposes has been evaluated in both xenograft and spontaneous (transgenic) tumor models in mice and rats. Imaging studies with CLR 124 [18-(*p*-[^{124}I]-iodophenyl) octadecyl phosphocholine], which is chemically and structurally identical to CLR 131, have demonstrated cancer-cell selective uptake and retention in all but 3 of over 60 tumor cell models assessed. CLR 131 antitumor activity has been documented in various tumor cell models, including glioma, multiple myeloma (MM), breast, prostate, colorectal, ovarian, renal, pancreatic, uterine, and lung cancers (Weichert *et al.*, 2014).

2.1.3.1 Tumor Selectivity

The malignant cell selectivity of the alkyl-phospholipids appears to reflect association with lipid rafts. The term "lipid rafts" refers to specialized plasma membrane microdomains, rich in cholesterol and sphingomyelin that spatially organize signaling pathways regulating cell proliferation and survival (Gao *et al.*, 2011; Lingwood & Simons, 2010).

CLR 131 and a variety of structurally related molecules (Mollinedo, 2007; van Blitterswijk & Verheij, 2008) use lipid rafts as portals of entry into the cell. There is greater abundance of lipid rafts in cancer cells as compared to normal cells (Li *et al.*, 2006), which is believed to be the mechanism for selective uptake of CLR 131. Following uptake, CLR1404 displays prolonged retention in organelle membranes. Retention of related compounds has been suggested to reflect decreased degradation by phospholipases (Barratt *et al.*, 2009).

The selective accumulation and retention of CLR 131 within malignant cells shows strong promise in the imaging domain for tumor detection (Deming *et al.*, 2014; Swanson *et al.*, 2015; Weichert *et al.*, 2014). In addition, with slow degradation once inside the cell, thereby resulting in prolonged tumor exposure, the therapeutic potential of CLR 131 becomes attractive (Morris *et al.*, 2015; Weichert *et al.*, 2014). With β-emissions from ^{131}I having a median range of several millimeters, radiation from CLR 131 can be sharply deposited within local tumors.

2.1.3.2 Preclinical studies using CLR 131 in combination with XRT

Preclinical studies using CLR 131 in murine model systems of HNC have been exceptionally promising. The experimental data confirms strong uptake and retention of CLR 131 in HNC xenografts, selective accumulation in tumor versus normal tissues, HNC xenograft growth inhibition with CLR 131, and more potent tumor growth inhibition when CLR 131 is combined with external beam radiation (Morris *et al.*, 2015). This promising combination will be tested in the current Phase 1 clinical trial.

2.1.3.3 Clinical Experience with CLR 131

To date, 113 subjects with advanced cancer have received CLR 131.

CLR 131 has been investigated in a Phase 1a dosimetry study in 8 subjects with advanced solid tumors. This study demonstrated that a single 10 mCi infusion of CLR 131 was exceptionally well tolerated. Whole body dosimetric analyses demonstrated that a dose of 20 mCi was predicted to deliver 40 cGy to marrow, and this information guided initial dosing in the subsequent therapeutic study.

CLR 131 was then examined in a Phase 1b therapy trial in 10 subjects with advanced solid tumors. Doses up to 25 mCi/m^2 were well tolerated without dose-limiting toxicity. Dose-limiting, but reversible, thrombocytopenia and leukopenia were observed at doses of 31.25 mCi/m^2 and higher. Hematocrit, renal function, and liver function were not significantly affected at doses up to 37.5 mCi/m^2. This study documented selective tumor uptake quantified by single photon-emission CT/CT (SPECT/CT) imaging. Stable disease was observed in 4 of 10 subjects, including 2 with stable disease for 20 weeks post-infusion.

CLR 131 in combination with dexamethasone is currently under investigation in a Phase 1 trial in subjects with relapsed/refractory multiple myeloma (MM) following treatment with both a proteasome inhibitor and an immunomodulatory agent. All subjects have been heavily pretreated. Seven dose cohorts were examined: 12.5 mCi/m^2, 18.75 mCi/m^2, 25 mCi/m^2, 31.25 mCi/m^2, and a multiple dose cohorts of 15.625 mCi/m^2, 18.75 mCi/m^2 and 20 mCi/m^2 administered twice, all in combination with 40 mg dexamethasone weekly. Thirty-one patients were dosed and the independent Data Monitoring Committee confirmed seven dose levels safe and tolerated. The overall response rate for patients receiving <60 mCi total body dose was 7% (1/15) and 27% (3/11) for patients receiving a $\geq$60 mCi total body dose. All evaluable patients achieved a minimum of stable disease, with at least one patient at each dose level achieving at least a minor response. CLR 131 has been shown to be well tolerated with the majority of adverse events being considered mild to moderate. The most common treatment emergent adverse events were cytopenias, primarily thrombocytopenia, with very predictable onset, time to nadir and recovery. Beyond cytopenias, fatigue was also a frequently reported adverse event. .

CLR 131 is also under investigation in a Phase 2 study in relapsed or refractory B-Cell malignancies (CLOVER-1) where 56 patients have been enrolled to date. Patients received either < 60 or ≥ 60 mCi total body dose CLR 131 (25 mCi/m^2 single bolus, 31.25 mCi/m^2 fractionated or 37.5mCi/m^2 fractionated) either as a bolus dose or fractionated with half on day 1 and half on day 7 ± 1 day. Patients enrolled in the final dosing group in Part A (Group 4) received an alternate two cycle fractionated dose schedule: fractionated 30 mCi/m^2 CLR 131 as 15 mCi/m^2 on Day 1, Day 15 (±1 day) for the first cycle, and then repeated Day 57 (± 1 day), and Day 71 (± 1 day) for the second cycle (total body dose ≥ 60 mCi). The adverse event profile remains consistent with the Phase 1 trial, with the primary treatment emergent adverse events including cytopenias; most

commonly thrombocytopenia. The time to onset, nadir, and recovery continue to be predictable and the events manageable. Fatigue has also been reported commonly.

CLR 131 is also under investigation in a Phase 1 study of solid tumor and malignant brain tumors in children, adolescents, and young adults. This is a dose escalation study with a starting dose of 15 mCi/m^2. To date, ten patients have been enrolled.

Additional information about these trials is available in the CLR 131 Investigator's Brochure (Supplementary Materials).

2.2 Rationale for a clinical study using CLR 131 in combination with EBRT

Locoregional recurrence in HNC represents a significant challenge. Approximately 50 % of HNC patients will experience loco-regional disease recurrence following initial therapy that commonly includes primary or postoperative radiation. Although some recurrent HNC patients can experience long-term tumor control following re-irradiation, this approach must be considered with great caution due to the risk of severe injury to normal tissue structures that maintain long-term recall from the prior radiation exposure.

Several studies have specifically examined the role of re-irradiation in HNC with general conclusions that there is considerable risk for high-grade toxicities (including death), but a defined opportunity for long-term survival (2 years) in approximately 10-20% of patients (A. M. Chen *et al.*, 2011; Dawson *et al.*, 2001; De Crevoisier *et al.*, 1998; Hehr *et al.*, 2005; Hoebers *et al.*, 2011; Kasperts *et al.*, 2005; Kramer *et al.*, 2005; Langer *et al.*, 2007; Mendenhall *et al.*, 2008; Nag *et al.*, 1998; Salama *et al.*, 2006; S. Spencer *et al.*, 2003; S. A. Spencer *et al.*, 2001; Stevens *et al.*, 1994).

Selection of patients who would most likely benefit from HNC re-irradiation remains an area of active investigation. Efforts to reduce the acute and long-term tissue injury profile by radiation with highly conformal techniques are clearly important in the retreatment setting. With the use of CLR 131, the dose of external beam radiation therapy can potentially be reduced or more precisely targeted, which serves to limit high dose radiation therapy to normal tissues in the head and neck.

The aim of this clinical trial is to evaluate the use of the novel radioisotope CLR 131 as a modality to provide "internal radiation" to recurrent disease in combination with EBRT. This combination regimen would be intended to provide definitive treatment of recurrent head and neck cancer by delivering radiation to HNC cells through CLR 131 uptake followed by the more traditional EBRT. We hypothesize that CLR 131 will reduce the overall dose of EBRT required for retreatment, and minimize the acute and long-term tissue injury that is commonly associated with standard reirradiation treatment plans.

Subjects with locoregionally recurrent HNC can be enrolled on this trial. These subjects will have a pre-planned radiation treatment dose that is designed based on the consensus opinion of the multidisciplinary head and neck oncology tumor board. The standard of care (SOC) radiation dose

for this patient population is 60-70 Gy absorbed dose to the recurrent tumor, irrespective of radiation delivery technique. Therefore, as long as the SOC radiation dose parameters are met, the EBRT described in this study is considered within standard of care.

Prior to treatment with CLR 131, the subject will have a clinical evaluation by a radiation oncologist who will design the radiation treatment field. Given the potential for increased toxicities both in the acute and long-term setting, these subjects will also be assessed for this clinical trial as a means for improving the toxicity profile of EBRT.

Subjects with recurrent and metastatic HNC can be enrolled on this trial provided locoregional treatment with EBRT is deemed to be clinically beneficial based on the consensus opinion of the multidisciplinary head and neck oncology tumor board. Because of the prior clinical experience of CLR 131 in advanced solid malignancies on a prior phase 1 clinical trial, these participants may also derive benefit from the systemic treatment of their metastatic disease with CLR 131. Clinical response of the metastatic disease will also be assessed during treatment based on RECIST 1.1.

2.2.1 Hypothesis

The hypothesis of this clinical trial is that reduction of the dose of external beam radiation therapy, when given in combination with CLR 131, will be safe and tolerable while maintaining favorable tumor response rates and diminishing the adverse impact of radiation treatment on subject specific symptoms, such as quality of life, salivary flow and swallowing function.

2.3 Potential Risks and Benefits

2.3.1 Potential Risks

2.3.1.1 CLR 131

CLR 131 has demonstrated a favorable safety profile in nonclinical toxicology studies.

In the initial clinical Phase 1a dosimetry study in subjects with advanced solid malignancies, CLR 131 was well tolerated; adverse events (AEs) included fatigue, constipation, and sialadenitis. During the Phase 1b dose escalation study, bone marrow suppression (including thrombocytopenia, anemia, decreased white blood cell [WBC] count, and neutropenia), fatigue, and an increase in gamma glutamyl transferase were observed. In the ongoing Phase 1 MM study, the most frequently reported AEs have been decreases in platelet count, hemoglobin, lymphocyte count, neutrophil count, and white blood count; for subjects receiving single or multiple dose CLR 131. Of note, subjects receiving multiple dose CLR 131 required fewer transfusions (platelet and red blood cell) and growth factor support than subjects receiving a comparable single dose (both 25 mCi/m^2 and 31.25 mCi/m^2) of CLR 131. [ClinicalTrials.gov NCT02952508]

The multiple dose regimen has been evaluated and found to be tolerable by a data monitoring committee of the Phase 1 multiple myeloma trial and has been used as the recommended dosing schedule for future trials. Thus, this clinical trial is evaluating the combination of CLR 131 given in 2 doses with external beam radiation therapy. This study will be the first to explore the combination of CLR 131 with EBRT.

CLR 131 is a radiopharmaceutical agent, and subjects should be monitored for signs and symptoms of bone marrow suppression, such as fever, fatigue, dyspnea, and bleeding.

Since CLR 131 is a radioactive drug, it is possible that subjects could expose others (like family or caregivers) to radiation. Specific instructions about how to minimize this risk will be provided to research participants.

Additional information about potential adverse events is available in the CLR 131 Investigator's Brochure (Supplementary Materials).

2.3.1.1.1 Thyroid-protection medication

Side effects of KI (potassium iodide) may include stomach or gastro-intestinal upset, allergic reactions, rashes, and inflammation of the salivary glands. In rare instances, it can cause "Iodism" (metallic taste, burning mouth and throat, sore teeth and gums, symptoms of a head cold, and sometimes upset stomach and diarrhea) or an allergic reaction can have more serious symptoms. These include fever and joint pains; swelling of parts of the body (face, lips, tongue, throat, hands, or feet); trouble breathing, speaking, or swallowing; wheezing or shortness of breath. Severe shortness of breath requires immediate medical attention.

2.3.1.1.2 Dose Limiting Toxicities (DLT) Probably Related to CLR 131

In this study, expected toxicities include febrile neutropenia, anemia, thrombocytopenia, and fatigue including, in some instances, Grade 3 and Grade 4. Per the CLR 131 Investigator Brochure, 90% of subjects are anticipated to have blood count recovery approximately 65 days after treatment with CLR 131. In this study, a DLT is defined as:

- Grade 4 neutropenia > 4 weeks
- Grade 4 anemia > 4 weeks
- Grade 4 thrombocytopenia > 4 weeks

- Grade 3 neutropenia > 8 weeks
- Grade 3 anemia > 8 weeks
- Grade 3 thrombocytopenia > 8 weeks

- Any other Grade 3 or 4 unexpected event at least possibly related to CLR 131

Growth factor support and blood transfusions are permitted in this study as clinically indicated by the treating physician.

Dose escalation will not be confirmed until all subjects in cohort recover to non-DLT levels or meet the criteria above.

2.3.1.2 External beam radiation therapy (EBRT)

Radiation side-effects in the treatment of head and neck cancer are well known. Though subjects for this trial will be given EBRT as part of standard of care, we are listing the side effects here to distinguish from those that are expected as part of CLR 131 administration.

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.

2.3.1.3 Modified Barium Swallow (MBS) Studies (standard of care)

To minimize risk, the procedure has been carefully planned. Radiation dose received during a MBS (between 0.2 and 0.85mSv) is lower than doses received from other common fluoroscopic and interventional radiology procedures. The risk of developing a fatal cancer from a MBS is 1 in 39,000. Occasionally, patients may be allergic to the flavoring added to the barium. There is a slight chance that barium could be retained in the gastrointestinal (GI) system, leading to a blockage. Women should inform their physician or x-ray technologist if there is any possibility that they are pregnant.

2.3.1.4 Single photon-emission computed tomography (SPECT) /CT

There is no additional risk associated with SPECT acquisition. However, a low-dose spiral computed tomography (CT) scan will accompany every SPECT acquisition for attenuation correction, anatomical conformation and dosimetry. The effective radiation dose associated with the low-dose spiral CT scan will differ with each individual; however, for the purposes of this study population we anticipate radiation exposure from CT scans to be ~1.5 mSv/scan (maximum total radiation from 5 scans would be ~7.5 mSv). For comparison, estimates for natural background radiation in the United States (vary based on location) is ~3.1 mSv/year.

2.3.1.5 Other risks from study-related procedures

- Blood draws for clinical laboratory testing: bruising, swelling at the injection site, dizziness and lightheadedness

- Saliva and oral swab collection: dry mouth (expected to resolve within a few minutes following collection)
- Maximum expiratory pressure (MEP) and voluntary cough: subject may feel slightly out of breath immediately following the measurement (expected to resolve within a few minutes of procedure).
- Maximum lingual pressure: subject may experience discomfort or soreness of the tongue measurement (expected to resolve within a few minutes of procedure).
- Questionnaires: risk of loss of confidentiality is possible but not likely with data security safeguards in place.

2.3.2 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 CLR 131, there is no proof of that at this stage. There is no standard treatment regimen for patients with locoregionally recurrent head and neck cancer, and thus re-irradiation with EBRT can be considered for patients in order to provide long term disease control. However, patients who undergo re-irradiation for recurrent disease experience significant toxicities and side effects. Thus, patients with locally recurrent head and neck cancer have an unmet need for treatment options with acceptable side effects and toxicities. This study is likely to yield knowledge about the use of CLR 131 in treating head and neck cancer when combined with external beam radiation, which could help future patients.

3 OBJECTIVES

3.1 Study Objectives

3.1.1 Primary Objective

- To evaluate the safety and tolerability of CLR 131 in combination with EBRT in subjects with recurrent cancers of the head and neck

3.1.2 Secondary Objectives

- To perform dosimetric evaluation of CLR 131 in subjects with recurrent cancers of the head and neck
- To assess tumor response following treatment with CLR 131 in combination with external beam radiation therapy
- To evaluate changes in swallowing function before and after treatment with CLR 131 in combination with external beam radiation therapy
- To evaluate changes in quality of life before and after treatment with CLR 131 in combination with external beam radiation therapy
- To evaluate salivary flow rate before and after treatment with CLR 131 in combination with external beam radiation therapy

3.2 Study Outcome Measures

3.2.1 Primary

- Incidence of adverse events assessed using Common Terminology Criteria for Adverse Events (CTCAE) version 5.0

3.2.2 Secondary

- Median radiation treatment time and median number of dose delays due to toxicity
- CLR 131 tumor uptake via SPECT/CT imaging and Monte Carlo calculations
- Overall response rate (ORR) defined as the proportion of subjects who experience either a partial response or complete response within 6 months post completion of EBRT as measured by standard of care imaging (e.g. CT, MR, PET-MR)
- Swallow function assessed by Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) scale
- Quality of life (QoL) assessed by MD Anderson Dysphagia Inventory score (MDADI)
- Salivary flow rate related quality of life assessed by stimulated salivary flow

4 STUDY DESIGN

This is a Phase 1, single center, dose escalation and dose expansion study of subjects with locoregionally recurrent head and neck cancer who may also have distant metastatic disease. All subjects will receive a dosimetry test dose of CLR 131 (flat dose of 15 mCi) to establish drug uptake by the tumor.

Subjects who have tumor uptake of the CLR 131 dosimetry test dose as determined on SPECT/CT imaging by the study radiologist will be eligible to participate on the treatment portion of this clinical trial. Any subject who demonstrates tumor uptake of CLR 131 by SPECT/CT imaging after the test dose will continue to participate in the treatment portion of the study. Up to six participants who do not demonstrate tumor uptake of CLR 131 by SPECT/CT will also continue with the treatment portion of the study. Based on prior experience of subjects receiving CLR 131, 75 % of eligible subjects are estimated to demonstrate CLR 131 uptake within their tumors.

Subjects showing uptake will receive a cumulative tumor dose of 60-70 Gy using personalized dose calculation of CLR 131 (via Monte Carlo) combined with external beam radiation. If the Monte Carlo dose estimate for any subject is greater than 60 Gy for the 2 doses of CLR 131 (highly unlikely based on preliminary data), then no additional external beam dose will be administered.

All subjects will start thyroid-protection medication the day prior to the CLR 131 dosimetry test dose and will continue to take thyroid protection medication for 14 days after the last CLR 131 dose.

Treatment Plan

Enrollment will start at dose level 1. Subjects will receive 2 doses of CLR 131 intravenously with the first dose on day 1 followed by the second dose on day 8. The dose of CLR 131 will be based on the dose escalation schema.

Dose Escalation Schema	
Dose Level	**Doses** of CLR 131**
-1*	12.5 mCi/m^2
1	15.6 mCi/m^2
2	18.75 mCi/m^2

*Dose level -1 is the de-escalation dose. The first four patients will be given Dose 1. Dose -1 will only be used if toxicities warrant de-escalation.

** Dose level listed is administered first on day 1 and again on day 8.

SPECT/CT imaging will be performed on days 2, 3, 4-6, and 7-8 of the treatment period to visualize and quantitate the biodistribution of CLR 131. Using the SPECT/CT imaging scans, the Bednarz lab will perform the Monte Carlo calculations to predict absorbed dose of CLR 131 to tumors and normal structures.

Based on the calculated absorbed dose of CLR 131 to the specific targeted tissue, the subject will undergo EBRT to complete the designated radiation dose outlined in the re-irradiation plan.

At baseline, 3, 6 and 12 months post completion of EBRT, subjects will be assessed for changes to head and neck specific subject health-related measures: quality of life and salivary flow rate. Swallow function will be assessed at baseline, 3 and 6 months post completion of EBRT (standard of care Modified Barium Swallow (MBS) and research-related oral profile exam) see Schematic of Study Design).

Enrollment to the study is anticipated to take approximately 20 months. Each subject will participate for approximately 27 months, although only about four months will be active participation. Details of the study schedule, including lab draws and specific study procedures are provided in section 7.

Incomplete dosing of CLR 131 within study timeframe:
In the event a participant is unable to receive the full study course of CLR 131 within the study timeframe such as a delay in drug manufacturing, the study team will evaluate if it is in the best interest of the study participant to continue with protocol therapy. If it is deemed appropriate for the subject to continue with the CLR 131 administration, their scheduled appointments, labwork and SSKI administration will be adjusted appropriately to accommodate the delay. If it is deemed in the participant's best interest to proceed to SOC EBRT, the following scenerios will occur:

- Only test dose (15 mCi) CLR 131 administered:
    - Continue SSKI until 14 days post CLR 131 administration
    - Proceed with EBRT and SOC follow-up.

- If test dose and a single therapeutic dose are administered:
    - Continue with SSKI until14 days post CLR 131 administration
    - Undergo imaging for calculations of EBRT dose de-escalation
    - Proceed to EBRT
        - Modify EBRT dose based on the single therapeutic injection
    - Continue follow-up per protocol.

5 STUDY ENROLLMENT AND WITHDRAWAL

5.1 Number of Subjects

Up to 12 subjects treated at the MTD are planned for the study. The number of subjects in the expansion cohort will depend on the number of subjects treated in the mTPI-2 design (Section 14.2). Adult men and women of all races and ethnic groups are eligible for this trial.

5.2 Inclusion Criteria

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

1. Subject must be informed of the investigational nature of the study and must be able to sign a written informed consent.
2. Subjects with histologically or cytologically confirmed solid malignancy that has recurred in the head and neck (above the clavicles) region, e.g., subjects with recurrent cutaneous squamous cell carcinoma, salivary gland tumors or esthesioneuroblastoma are eligible for this clinical trial.
3. Subject is 18 years of age or older.
4. Subjects must have undergone previous curative intent therapy, with radiation as a primary or adjuvant therapy.
5. Subjects may have distant metastatic disease, as long as the locoregional site of recurrence is deemed eligible for radiation therapy, and treatment of the loco-regional disease is deemed as taking precedence over treatment of the remaining systemic disease.
6. Subjects must have at least one evaluable (measurable or non-measurable) recurrent lesion that is amenable to radiation therapy.
7. Subjects must demonstrate uptake of CLR 131 via SPECT/CT imaging, as determined by the study radiologist, in the specified site of recurrent/metastatic disease that is to be treated with radiation therapy. There is a subset of up to 6 patients who may continue with CLR 131 treatment without uptake on the SPECT/CT scan after the test dose.
8. Subjects must have an ECOG performance status of 0 – 1.
9. Subjects must have a life expectancy of at least 6 months.
10. The subject has adequate hematologic function, as evidenced by:
    - an absolute neutrophil count (ANC) ≥ 1500 / µL
    - hemoglobin ≥9 g/dL (5.58 mmol/L)
    - and platelets ≥100,000 / µL
        - If full-dose anticoagulation therapy is used, platelets ≥ 150,000 / µL are required.

- If subject is on full-dose anticoagulation therapy, the anticoagulation therapy must be reversible, and reversal of the anticoagulation therapy must not be life-threatening, as judged by the investigator.

11. The subject has adequate renal function as defined by:
    - serum creatinine ≤ 1.5 times the upper limit of normal (ULN) or Cockcroft-Gault calculated creatinine clearance ≥ 60 ml/min
12. The subject has adequate hepatic function as defined by:
    - total bilirubin ≤ 1.5 mg/dL (25.65 µmol/L)
    - aspartate transaminase (AST) and alanine transaminase (ALT) ≤ 3.0 times the ULN
13. Women of childbearing potential (WOCP) have a confirmed negative urine pregnancy test within 24 hours prior to test dose of CLR 131.
14. Subjects must use a medically acceptable method of birth control such as an oral, implantable, injectable, or transdermal hormonal contraceptive, an intrauterine device (IUD), a double barrier method (condoms, sponge, diaphragm, or vaginal ring with spermicidal jellies or cream), or total abstinence during the study participation and for 6 months after last dose of study drug. Women who are postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy, or hysterectomy) are not considered to be WOCP.
15. Men who are not surgically or medically sterile agree to use an acceptable method of contraception. Male subjects with female sexual partners who are pregnant, possibly pregnant, or who could become pregnant during the study must abstain from intercourse for three weeks after each CLR 131 dose and agree to use condoms at least 6 months after the last dose of study drug. Total abstinence for the same study period is an acceptable alternative.

5.3 Exclusion Criteria

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

1. Recurrent tumor recommended for surgical resection based on multidisciplinary Head and Neck Oncology Tumor Board Review
2. Thyroid cancer
3. Known hypersensitivity to iodine
4. Other concurrent severe and/or uncontrolled concomitant medical or psychiatric conditions (e.g. active or uncontrolled infection, uncontrolled diabetes) that could cause unacceptable safety risks or compromise compliance with the protocol, per investigator discretion

5. Chemotherapy or major surgery within 4 weeks, or radiotherapy within 2 weeks prior to test dose of CLR 131.
6. Subjects with clinically significant adverse events due to agents administered more than 4 weeks prior to test dose of CLR 131 (alopecia and fatigue excluded). Clinical significance to be determined by investigator.
7. The subject is pregnant, breastfeeding, or expecting to conceive or father children within the projected duration of the trial, starting with the screening visit through 6 months after the last dose of trial treatment.
8. Any ongoing or active infection, including active tuberculosis, hepatitis B or C, or known infection with the human immunodeficiency virus (HIV)
9. Concurrent treatment with any other anti-cancer or investigational agents. Subjects cannot be receiving concomitant chemotherapy, radiotherapy, experimental therapy or any other therapy not otherwise outlined by the trial for the purposes of anti-cancer treatment.
10. Patient with a history of or concurrent second primary malignancy (stage III or IV) within 5 years to study enrollment are excluded.
11. Patients with a history of prior invasive malignancy (except early-stage I or II non-melanomatous skin cancer, carcinoma in situ of the breast, cervical carcinoma in situ, stage I-II papillary thyroid cancer, or low or very low-risk prostate cancer which has been completely treated with surgery or radiation) treated within 2 years of study enrollment are excluded.
12. Subjects that have had total body or hemibody irradiation, or have had prior systemic radioisotope therapy (except for benign thyroid disease)
13. Poor venous access and will be unable to receive study drug into a peripheral venous catheter.
14. Significant traumatic injury within 6 weeks prior to enrollment
15. Extradural tumor in contact with the spinal cord or tumor located where swelling in response to therapy may impinge upon the spinal cord
16. Any history of cerebrovascular accident (CVA) or transient ischemic attack within 12 months prior to study entry
17. History of myocardial infarction, ventricular arrhythmia, stable/unstable angina, symptomatic congestive heart failure, coronary/peripheral artery bypass graft or stenting or other significant cardiac disease within 6 months prior to study entry
18. QT interval corrected for heart rate using Fridericia's formula (QTcF) ≥480 ms.
19. Any condition requiring the use of immunosuppression, excluding rheumatologic conditions treated with stable doses of corticosteroids (equivalent to ≤ prednisone 10 mg daily)
20. Ongoing hemodialysis or peritoneal dialysis
21. Poorly controlled severe COPD

22. Uncontrolled hypothyroidism or hyperthyroidism
23. Any medical condition that predisposes the subject to uncontrolled bleeding such as hemophilia, factor deficiencies, severe liver disease, or von Willebrand disease.

5.4 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 patient population will depend on patient sources available to the clinical site.

Subjects will be recruited from the treating physicians' own clinical practice, through clinic contacts, and referring physicians.

5.4.1 Subject remuneration

Subjects will be eligible to receive remuneration to offset the barriers of additional visits required to participate in this study. Subjects are eligible to receive $50 total for completing the SPECT/CT scan(s) needed following the test dose and an additional $200 after completing the fourth SPECT/CT scan following the first treatment dose of CLR 131.

5.5 Treatment Assignment Procedures

Subjects who agree to participate and who provide written informed consent will be enrolled via the University of Wisconsin Carbone Cancer Center (UWCCC) Oncore database by the Radiation Oncology research team prior to study-specific participation. All subjects must meet eligibility criteria as listed above. The research staff will verify eligibility, assign a case number, and register the subject in OnCore prior to study-specific participation. The following information will be recorded:

- Protocol number
- Subject's name
- Subject's medical record number
- Subject demographic data

The subject will also be registered with Cellectar Biosciences to ensure drug product availability and shipment. Information to be provided to Cellectar Biosciences includes: assigned subject identification number, initials, year of birth, body surface area, and dates of planned CLR 131 administration.

5.5.1 Evaluable Subject

For evaluation of safety endpoints, any subject that receives any portion of one treatment dose of CLR 131 will be included.

For evaluation of efficacy, subjects must receive all doses of CLR 131 in their entirety and at least one post-infusion efficacy assessment.

5.6 Subject Withdrawal

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, 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 investigator;
- 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.
- 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).

5.6.1 Handling of Subject Withdrawals or Subject Discontinuation of Study Intervention

If a subject decides to withdraw from the study (and not just from protocol therapy) all efforts should be made to complete and report study assessments as thoroughly as possible. The subject should be encouraged to complete the withdrawal visit procedures outlined in Section 7.4. A member of the research team should contact the subject or a responsible relative by telephone to establish as completely as possible the reason for the study withdrawal. A complete final evaluation at the time of the subject’s study withdrawal should be made with an explanation of why the subject is withdrawing from the study. If the reason for removal of a subject from the study is an adverse event, it will be recorded on the eCRF.

If a subject withdraws from the study prematurely, s(he) must continue taking the thyroid-protection medication for 14 days after the last CLR 131 infusion to ensure appropriate protection of the thyroid.

5.7 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, Cellectar and regulatory authorities. If the study is prematurely terminated or suspended, the principal investigator will promptly inform the institutional review board (IRB) and will provide the reason(s) for the termination or suspension.

Reasons for early study discontinuation may include, but are not limited to:

- Unacceptable toxicity of study drug
- Request to discontinue the study from a regulatory authority
- Protocol violations
- Poor enrollment
- Company business decision
- Difficulties in manufacturing the investigational product

6 STUDY INTERVENTION

6.1 Study Product Description

CLR 131 (also referred to as I-131-CLR1404 or [131I]-CLR1404) is supplied as a ready-for-use radiopharmaceutical for IV dosing. **Two formulations of CLR 131 are used:**

- **For CL1, CLR 131** is provided as a clear, faint yellow to yellow, sterile solution consisting of CLR 131 (18-(p-[^{131}I]-iodophenyl) octadecyl phosphocholine) and CLR 1404 (18-(p-iodophenyl) octadecyl phosphocholine) in sodium chloride injection US Pharmacopeia (USP), ethanol USP, polysorbate 20 National Formulary, and sodium ascorbate USP.

- **For CL2, CLR 131** is provided as a clear, colorless to yellow, sterile solution consisting of CLR 131 (18-(p-[^{131}I]-iodophenyl) octadecyl phosphocholine) and CLR 1404 (18-(p-iodophenyl) octadecyl phosphocholine) in sodium chloride injection US Pharmacopeia (USP), ethanol USP, polysorbate 20 National Formulary, gentisic acid, and sodium ascorbate USP.

For both formulations, the study drug is packaged in a single-use vial and must be filtered through a 25 mm 0.2 micron sterile filter prior to administration.

CLR 131 is radioactive and should only be prepared, assayed, and administered by personnel who are trained to handle radioactive materials. Proper radiation shielding should be used during storage, preparation, assay, and administration of CLR 131. The study drug will arrive from Cellectar Biosciences in a lead shipping container and should remain in the lead shipping container for storage until use.

CLR 131 Injection is shipped at room temperature (20 – 25 °C; 68 – 77 °F) with excursions during shipping of -40 – 70 °C (-40 – 158 °F) allowed. When received at the site, the drug product is to be stored as per the lead shield label.

- For CL1 formulation (identified in lot number as (N-xxxxxxCL1-x), the drug product is to be stored refrigerated (2 – 8 °C; 36 – 46 °F). If CLR 131 is refrigerated ≤ 72 hours after radiolabeling the shelf-life is 14 days; if the drug product is refrigerated > 72 hours after radiolabeling the shelf-life is 11 days.
- For CL2 formulation (identified in lot number as (N-xxxxxxCL2-x), the drug product is to be stored upright at 15 – 25 °C, as directed on the label.

The physical (radioactive) half-life of I-131 is 8.02 days. I-131 decays with beta emissions of 334 keV (7 %) and 606 keV (90 %) and subsequent gamma emissions of 284 keV (6 %), 364 keV (82 %), and 637 keV (7 %).

See the CLR 131 Radiopharmacy Manual (Supplementary Materials) for specific handling, preparation, administration, and storage requirements.

6.1.1 Acquisition

CLR 131 will be provided by Cellectar Biosciences' designated manufacturer and delivered directly to the institution in a just-in-time manner.

6.1.2 Formulation, Packaging, and Labeling

CLR 131 Injection:

- Is packaged in single use glass vial(s);
- Must be filtered through a 25 mm 0.2 micron sterile luer-lock syringe filter (or equivalent) prior to administration;
- Must be diluted with 0.9 % Sodium Chloride for Injection, USP and thoroughly mixed prior to administration via slow IV infusion;

6.1.3 Product Storage and Stability

CLR 131 Injection:

- Should not be subjected to temperatures below -20 degrees centigrade (-4 degrees Fahrenheit);
- Should be stored as per the lead shield label and infused at room temperature; and
- When product is prepared in an appropriate sterile environment as per the instructions in the CLR 131 Radiopharmacy and Infusion Manual, the beyond-use date is 48 hours post preparation, if kept at room temperature after preparation and the 48 hours falls within the expiry of the drug product.

Note: the CLR 131 Radiopharmacy Manual v6.0 and vial and pig labels incorporate appropriate language to guide site staff on appropriate storage of CLR 131.

6.2 Dosage, Preparation and Administration of Study Product

Each subject will receive CLR 131 through a freely-running peripheral IV catheter over a period of approximately 30 minutes. The dose of CLR 131 will be calculated for each subject based on total body surface area (BSA) (not to exceed 2.5 m^2) calculated from actual body weight and height. The subject will be clinically monitored for adverse reactions during the infusion and for 1 hour post-infusion.

6.3 Thyroid Protection Medication

To protect the thyroid from uptake of radioactive iodine, administration of thyroid-protection medication is required. Thyroid-protective agents should be administered beginning the day prior to the dosimetry test dose of CLR 131 and continue for 14 days after the last dose of CLR 131.

Thyroid protection medication administration

CLR 131 dose	Duration of thyroid protection medication

Dosimetry test dose only	15 days
Dosimetry test dose +1 Treatment dose	25-30 days, must take14 days past last dose
Dosimetry test dose +2 Treatment doses	32-38 days, must take 14 days past last dose

Potassium iodide tablets 130 mg orally once daily are the preferred thyroid protection medication. Acceptable alternatives, per institutional preference, include the following:

- Saturated solution of potassium iodide (SSKI) 2 drops orally twice daily
- Lugol's 5 % solution 0.8 mL (approximately 16 drops) orally twice daily

Subjects must receive two doses of SSKI, two doses of Lugol's 5 % solution or one potassium iodide tablet (130 mg) prior to CLR 131 infusion.

If a subject withdraws from the study prematurely, they must continue taking thyroid protection medications for 14 days after the final CLR 131 infusion to ensure appropriate protection of the thyroid.

6.4 Modification of Study Product Administration for a Subject

There are no modifications for dose of CLR 131 or the thyroid protection medication.

6.5 Accountability Procedures for the Study Product

The clinical site staff must maintain a careful inventory of the study drug. Study drug use will be recorded on a study drug inventory form. At a minimum, this form will contain the following information:

- Subject number and initials for each subject receiving study drug
- Date, quantity and dose (mCi) of study drug received by the clinical site
- Date, quantity and dose (mCi) of study drug dispensed
- Date, quantity and dose (mCi) administered

Periodically, a Cellectar Biosciences' representative will reconcile the information on the study drug inventory form with the actual inventory of study drug used at the clinical site. All used and expired radioactive vials of CLR 131 will be stored at the clinical site in long half-life radioactive storage per the clinical site's standard operating procedures (SOPs) until background levels are reached (approximately 80 days). Once background levels are reached, the Cellectar Biosciences' representative will return to do a final accountability check of the now-decayed vials. The clinical monitor will instruct the site on disposition of the vials either to ship to Cellectar Biosciences for disposal or discard per their SOP for waste disposal.

6.6 Assessment of Subject Compliance with Study Product Administration

Thyroid-protection medication, including instructions for use and a diary, will be provided at screening. The subject's proper use of thyroid protection medication will be confirmed prior to every CLR 131 infusion and at appropriate follow-up visits.

It is recommended that the Investigator or his/her designee contact subjects by phone on the day prior to the dosimetry test dose to ensure thyroid-protection medication is started and a minimum of 2 doses of SSKI, 2 doses of Lugol's 5 % solution, or 1 potassium iodide tablet (130 mg) are taken prior to CLR 131 infusion.

6.7 SPECT/CT Dosimetry Evaluation

6.7.1 Tumor and Organs at Risk (OAR) Dosimetry

Subjects will obtain SPECT/CT images of the tumor and organs at risk at sequential imaging time points (days 2, 3, 4-6, and 7-8) after administration of the first treatment dose of CLR 131.

SPECT/CT images of tumor and organs at risk will be reconstructed using quantitative SPECT reconstruction methods with compensation for attenuation, scatter and the full collimator-detector response including septal penetration and scatter. A registered CT image will be used as the attenuation map for the SPECT images. Image data will be converted to activity per cubic centimeters using a sensitivity measurement made using a point source in air. For studies where the count rate is such that greater than 5% count rate losses are expected, deadtime corrections will be applied. The time activity curve in each pixel will be computed and fit with a mono-or bi-exponential function when possible or a piece-wise linear fit when more advanced fitting options are not possible. The fits will be integrated and divided by the injected activity to provide a 3D residence time image. This will be converted to a dose image using the RAPID Monte Carlo dose estimation code (A. Besemer & Bednarz, 2014; A. E. Besemer *et al.*, 2017; A. E. Besemer *et al.*, 2018). The average dose and 3D dose distribution in each tumor and organs at risk will then be computed inside volumes-of-interest defined using CT and SPECT images.

6.8 External beam radiation therapy (EBRT)

External beam radiation therapy will be used in combination with CLR 131 infusions to deliver a total dose of 60-70 Gy to the recurrent tumor in subjects determined by study radiologist to exhibit uptake of CLR 131.

The standard of care radiation therapy for this patient population is 60-70 Gy absorbed dose, irrespective of radiation delivery. Therefore, as long as the SOC radiation dose parameters are met, EBRT described in 6.8 is considered within standard of care. The total dose (60-70 Gy) delivered to the recurrent tumor will be at the discretion of the treating Radiation Oncologist.

6.8.1 Dose specifications and target definition

The recurrent gross tumor volume (rGTV), as defined by diagnostic imaging including CLR 131 uptake imaging and physical exam findings, will receive daily fractions of 2.0-2.5 Gy. The rGTV

will undergo a geometric expansion of 3-5 mm to create the recurrent clinical target volume (rCTV), which accounts for coverage of areas at high-risk for harboring subclinical disease. The rCTV can be modified by the treating Radiation Oncologist to account for areas thought to be free of disease (e.g. air space, bone). The rCTV will be expanded by 2-3 mm to create a recurrent planning target volume (rPTV). Elective treatment volumes treated to lower dose are generally discouraged but permitted at the discretion of the treating physician.

6.8.2 Plan evaluation

Plans will be normalized so that 95 % of the rPTV is covered by the prescription dose (PD). The dose to 1cc of the rPTV should not exceed 115 % of the PD. The dose to 0.3 cc of the rPTV should not be less than 92 % of the PD.

6.8.3 Technical factors

Participants will undergo CT scan simulation using ≤ 3 mm slices. Subjects will be immobilized using an Aquaplast mask. The scan should be performed with IV contrast unless the subject has contra-indications (e.g. IV contrast allergy or poor kidney function). Treatment will be delivered via linear accelerated-based (LINAC) intensity modulated radiotherapy (IMRT) using high energy photon beams. Subjects will be treated with image-guidance radiotherapy. Images will be approved prior to the first treatment and following all remaining treatments by a staff Radiation Oncologist. Images will be registered either manually or automatically. The region-of-interest for image fusion should include the primary tumor and adjacent spinal cord. Following registration, translation corrections should be applied to the treatment couch.

6.8.4 Definition of organs at risk and recommended dose constraints

Organs at risk (OARs) in subjects undergoing re-irradiation may have already approached or exceeded their respective recommended dose limitation. For example, during the initial treatment course, one or both parotid glands may have already exceeded the recommended dose of less than 26 Gy. Therefore, in situations such as these, best clinical judgement will be exercised by the treating radiation oncologist for dose constraints.

The concept of dose forgiveness with regard to the time from prior radiation to re-irradiation, especially for critical structures such as the spinal cord, will be taken into account by the treating Radiation Oncologist when deciding on final OAR doses.

Recommended dose to OAR may or may not be achievable based upon the prior radiation and contribution of CLR 131 to the total dose.

Spinal cord: The spinal cord begins at the cranial-cervical junction (i.e. between the foramen magnum and the top of the C1 vertebral body). Superior to this is the brainstem and inferior is the spinal cord. The inferior border of the spinal cord is at approximately T3-4 (i.e. 2 cm below the lowest slice containing rPTV). The spinal cord will be defined based on the treatment planning CT scan. All attempts to limit the combined total dose from the previous and current radiation treatment regimen (CLR 131 and EBRT) to less than 60 Gy will be made. Higher point doses can

be considered and are at the discretion of the treating physician, however the spinal cord maximum point dose including prior radiation course will not exceed 65 Gy.

Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction between the foramen magnum and top of the C1 vertebral body. The brainstem will be contoured to the level of the posterior clinoid. The brainstem will be defined based on the treatment planning CT scan. All attempts to limit the combined total dose from the previous and current radiation treatment regimen (CLR 131 and EBRT) to less than 70 Gy will be made. Higher point doses can be considered and are at the discretion of the treating physician, however the brainstem maximum point dose including prior radiation course will not exceed 72 Gy.

Parotid glands: Parotid glands will be defined based on the treatment planning CT scan. The contours will not include the accessory duct (i.e. gland anterior to the masseter muscle). The treatment planning goal for the parotid gland that received a lower previous radiotherapy dose should be a mean dose of < 26 Gy, but ideally as low as possible given data suggesting a no threshold dose response. Depending on the dose received by the parotid gland receiving a higher mean dose from the previous treatment, a constraint should be made by the treating physician.

Glottic/Supraglottic larynx (GSL): This will be defined as a volume that begins just inferior to the hyoid bone and extends to the cricoid cartilage inferiorly and extends from the anterior commissure to include the arytenoids. This includes the infrahyoid and excludes the suprahyoid epiglottis. The GSL mean dose from retreatment should be ≤ 35 Gy.

Mandible: This includes the entire boney structure of the mandible from TMJ through the symphysis. The recommended maximum dose within the mandible should be < 35 Gy. This assumes a maximum dose approaching 60 Gy from the previous radiotherapy treatment plan. Therefore, a goal of < 105 Gy should be achievable with contribution from CLR 131.

Pharyngeal constrictors: This includes the structure along the posterior pharyngeal wall from the inferior border of the pterygoid plates to the inferior border of the cricoid. A planning goal for a mean dose of < 35 Gy from the retreatment should be utilized.

6.8.5 Prioritization for IMRT planning

1. Spinal Cord
2. Brainstem
3. rPTV70
4. Mandible
5. GSL
6. Contralateral parotid gland
7. Ipsilateral parotid gland
8. Pharyngeal constrictors

6.9 Concomitant Medications/Treatments

All intercurrent medical conditions will be treated at the discretion of the Investigator according to acceptable community standards of medical care. All concomitant medications and treatments will be documented appropriately and recorded until 28 days after last EBRT treatment or 85 days after first treatment dose of CLR 131, whichever is later.

The following medications are not permitted during the study unless mandated by clinical circumstance:

- Any other investigational treatment
- Any other systemic antineoplastic therapy including, but not limited to, cytotoxic chemotherapy, immunotherapy, monoclonal antibody therapy, systemic radioisotope therapy
- Prophylactic hematopoietic growth factors (note: therapeutic hematopoietic growth factors are permitted at the discretion of the treating physician)

Pneumocystis jiroveci pneumonia (PJP) and viral prophylaxis for subjects with lymphopenia should be considered and is at the discretion of individual investigators.

Initiation of platelet transfusions are suggested for subjects with a platelet count $\leq$ 20,000 / µL or those subjects with symptomatic thrombocytopenia (evidence of bruising or bleeding).

Cellectar Biosciences advises investigators to refrain from initiating highly myelosuppressive therapy in subjects progressing within 85 days of CLR 131 infusion until their blood counts have fully recovered to previous baseline.

There are no known interactions with other medications.

After the recording period only medications used to treat a cancer recurrence will be recorded.

7 STUDY SCHEDULE

7.1 Screening

The screening evaluation will occur within 42 days of the test dose of CLR 131. All subjects must provide informed consent prior to any procedures being done specifically for the study and must satisfy the entry criteria. Procedures and data collection at screening are:

- Signed informed consent form (ICF)
- Demographics (birth date, gender, race, ethnicity)
- Medical history, including comprehensive treatment history for underlying malignancy
- Review of concomitant medications
- Physical examination
- Vital signs
- Height, weight
- ECOG performance status
- Complete blood count (CBC) with differential (within 2 weeks prior to test dose to determine eligibility)
- Serum chemistries (within 2 weeks prior to test dose to determine eligibility)
- EKG (within 2 weeks prior to test dose to determine eligibility)
- Urine pregnancy test for WOCP (within 24 hrs prior to the dosimetry test dose)
- Serum thyroid-stimulating hormone (TSH) and free thyroxine (T4)
- Dispense thyroid-protection medication and review instructions with subjects. Thyroid-protection medication must be taken within 24 hours before CLR 131 dosing and for 14 days after the last CLR 131 dose.
- Adverse event evaluation
- Distribute medication diaries
- Quality of Life surveys
- Saliva and oral swab collection
- Modified barium swallow study
- Oral profile exam
- Diagnostic cross-sectional imaging (any combination of CT, MR, or PET-MR) scans) collected from the scans performed as part of standard clinical care.
- Dosimetry Test Dose
- SPECT/CT imaging

7.1.1 Dosimetry Test Dose

On the day of dosing, prior to infusion, the following tests and procedures will be done:

- Confirm subject is taking thyroid-protection medication as directed
- Urine pregnancy test for WOCP (within 24 hrs prior to the dosimetry test dose)
- Vital signs will be collected prior to and 1 hour post CLR 131 infusion

CLR 131 will be administered through a freely running peripheral IV catheter via a slow infusion of approximately 30 minutes duration. For the dosimetry test dose, the dose of CLR 131 will be a flat dose of 15 mCi.

- SPECT/CT imaging will be performed approximately three days after infusion to assess tumor uptake of CLR 131. If a subject does not demonstrate CLR 131 uptake on the day 3 SPECT/CT scan, then a repeat SPECT/CT can be performed 7 days after the CLR 131 test dose to reassess for uptake.
- Subjects who demonstrate uptake of CLR 131 on either the day 3 or day 7 SPECT/CT scan, along with up to six patients who do not demonstrate uptake of CLR 131 are eligible for the treatment doses of CLR 131.

7.2 Treatment Period

7.2.1 Treatment Dose

The targeted time between the dosimetry test dose and treatment dose will be 7-14 days, but will allow for to up to four weeks. Dosing dates for treatment can be scheduled to start -1 or +3 days to accommodate clinic scheduling (e.g., holidays, weekends, treating physician schedules, etc.).

7.2.1.1 Treatment Dose Administration

Subjects who have uptake on SPECT/CT imaging scans are eligible for the treatment portion of the clinical trial. These subjects will be treated and evaluated as follows:

- Vital signs will be collected prior to and 1 hour post CLR 131 infusion
- On day 1 of the treatment period, CLR 131 will be administered through a freely running peripheral IV catheter via a slow infusion of approximately 30 minutes duration. The dose of CLR 131 will be calculated for each subject based on total BSA (not to exceed 2.5 m^2) calculated from actual body weight and height at screening.
- SPECT/CT imaging will be performed on days 2, 3, 4-6, and 7-8.
- A second treatment dose of CLR 131 will be given on day 8.
- CBC with differential and serum chemistries weekly for 12 weeks (beginning at day 1 of first treatment dose)

- Confirm subject is taking thyroid protection medication as directed.
- Adverse event evaluation
- Urine pregnancy test for WOCP (within 24 hrs prior to each CLR 131 dose)

7.2.1.2 External beam radiation therapy (EBRT) (approximately 7-14 days after the last CLR 131 treatment dose)

Based on the calculated absorbed dose of CLR 131 to the specific targeted tissue, the subject will undergo standard of care EBRT to complete the designated radiation dose outlined in the re-irradiation plan.

An EKG will be performed on the first day of the SOC EBRT. During the course of EBRT, subjects will be evaluated for any adverse events.

7.3 Post Treatment Period

7.3.1 One Month Post CLR 131 Infusion (± 2 weeks)

One month (± 2 weeks) after the first therapeutic CLR 131 dose, the following tests and procedures will be done:

- Review of concomitant medications
- Physical examination
- Vital signs
- Weight
- ECOG PS
- CBC with differential
- Serum chemistries
- Confirm subject is taking thyroid-protection medication as directed
- Adverse event evaluation

7.3.2 3 Months Post EBRT (± 4 weeks)

Three months (± 4 weeks) after EBRT is completed, the following tests and procedures will be done:

- Review of concomitant medications
- Physical examination
- Vital signs
- Weight
- ECOG PS

- CBC with differential
- Serum chemistries
- TSH and free T4
- Adverse event evaluation
- Oral profile exam
- Modified barium swallow study
- Quality of Life surveys
- Saliva and oral swab collection
- Diagnostic cross sectional imaging (any combination of CT, MR, or PET-MR scans) collected from the scans performed as part of standard clinical care

7.3.3 6 months Post EBRT (± 4 weeks)

Six months (± 4 weeks) after EBRT is completed, the following tests and procedures will be done:

- Review of concomitant medications
- Physical examination
- Vital signs
- Weight
- ECOG PS
- TSH and free T4
- Adverse event evaluation
- Oral profile exam
- Modified barium swallow study
- Quality of Life surveys
- Saliva and oral swab collection

7.3.4 12 months Post EBRT (± 6 weeks)

Twelve months (± 6 weeks) after EBRT is completed, the following tests and procedures will be done:

- Review of concomitant medications
- Physical examination
- Vital signs
- Weight

- ECOG PS
- TSH and free T4
- Adverse event evaluation
- Quality of Life surveys
- Saliva and oral swab collection
- Diagnostic imaging (any combination of CT, MR, or PET-MR scans) collected from the scans performed as part of standard clinical care

7.3.5 24 months Post EBRT (± 6 weeks)/End of Study Visit

(Note: this follow-up assessment will not be completed if the subject has initiated a new, anti-cancer therapy prior to the 24 month visit.)

Twenty-four months (± 6 weeks) after EBRT is completed, the following tests and procedures will be done:

- Physical examination
- TSH and free T4
- Adverse event evaluation
- Diagnostic imaging (any combination of CT, MR, or PET-MR scans) collected from the scans performed as part of standard clinical care

7.4 Withdrawal Visit (+ 30 days)

If a subject withdraws or the investigator terminates subject participation prior to 24 months post EBRT, the following tests and procedures will be done:

- Review of concomitant medications
- Physical examination
- Vital signs
- Weight
- ECOG PS
- Adverse event evaluation

7.5 Unscheduled Visit

Unscheduled visits with clinically significant tests or procedures will be captured in the OnCore database. Subjects who have an urgent or emergent medical condition will be seen by the treating physician and/or emergency room and treated as clinically indicated. Medical records will be obtained to evaluate for any adverse events, which will be documented in the clinical study database. In addition, the principal investigator, in conjunction with the treating physician, will

determine the attribution of any adverse events to the medical condition, disease, investigational agents, or any other probable causes.

8 STUDY PROCEDURES /EVALUATIONS

8.1 Study Procedures/Evaluations

8.1.1 Demographics

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).

8.1.2 Medical History

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 (within 42 days prior to the CLR 131 dosimetry test dose infusion). This will be recorded for the study from medical records maintained as part of standard clinical care.

8.1.3 Concomitant Medication Review

All current and recent medications will be reviewed and recorded in the CRF. The medication review must be completed within 42 days prior to the dosimetry test dose infusion of CLR 131(screening period). A review of concomitant medications will occur at one month post the first CLR 131 therapeutic infusion; at 3, 6, and 12 months post EBRT; and at the withdrawal visit. This will be recorded for the study from medical records maintained as part of standard clinical care for the screening period as well as the 3, 6, and 12 month post EBRT visits. These are research-related reviews for the one month post first CLR 131 therapeutic infusion visit and at the withdrawal visit (if terminated early).

8.1.4 Physical Exam

A detailed physical exam will be completed at screening; at one month post the first CLR 131 therapeutic infusion; at 3, 6, and 12 months post EBRT; and at the withdrawal visit. This will be recorded for the study from medical records maintained as part of standard clinical care for the screening period as well as the 3, 6, and 12 month post EBRT visits. These are research-related reviews for the one month post first CLR 131 therapeutic infusion visit and at the withdrawal visit (if terminated early).

8.1.5 Vital Signs

Vital signs (blood pressure, pulse, respiratory rate, and temperature) will be recorded prior to and 1 hour post each CLR 131 infusion and at the following timepoints: screening; one month post the first CLR 131 therapeutic infusion; at 3, 6, and 12 months post EBRT; and at the withdrawal visit. This will be recorded for the study from medical records maintained as part of standard clinical care for the screening period as well as the 3, 6, and 12 month post EBRT visits. These are research-related reviews for the CLR 131 infusion timepoints, as well as one month post first CLR 131 therapeutic infusion visit and at the withdrawal visit (if terminated early).

8.1.6 *Height*

Height will be recorded at screening. This is a standard procedure being done within routine care guidelines.

8.1.7 Weight

Weight will be recorded at screening; at one month post the first CLR 131 therapeutic infusion; at 3, 6, and 12 months post EBRT; and at the withdrawal visit (if applicable). This will be recorded for the study from medical records maintained as part of standard clinical care for the screening period as well as the 3, 6, and 12 month post EBRT visits. These are research-related measures for the one month post first CLR 131 therapeutic infusion visit and at the withdrawal visit (if terminated early).

8.1.8 ECOG Performance Status

Determination of the subject's performance scale (PS) based on the Eastern Cooperative Oncology Group (ECOG) rating scale (Appendix B) will be made at screening; at one month post the first CLR 131 therapeutic infusion; at 3, 6, and 12 months post EBRT; and at the withdrawal visit (if applicable). This will be recorded for the study from medical records maintained as part of standard clinical care for the screening period as well as the 3, 6, and 12 month post EBRT visits. These are research-related measures for the one month post first CLR 131 therapeutic infusion visit and at the withdrawal visit (if terminated early).

8.1.9 Administration of Thyroid Protection Medication

Thyroid-protection medication, including instructions for use and a diary, will be provided at screening. The subject's proper use of thyroid-protection medication will be confirmed at Day 1, prior to every CLR 131 infusion, and at applicable follow-up visits to ensure the appropriate use. Refer to Section 6.3 for dosing and duration details.

It is recommended that the Investigator or his/her designee contact subjects by phone on the day prior to the dosimetry test dose to ensure thyroid-protection medication is started and a minimum of 2 doses of SSKI, 2 doses of Lugol's 5 % solution, or 1 potassium iodide tablet (130 mg) are taken prior to CLR 131 infusion.

The administration of thyroid-protection medications is a standard clinical procedure being done for research-related purposes associated with the administration of the research drug CLR 131.

8.1.10 Administration of CLR 131

CLR 131 will be administered through a freely running peripheral IV catheter via a slow infusion of approximately 30 minutes duration. The dose of CLR 131 will be calculated for each patient based on total BSA (not to exceed 2.5 m^2) calculated from actual body weight and height at screening.

UW Hospital has established guidelines regarding the administration of radioactive material and release criteria following such administration. All institutional policies will be followed in this study. The institutional policies will be followed in determining whether the CLR 131 administration will be

done as an outpatient or inpatient. Suggested guidelines for monitoring for radioactivity and criteria to use for discharge are outlined in Section 10.1.

See the CLR 131 Radiopharmacy Manual (Supplementary Materials) for specific administration requirements.

The administration of CLR 131 is a research-related procedure.

8.1.11 Adverse Event Evaluation

Adverse event assessment will be performed at screening (standard of clinical care); at Day 1 prior to each CLR 131 infusion (research-related); weekly during EBRT (research related); at 3, 6, and 12 months post EBRT (standard of clinical care); and at the withdrawal visit (research-related if applicable). Adverse events will be assessed as described in Section 11, Assessment of Safety.

8.1.12 SPECT/CT Imaging

SPECT/CT imaging will be completed at two potential timepoints after the CLR 131 dosimetry test dose to evaluate for tumor uptake: (a) approximately three days and (b) approximately 7 days after the CLR 131 test dose. The SPECT/CT scan on day 7-8will be completed only if CLR 131 uptake by the tumor is not demonstrated on the day 3 scan. Uptake in the specified site of recurrent/metastatic disease that is to be treated with radiation therapy will be determined by the study radiologist.

Subjects with demonstrated uptake on either SPECT/CT scan (day 3 or day 7) after the test dose and up to six subjects who do not demonstrate uptake of CLR 131 will receive treatment doses of CLR 131. These subjects will have additional SPECT/CT imaging completed in order to visualize and quantitate the biodistribution of the CLR 131 treatment dose. Based on these SPECT/CT imaging scans, the Bednarz lab will utilize the Monte Carlo method to predict absorbed dose of CLR 131 to tumors and normal structures.

SPECT/CT imaging, which is a research-related procedure, will be performed on days 2, 3, 4-6, and 7-8 following the first CLR 131 treatment dose.

8.1.13 Electrocardiogram (EKG)

An EKG will be performed at the baseline/screening visit, as well as on the first day of treatment for EBRT. This is a research-related procedure.

8.1.14 Quality of Life Measures

Quality of life (QoL) surveys will be collected at screening and at 3, 6, and 12 months post EBRT. The surveys are anticipated to take ~ 20 minutes to complete.

- SF-12
- EORTC QLQ-C30
- EORTC QLQ-H&N35
- MDADI

- EAT-10
- XeQoLS

The completion of QOL surveys is a research procedure.

Validated health outcome surveys will be used to assess subject perception of mental and physical health, QOL, cancer-related H&N functioning, swallowing-related QOL and xerostomia before and after re-irradiation (Connor *et al.*, 2006).

Each subject will serve as their own control with complete QOL evaluation prior to and following treatment. This will take into account various baseline dysfunctions that may be present from prior HNC therapy.

Perception of general health and QOL will be evaluated using the Medical Outcomes Trust Short Form 12 (SF-12) (Ware *et al.*, 1995) and the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30) (Hammerlid *et al.*, 2001; Hjermstad *et al.*, 1995; Kemmler *et al.*, 1999). The SF-12 is a shorter version of the widely-used SF-36 and was chosen for its well-established acceptance as a valid and reliable measure of perception of physical and mental health across a large range of disease entities, including HNC (Gandek *et al.*, 1998; Terrell *et al.*, 1997; Terrell *et al.*, 2004). The EORTC QLQ-C30 was chosen for its sensitivity to cancer-related QOL and symptomatology, such as nausea/vomiting, fatigue and pain, and because it was identified previously as being well-developed, reliable, valid, and responsive (Ringash & Bezjak, 2001).

Specific cancer-related H&N functioning will be assessed with the EORTC QOL Questionnaire H&N35 (EORTC QLQ-H&N35) (Bjordal *et al.*, 1999; Sherman *et al.*, 2000). This validated instrument incorporates items related to swallowing, eating, dry mouth, and saliva production and is sensitive to cancer site and stage (Bjordal *et al.*, 1999). The EORTC QLQ-C30 and QLQ-H&N35 will be administered together and will yield a global health status score.

The MD Anderson Dysphagia Inventory (MDADI) and Eating Assessment Tool (EAT-10) will be used to investigate swallow-related QOL (P. H. Chen *et al.*, 2009; Rosenthal *et al.*, 2007; Rosenthal *et al.*, 2008) and the Xerostomia-related QOL scale (XeQoLS) will be used to measure subject-perceived dry mouth and its implications for QOL (Henson *et al.*, 2001; Rogers *et al.*, 2010).

8.1.15 Oral Swab and Saliva Collection and Analysis

Oral swab and saliva collection and analysis will occur at screening, and at 3, 6 and 12 months post EBRT. This is a research procedure which will take ~10-20 minutes.

Participants will be asked to refrain from all intake of food and drink, smoking, and use of toothpaste for one hour prior to collection. Samples from the buccal mucosa and tongue dorsum will be obtained using a cotton tip collection swab.

Saliva (unstimulated and stimulated) and saliva flow rates will be collected. Guidelines for collecting unstimulated and stimulated saliva developed by the University of Southern California (USC) School of Dentistry (Navazesh & Kumar, 2008) will be adapted and used in this project. Unstimulated whole saliva production will be collected first for each subject, followed by collection of saliva during unflavored gum base chewing to obtain a sample of stimulated saliva (Dawes, 1987; Logemann *et al.*, 2001). Salivary compositional analyses will focus on qualitative aspects of saliva previously found to change following radiation treatment: salivary viscosity (Sim *et al.*, 2018; Tolentino Ede *et al.*, 2011), pH (Chitra & Shyamala Devi, 2008; Sim *et al.*, 2018), total protein concentration (mg/mL) (Richards *et al.*, 2017; Valdez *et al.*, 1993), amylase (mU/mL) (Almstahl *et al.*, 2001; Chitra & Shyamala Devi, 2008), mucin (MUC5B, mU/mL) (Almstahl *et al.*, 2001; Dijkema *et al.*, 2012) and alpha and beta microbiota diversity (Hu *et al.*, 2013).

At the same time as saliva collection, a mucositis grade will be determined by the study team using the World Health Organization (WHO) Oral Mucositis Assessment Scale. Also, the study team will grade oral health using the Kayser-Jones Brief Oral Health Status Examination (BOHSE), a valid and reliable scoring instrument developed for use with older adults by non-dental health care providers (Kayser-Jones *et al.*, 1995).

8.1.16 Oral profile exam (research procedure)

Subjects will participate in an oral exam which will involve the following measurements: residual mucosal saliva (RMS), resting swallow frequency, maximum expiratory pressure, peak airflow during voluntary cough, and maximum lingual pressures. Oral exams will occur during the screening and at the 3 and 6 month post EBRT visits. This is a research procedure which is estimated to take a total of 15-20 minutes per visit.

8.1.16.1 Residual Mucosal Saliva (RMS)

RMS, which correlates with hyposalivation and dryness perception, will be collected from the anterior hard palate (AHP), buccal (BUC), anterior tongue (AT), and lower labial (LL) surfaces using SialoPaper strips (Oraflow Inc., Smithtown, NY, USA). These strips will be applied for 10 seconds and measured using Periotron device (Oraflow Inc.).

8.1.16.2 Resting swallow frequency

Resting swallow frequency will be measured with combined methods: respiratory bellows around the diaphram, motion sensor around neck, and visual observation by research staff.

8.1.16.3 Maximum Expiratory Pressures (MEP)

Digital manometers will measure MEPs (cm H_2O) as a measure of expiratory force generation in all patients enrolled. The MEP will be calculated as the best of three trials within 10 % variance.

8.1.16.4 Peak airflow during voluntary cough (PCF)

Peak airflow during voluntary cough (PCF) will be measured using a peak airflow meter (Mini Wright Peak Flow Meter). Participants will be asked to inhale to total lung capacity (TLC) and to

"cough hard like there is something stuck in the throat" while standing. The PCF will be calculated as the best of three trials within 10 % variance.

8.1.16.5 Maximum Lingual Pressures (MLP)

Participants will have maximum lingual pressures measured using an Iowa Oral Performance Instrument (IOPI). Participants will press as hard as they can with their tongue against a pressure bulb positioned between the tongue and hard palate.

8.1.17 Modified Barium Swallow Study

Modified barium swallow (MBS) studies will be performed at screening, 3 and 6 months post EBRT. This is a standard clinical procedure being done within routine care guidelines. The procedures below are detailed for the purposes of this study to control for consistent treatment within this study group.

All subjects will be examined using videofluoroscopy (Supplemental Materials). Each subject will be seated in the lateral plane while radiographic images of bolus swallows are captured in continuous acquisition mode keeping the entire oral cavity and pharynx in view.

Subjects will swallow pre-measured mL boluses of thin liquid barium. Other consistencies assessed will include nectar and honey thick barium liquids, puree (pudding) thick barium, mechanical soft and regular solids, including a pill (barium capsule) and a shortbread cookie coated with pudding-thick barium.

Evaluation measures were chosen because similar measurements have been shown to be sensitive to hyposalivation (Rogus-Pulia & Logemann, 2011).

Our ability to assess and measure parameters related to swallowing is demonstrated by our prior work (List *et al.*, 1996a; List *et al.*, 1990; List *et al.*, 1996b). In addition to the videofluoroscopic swallowing assessments, diet will be rated using the Performance Status Scale (PSS) Normalcy of Diet Rating and the Functional Oral Intake Scale (FOIS).

To perform the rated measures, such as oral residue and Dynamic Imaging Grade of Swallowing Toxicity (DIGEST) scores, video recordings for all subjects at all timepoints will be presented in random order to two trained raters, who will be speech-language pathologists who specialize in swallowing and were not involved in the data collection. Ten percent of samples will be included twice to measure intra-rater reliability. To encourage adequate inter-rater reliability, raters will view a training sequence that does not include test items and provides anchors for each parameter until 90 % agreement is reached. Any occurrences of penetration or aspiration will be noted and rated using the Penetration Aspiration Scale (Robbins *et al.*, 1999; Rosenbek *et al.*, 1996).

8.1.18 Diagnostic Imaging

Diagnostic imaging will be performed at screening, 3 months post EBRT, and 12 months post EBRT. Imaging studies can be obtained at any time if clinically indicated by the treating physician.

Imaging studies may consist of any combination of CT, MR, or PET-MR scans, as clinically indicated. If cross sectional imaging is unable to be obtained, other imaging modalities may be used (see section 9.3). The imaging study performed at screening should be repeated at subsequent assessments.

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

8.2 Laboratory Procedures/Evaluations

Laboratory testing will be completed by CLIA-certified labs.

8.2.1 Clinical Laboratory Evaluations

8.2.1.1 Complete Blood Count with Differential

Blood will be drawn for CBC with differential at screening (standard of clinical care); weekly for 12 weeks beginning with day 1 treatment dose (research-related procedure); and at 3 months post EBRT (standard of clinical care).

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.

8.2.1.2 Serum Chemistries

Blood will be drawn for serum chemistries at screening, weekly for 12 weeks starting with first treatment dose of CLR 131 and at 3 months post EBRT. This is a standard procedure being done for research-related purposes of radiotherapeutic administration.

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, and phosphorus.

8.2.1.3 Pregnancy Test

A urine pregnancy test will be completed within 7 days prior to the CLR 131 dosimetry test dose in women of childbearing potential. 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.

8.2.1.4 Thyroid Function Tests

Blood will be drawn for serum analysis of TSH and free T4 at screening; 3, 6, and 12 months post EBRT. This is a research procedure for the screening, 3 and 6 month post EBRT visits. This is a standard clinical procedure performed within routine guidelines for the 12 month post EBRT visit.

9 CRITERIA FOR DISEASE ASSESSMENT

For the purposes of this study, subjects will be evaluated for evidence of response and progression at 3 and 12 months post-completion of the EBRT portion of the protocol – see study calendar. Only those subjects who receive a treatment dose of study drug will be assessed for response and/or progression. Those with inadequate uptake after the dosimetry test dose will only be followed for safety measures.

Response and progression will be evaluated in two distinct fashions. For those without evidence of metastatic disease at the time of study enrollment, response and progression will be evaluated using the new international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 Committee (Eisenhauer *et al.*, 2009).

For those with metastatic disease at the time of study enrollment, study lesions will be defined within the locoregional recurrence field that will be receiving EBRT. Those lesions will be assessed for response and progression using RECIST 1.1 criteria. Lesions outside of the radiation field can be assessed for response to CLR 131 alone. Once palliative systemic therapy is initiated for systemic disease burden, subjects will be censored as having disease progression, regardless of the status of the locoregional target lesions.

Note: Lesions are either measurable or non-measurable using the criteria provided below.

9.1 Measurable Disease

Measurable lesions are defined as those that can be accurately measured in at least one dimension (longest diameter to be recorded) as > 20 mm with conventional techniques (CT, MRI, x-ray) or as > 10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). To be considered pathologically enlarged and measurable, a lymph node must be ≥ 15 mm in short axis when assessed by CT scan.

9.2 Non-measurable Disease

All other lesions (or sites of disease), including small lesions (longest diameter < 20 mm with conventional techniques or < 10 mm using spiral CT scan 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/pulmonis, inflammatory breast disease, abdominal masses (not followed by CT or MRI), and cystic lesions are all non-measurable.

9.3 Guidelines for Evaluation of Measurable Disease

Measurements will be recorded for the study from standard of care scans in the medical records maintained as part of standard clinical care. All measurements should be taken and recorded in metric notation using a ruler or calipers. All baseline evaluations should be performed as closely as possible to the beginning of treatment and never more than 4 weeks before the beginning of the treatment.

Note: Tumor lesions that are situated in a previously irradiated area can be considered measurable only if there is documented growth of the lesion, and at least 8 weeks have elapsed since completion of radiation treatments.

When possible, the same method of assessment and the same technique should be used to characterize each identified and reported lesion at baseline and during follow-up. Imaging-based evaluation is preferred to evaluation by clinical examination when both methods have been used to assess the antitumor effect of a treatment.

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

Chest x-ray: Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT is preferable.

Conventional CT and MRI: These techniques should be performed with cuts of 10 mm or less in slice thickness contiguously. Spiral CT should be performed using a 5 mm contiguous reconstruction algorithm. This applies to tumors of the chest, abdomen, and pelvis. Head and neck tumors and those of extremities usually require specific protocols.

Ultrasound: When the primary endpoint of the study is objective response evaluation, US should not be used to measure tumor lesions. It is, however, a possible alternative to clinical measurements of superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation has not yet been fully and widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may only be available in some centers. Therefore, the utilization of such techniques for objective tumor response should be restricted to validation purposes in reference centers. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained.

10 RADIATION SAFETY

10.1 Radiation Safety Monitoring and Release Criteria

UW Hospital has established guidelines/policy regarding the release criteria following administration of radioactive material. All institutional policies will be followed in this study. The guidelines below are recommendations only, and the regulations of the institution will take precedence.

Prior to the initiation of this trial, the Radiation Safety Officer will be contacted to determine the release criteria to be followed for subjects participating in the trial. The institution's Radiation Safety Officer will conduct all appropriate training of research staff.

Sponsor suggested guidelines for monitoring for radioactivity and criteria to use for discharge are:

- Starting one day after the CLR 131 infusion, medical physics/radiation oncology personnel will monitor subject radiation levels at 1 meter from umbilicus.
- Subjects will be discharged from the hospital when their radiation level is < 7 mrem/hr and the discharge is cleared by radiation safety personnel.

10.2 Subject Radiation Precautions

Prior to the initiation of this trial, the Radiation Safety Officer will be contacted to determine all required precautions to be followed by subjects participating in the trial. The Radiation Safety Officer will perform all appropriate training of research staff.

Written instructions, approved by the institution's Radiation Safety Officer, describing methods to limit radiation dose to others must be given to the subject prior to CLR 131 infusion. The following precautions, conservatively derived from recommendations of the Society of Nuclear Medicine and Molecular Imaging (Silberstein *et al.*, 2012) and the American Thyroid Association Taskforce on Radioiodine Safety, 2011, are suggested for subjects following the administration of CLR 131 to lessen the risk to others:

For three weeks after each dose of CLR 131:

- Sleep alone and abstain from intercourse
- Do not sleep with infants, small children or pregnant women for three weeks after CLR 131 infusion

For one week after each dose of CLR 131:

- Avoid participating in feeding, clothes changing and similar care of infants and small children
- Limit time with and maintain a distance of approximately 3-6 feet from pregnant women and children
- Do not prepare food for others that requires prolonged handling with bare hands

- Do not share dishes, utensils, towels or face cloths with others prior to washing
- Do not share razors, toothbrushes, food or drinks with others
- Flush toilet twice after use and wash hands for 20 seconds afterwards. Men should urinate sitting down.
- Rinse the sink and wash hands thoroughly after brushing teeth
- Do not stay in a location other than a private residence (such as a hotel)
- Limit the time spent in public places to 1-2 hours if you can maintain 3 feet distance from others and avoid places such as theaters, sports arenas or stadiums, and so forth, where the option of getting a seat farther away from others may not always be possible
- Bathe/shower daily for at least three days after CLR 131 infusion
- Avoid prolonged use of public transportation the first day after CLR 131 infusion

11 ASSESSMENT OF SAFETY

11.1 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. Adverse event data collection and reporting, which are required as part of every clinical trial, are done to ensure the safety of subjects enrolled in the studies as well as those who will enroll in future studies using similar agents. Adverse events are reported in a routine manner at scheduled times during a trial. Additionally, certain adverse events must be reported in an expedited manner to allow for optimal monitoring of patient safety and care. The first step is to identify the event using the Common Terminology Criteria for Adverse Events (CTCAE). The CTCAE document provides descriptive terminology for adverse event reporting. A grading (severity) scale is provided for each adverse event term.

All AEs, whether serious or not, will be described in the source documents and the AE page of the Case Report Form (CRF). 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 adverse events 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 (see below)
- Subject’s condition is intermittent or continuing
- The grade of the event based on the CTCAE v5.0

11.1.1 Unanticipated Problems

The Office for Human Research Protections (OHRP) considers unanticipated problems 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.

11.1.2 Adverse Events

An adverse event is any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

11.1.3 Serious Adverse Events (SAE)

A serious adverse event is defined as any adverse event that meets one 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 defect

Planned hospitalizations for disease-related surgery, routine procedures, non–disease-related procedures, and inpatient hospitalization for radiation protection/exposure levels are not considered SAEs.

11.2 Time Period and Frequency for Event Assessment and Follow-Up

Unanticipated problems will be recorded in the data collection system throughout the study.

The PI will record all adverse events with start dates occurring any time after informed consent is obtained until 28 days after the last EBRT treatment or 85 days after first treatment dose of CLR 131, whichever is later. 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.

11.2.1 Adverse Events

- AEs will be recorded from time of informed consent until 28 days after last EBRT treatment or 85 days after first treatment dose of CLR 131, whichever is later.
- AEs will be recorded per the reporting time above regardless of whether or not they are considered related to the study drug(s).
- AEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- All AEs considered related to study drug(s) will be followed until resolution to ≤ Grade 1 or baseline, deemed clinically insignificant, and/or until a new anti-cancer treatment starts, whichever occurs first. If the subject begins a new anticancer therapy, the AE reporting period for non-serious AEs ends at the time the new treatment is started.
- Only clinically significant laboratory abnormalities will be captured as adverse events on the appropriate study specific eCRF form within OnCore.

11.2.2 Serious Adverse Events

- SAEs, both related or unrelated to the study, will be recorded from time of informed consent until 28 days after last EBRT treatment or 85 days after first treatment dose of CLR 131, whichever is later.
- Any SAEs experienced after this period will only be reported if the investigator suspects a causal relationship of possibly, probably or definitely related to the study treatment.
- SAEs will be reported on the SAE Submission Form and entered in SAE tab in OnCore within the timeframe listed in *Table 2*.
- SAEs will be recorded in the subject's medical record and on the appropriate study specific eCRF form within OnCore.
- All SAEs, regardless of relation to study drug, will be followed until resolution to ≤ Grade 1 or baseline and/or deemed clinically insignificant and/or until a new anti-cancer treatment starts, whichever occurs first.
- Recurrent episodes, complications, or progression of the initial SAE will be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information.

Reporting and submission requirements are described in Section 11.4.

11.2.3 Other Reportable Events

Reporting timeframes begin when PI learns of the occurrence of the event.

Table 1: 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
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.

11.3 Characteristics of an Adverse Event

11.3.1 Relationship to Study Intervention

The PI will determine the relationship of adverse events to the research intervention using the following scale:

- Definite = AE is definitely related to the study procedures
- Probable = AE is likely related to the study procedures
- Possible = AE is possibly related to the study procedures
- Unlikely = AE is doubtfully related to the study procedures
- Unrelated = AE is definitely not related to the study procedures

11.3.2 Expectedness

The Study PI will be responsible for determining whether an adverse event is expected or unexpected. An adverse event 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 adverse events associated with CLR 131 treatment. The most significant toxicities associated with CLR 131 involve myelosuppression such as neutropenia, anemia, and thrombocytopenia, which in some cases are Grade 3 or 4. These adverse events are expected to occur within 4 weeks from the first CLR 131 dose and are expected to be resolved by approximately 65 days after the last treatment dose of CLR 131. Thus, the DLT period has been defined to account for the expected toxicities of CLR 131 in section 2.3.1.1.1

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

11.3.3 Severity of Event

Adverse events will be documented and recorded at each visit using NCI CTCAE version 5.0.

11.4 Reporting Procedures

11.4.1 Unanticipated Problem (UP) Reporting to IRB, Cellectar and UWCCC DSMC

Incidents or events that meet the OHRP criteria for unanticipated problems require the creation and completion of an unanticipated problem report form. OHRP recommends that investigators include the following information when reporting an adverse event, or any other incident, experience, or outcome as an unanticipated problem 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 unanticipated problem;
- a description of any changes to the protocol or other corrective actions that have been taken or are proposed in response to the unanticipated problem.

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

- Unanticipated problems that are serious adverse events will be reported to the IRB, Cellectar Biosciences (*clinical@cellectar.com*) and to the UWCCC DSMC per *Table 2* timeline.
- Any other unanticipated problem will be reported to the IRB, Cellectar Biosciences (*clinical@cellectar.com*) and the UWCCC DSMC per *Table 1* timeline.
- All unanticipated problems 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.

11.4.2 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 2* below. All serious adverse events must also be reported to the UWCCC DSMC. All serious adverse events must also be reported to the UW IRB (if applicable), and any sponsor/funding agency not already included in the list.

SAEs experienced by a subject after the active reporting period has ended should be reported to Cellectar Biosciences if the PI becomes aware of them; at a minimum, all SAEs that the PI believes have at least a reasonable possibility of being related to investigational product are to be reported to Cellectar Biosciences.

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

Table 2: FDA Reporting Requirements.

FDA Reporting Requirements for Serious Adverse Events (21 CRF Part 312)
NOTE: Investigators **MUST** immediately report to the UWCCC DSMC, Cellectar Biosciences, and the IRB (if applicable) and any other parties outlined in the protocol ANY Serious Adverse Events, whether or not they are considered related to the investigational agent(s)/intervention (21 CFR 312.64).
An adverse event is considered serious if it results in ANY of the following outcomes:

1) Death.
2) A life-threatening adverse event (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 SERIOUS adverse events that meet the above criteria **MUST** be immediately reported to Cellectar and UWCCC DSMC within the timeframes detailed in the table below:

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

***Planned hospitalizations for disease-related surgery, routine procedures (such as G-tube placement), non–disease-related procedures, and inpatient hospitalization for radiation protection/exposure levels are not considered SAEs. A hematologic adverse event grade 1-4 will not be defined as an SAE if it can be managed with blood product transfusions, unless it exceeds the window for a dose limiting toxicity.**

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 28 days after last EBRT treatment or 85 days after first treatment dose of CLR 131, whichever is later and have an attribution of possible, probable, or definite require reporting as follows:

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

- All Grade 3, 4, and 5 AEs

Expedited 10 calendar day reports for:

- Grade 2 AEs resulting in hospitalization or prolongation of hospitalization

11.4.2.1 Reported within 24 Hours

Serious Adverse Events requiring reporting within 24 hours (as described above) must also be reported to the UWCCC DSMC within one business day. See 11.4.2.1.1.1. SAEs will also be reported to Cellectar Biosciences within 24 hours of discovery of the event. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (FDA Medwatch Form #3500 and/or any other documentation available at that time of initial reporting). 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 follow up SAE documentation will also be submitted to Cellectar Biosciences (clinical@cellectar.com). 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, and Cellectar Biosciences.

11.4.2.1.1 Report to the UWCCC, and Cellectar Biosciences:

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. UWCCC PIs: Justine Yang Bruce, MD and Paul Harari, MD
c. UWCCC PM: Diana Trask
d. Cellectar Biosciences (*clinical@cellectar.com*)
e. Medpace: medpace-safetynotification@medpace.com
f. Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

11.4.2.1.2 Report to the IRB

Consult the UW-IRB website for reporting guidelines.

11.4.2.2 Reported within 10 Calendar Days

Serious Adverse Events requiring reporting within 10 calendar days (as described above) must also be reported to the Data and Safety Monitoring Board (DSMC) Chair via an email to saenotify@uwcarbone.wisc.edu. SAEs will also be reported to Cellectar Biosciences. The OnCore SAE Details Report must be submitted along with other report materials as appropriate (FDA Medwatch Form #3500 and/or any other documentation available at the time of initial reporting). 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, and Cellectar Biosciences.

11.4.2.2.1 Report to the UWCCC and Cellectar Biosciences:

Reference the **SAE SOP** 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 [10] day reports.

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

a. *saenotify@uwcarbone.wisc.edu*
b. UWCCC PIs: Justine Yang Bruce, MD and Paul M. Harari, MD
c. UWCCC PM: Diana Trask
d. Cellectar Biosciences (*clinical@cellectar.com*)
e. Medpace: medpace-safetynotification@medpace.com
f. Any other appropriate parties listed on the SAE Routing Form (for follow-up reports only)

11.4.2.2.2 Report to the IRB:

Consult the UW-IRB website for reporting guidelines.

11.4.3 Reporting of SAEs and AEs to FDA

As Cellectar Biosciences holds the IND for CLR 131, they assume responsibility for reporting all events in accordance with FDA 21 CFR 312.32. Cellectar has contracted with a CRO, Medpace for SAE management for the IND.

Medpace clinical Safety Contact information:

US: Phone: 1-513-579-9911, dial 3
Or 1-800-730-5779, dial 3
FAX: 1-513-570-5196
Or 1--866-336-5320

Email: Medpace-safetynotification@medpace.com

11.4.4 Reporting of Pregnancy

- Pregnancy will be reported from time of first study drug until 85 days after discontinuation of CLR 131.
- Pregnancy will be reported to UW within 1 business day of discovery of the event.

To ensure subject safety, each pregnancy in a subject on study treatment will be reported to UW within 1 business day of learning of its occurrence. The pregnancy will be followed to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

11.5 Halting Rules

During the conduct of this study, adverse events and serious adverse events that are categorized as probably related to CLR 131 will be evaluated and analyzed weekly by the principal investigators. If >25 % of subjects have serious adverse events that are probably related to CLR 131 treatment, then enrollment for the study will be suspended for further analysis. Subsequent review of serious, unexpected, and related AEs will be evaluated by the DSMC, IRB, Cellectar Biosciences. Cellectar Biosciences and local regulatory authorities retain the authority to suspend additional enrollment and administration of CLR 131 for the entire study, as applicable.

12 STUDY OVERSIGHT

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

- Review clinical trials conducted at the UWCCC for subject safety, protocol compliance, and data integrity.
- Review Serious Adverse Events (SAE) requiring expedited reporting, as defined in the protocol, for clinical trials conducted at the UWCCC, and studies conducted at external sites for which the UWCCC acts as an oversight body.
- Review reports generated through the UWCCC DSMS elements (Internal Audits, Quality Assurance Reviews, Response Reviews, Compliance Reviews, and Protocol Summary Reports).
- Notify the protocol Principal Investigator of DSMC decisions and, if applicable, any requirements for corrective action related to data or safety issues.
- Work 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, when appropriate.
- Ensure notification of SAEs which require expedited reporting are provided to external sites participating in multi-institutional clinical trials coordinated by the UWCCC.

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 DSMB are as follows:

Intensive Monitoring

Protocols subject to intensive monitoring generally include UW Institutional Phase I. 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 UWCCC DSMC. All reports from the UWCCC DSMC will be provided to Cellectar Biosciences.

Review and Oversight Requirements

- Study Progress Review
  - Protocol Summary Reports (PSR) are required to be submitted to UWCCC DSMC quarterly. The PSR provides a cumulative report of SAEs, as well as instances of noncompliance, protocol deviations, and unanticipated problems, 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.

13 CLINICAL SITE MONITORING

Cellectar Biosciences or their designee may periodically monitor the data for the study. A clinical monitor will make regularly scheduled trips to the clinical sites to review the progress of the study. The actual frequency of monitoring trips will depend on the enrollment rate and performance at the site. At each visit, the monitor will review various aspects of the study including, but not limited to, screening and enrollment logs, compliance with the protocol and with the principles of ICH GCP, completion of CRFs, source data verification, and study drug accountability and storage.

In addition to the above, a representative from Cellectar Biosciences' auditing staff or government inspectors may review the conduct/results of the study at the clinical site. The Investigator must promptly notify Cellectar Biosciences of any audit requests by regulatory authorities.

14 STATISTICAL CONSIDERATIONS

14.1 Study Hypotheses

Reducing the dose of external beam radiation therapy, when given in combination with CLR 131, will be safe and tolerable while maintaining favorable tumor response rates and diminishing the adverse impact of radiation treatment on subject specific symptoms, such as quality of life, salivary flow and swallowing function.

14.2 Sample Size Considerations

An mTPI-2 design, an extension of modified toxicity probability interval (mTPI-2), will be used to identify the MTD using cohorts of 4 subjects and up to 3 dose levels of CLR 131(Ji *et al.*, 2007; Ji & Wang, 2013). The first 4 subjects will be treated at Dose Level 1. The maximum number of subjects treated at a dose level will be 8, with one exception: if 1 out of 8 subjects experiences a DLT at Dose Level 1, the study team will consider the possibility of treating 2 additional subjects at Dose Level 1. The trial can be monitored using columns 4 and 8 of *Table 3* below, which contains the dose-escalation rules. Dose escalation will not be confirmed until all subjects in cohort recover to non-DLT levels or meet the criteria above. If 0 out of 4 subjects experiences a DLT at Dose Level 2, the study will move directly to the expansion phase.

Dose Level	Doses* of CLR 131
-1	12.5 mCi/m^2
1**	15.6 mCi/m^2
2	18.75 mCi/m^2

*Dose level listed is administered on first on day 1 and again on day 8.
**The first 4 subjects will be treated at dose level 1. Dose level -1 will be used as a de-escalation dose.

Table 3: Dose escalation rules

	1	2	3	4	5	6	7	8	9	10
0	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**	**E**
1	**D**	**D**	**D**	**S**	**S**	**S**	**S**	**S**	**S**	**E**
2		**DU**	**DU**	**D**	**D**	**D**	**S**	**S**	**S**	**S**
3			**DU**	**DU**	**DU**	**DU**	**D**	**D**	**D**	**D**
4				**DU**	**DU**	**DU**	**DU**	**DU**	**DU**	**D**
5					**DU**	**DU**	**DU**	**DU**	**DU**	**DU**
6						**DU**	**DU**	**DU**	**DU**	**DU**
7							**DU**	**DU**	**DU**	**DU**
8								**DU**	**DU**	**DU**
9									**DU**	**DU**
10										**DU**

Column indicates the number of subjects treated. **Row** indicates the number of subjects with DLTs**. E**: Escalate to the next higher dose; **S**: Stay at the same dose; **D**: De-escalate to the previous lower dose; **DU**: De-escalate to the previous lower dose and the current dose will never be used again in the trial; sample size = **10**, target toxicity probability = **0.2**, epsilon 1 =**0.1**, epsilon 2 =**0.1.**

The number of participants treated in the expansion cohort is dependent on the number of participants treated at the MTD in the dose escalation phase using the the mTPI-2 design. Up to 12 subjects will be treated at the MTD. Statistical analysis for outcomes is based on participants treated at the MTD, including dose escalation patients treated at the MTD.

In recent years, the head and neck oncology program at UW has evaluated approximately 75-100 patients per year with recurrent HNC. We estimate that approximately half of these patients would be potential candidates for this trial. Assuming enrollment of 50 % of eligible patients, and CLR 131 uptake in 75 % of subjects administered a dosimetry test dose, we anticipate no problems to accrue the necessary subjects over 24 months.

14.3 Final Analysis Plan

14.3.1 Analysis of Primary Endpoints

Adverse events will be reported using frequency tables. Confidence intervals will be constructed using exact statistical methods (such as exact binomial confidence interval) due to small sample size.

14.3.2 Analysis of Secondary Endpoints

Median radiation treatment time and median number of dose delays due to toxicity will be reported. CLR 131 tumor uptake via SPECT/CT imaging and Monte Carlo calculations will be reported. Quality of life measures (including swallow function assessed by DIGEST scale and

QOL assessed by MDADI score) will be analyzed using frequency tables and confidence intervals constructed using exact statistical methods (such as exact binomial confidence interval) or summary statistics. Comparison of continuous and categorical QOL measures before and after treatment will be described using summary statistics and analyzed using the Wilcoxon signed rank test and McNemar's test, respectively. ORR will be reported as a proportion with an exact confidence interval. Stimulated salivary flow will be reported before and after treatment using summary statistics.

15 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 subjects. Study staff will permit authorized representatives of Cellectar Biosciences, and 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.

16 QUALITY CONTROL AND QUALITY ASSURANCE

16.1 Monitoring, Auditing, and Data Quality Control and Assurance Measures

All personnel involved in FDA regulated clinical trial activities are required to complete the Human Subjects Training and Good Clinical Practice (GCP) via CITI every 3 years. Training is monitored at each IRB continuing review and with the submission of protocol amendments.

At the protocol level, the Principal Investigators will assign and document protocol responsibilities based on study roles. Training on all IRB approved protocols (initial version and subsequent amendments) are documented for each person listed as key personnel on the University of Wisconsin Health Sciences IRB application. These documents are retained with the study regulatory files, and collection is coordinated by Human Oncology regulatory staff.

Eligibility checklists are signed by the study coordinator and the treating physician prior to enrollment. Adverse event grading and attributions are assigned by physicians at clinic visits and will be signed by the physician at that time.

Other relevant UWCCC SOPs include:

- Adverse Event Assessment and Documentation_SOP
- CTRP and ClinicalTrials.gov Reporting_SOP
- Delegation of Authority Log_SOP
- Informed Consent Process_SOP
- Maintaining a Regulatory File_SOP
- OnCore Data Quality Assurance_SOP
- Protocol Deviation_Guidance
- Reportable Events_SOP
- Reporting of Serious Adverse Events (SAEs) at UWCCC, 1SP, JC, And Affiliate Sites_SOP
- Source Documentation_SOP
- Study Close Out_SOP

17 ETHICS/PROTECTION OF HUMAN SUBJECTS

17.1 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.

17.2 Institutional Review Board

The protocol, informed consent form(s), recruitment materials, and all subject materials will be submitted to the IRB for review and approval. Approval of both the protocol and the consent form must be obtained before any subject is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented in the study.

17.3 Informed Consent Process

Informed consent is a process that is initiated prior to the individual agreeing to participate in the study and continues throughout study participation. Extensive discussion of risks and possible benefits of study participation will be provided to subjects and their families, if applicable. A consent form describing in detail the study procedures and risks will be given to the subject. Persons who are not fluent in English and persons with impaired decision-making capacities will not be eligible for enrollment in this study.

Consent forms will be IRB-approved, and the subject 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 subject and answer any questions that may arise. The subject will sign the informed consent document prior to any study-related assessments or procedures. Subjects 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. A copy of the signed informed consent document will be given to subjects for their records. The rights and welfare of the subjects 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.

17.4 Exclusion of Women, Minorities, and Children (Special Populations)

Children are excluded from this study because insufficient data are available in adults to judge potential risks in children.

Adults of any gender or racial/ethnic group may participate in this study.

17.5 Subject Confidentiality

Subject confidentiality is strictly held in trust by the investigators, study staff, and the 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 subjects.

All members of the study team will be listed on the IRB application and are required to undergo annual HIPAA training to ensure responsible conduct regarding protected health information (PHI) in research. In addition, Human Subjects Training and Good Clinical Practice trainings are required every three years for members of the study team.

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 sponsor. All PHI is stored securely on password protected servers.

The study monitor or other authorized representatives of the sponsor may inspect all study documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) for the study subjects. The clinical study site will permit access to such records.

To further protect the privacy of study participants, the study team has applied for and received a Certificate of Confidentiality (CoC) for this study from the FDA. A Certificate of Confidentiality prohibits study team members from disclosing information or biospecimens that may identify study participants in legal proceedings or in response to a legal request without their consent.

17.6 Future Use of Stored Specimens and Other Identifiable Data

All specimens for this study will be exhausted for use in this study. No study-related specimens will be banked after the study has ended.

18 DATA HANDLING AND RECORD KEEPING

This study will report clinical data using the UWCCC data management system 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, adverse events and other information will be maintained with the UWCCC data management system.

Participant data will be collected using protocol specific case report forms (CRFs). The CRFs 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 UWCCC data management system at time of study entry, completing CRFs based on the subject specific calendar, and updating the subject record until subject death or end of required study participation.

18.1 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. Unanticipated problems and adverse events must be reviewed by the investigator or designee.

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

18.2 Data Capture Methods

Data will be collected through the web-based clinical research platform, OnCore (Forte Research), a system compliant with Good Clinical Practices and Federal Rules and Regulations. UWCCC personnel will coordinate and manage data for quality control assurance and integrity. All data will be collected and entered into OnCore by study site personnel. We will also utilize REDCap for Biospecimen tracking purposes. The data in REDCap will be coded, and no subject identifiers will be stored in the Biospecimen REDCap Database.

18.3 Types of Data

Subject demographics, subject medical history, subject specific study treatment calendars, adverse events, 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 the UWCCC data management system.

18.4 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 Data Safety Monitoring Committee (DSMC).

Protocol Safety Reports include information such as accrual, adverse events, serious adverse events, and unanticipated problems. Annual review by the UW Health Sciences IRB will review accrual, reportable events, and study progress.

18.5 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.

18.6 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.

19 PUBLICATION/DATA SHARING POLICY

This study will comply with 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.

The study investigators will have sole right to determine the content of the presented and published data. As PIs, Drs. Bruce and Harari will retain a spot as both first and last author on all manuscripts, unless either elects to forgo this. Co-Is will have input into all remaining authorship spots.

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APPENDICES

Appendix A: SCHEDULE OF EVENTS

Appendix B: ECOG EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

APPENDIX A: SCHEDULE OF EVENTS

Assessment	Screening Period		Treatment Period				Post Treatment					With-drawal
	D-42 to D-1	*Dosimetry Test Dose*	*Treatment dose 1*	*Treatment dose 2*	*EBRT*	*Safety Monitoring Visits*[12]	*1 mo post CLR 131 Infusion (± 2 wks)*	*3 mo post EBRT (± 4 wks)*	*6 mo post EBRT (± 4 wks)*	*12 mo post EBRT (± 6 wks)*	*24 mo post EBRT (± 6 wks)*[17]	*With-drawal*[14]
Informed consent	X											
Demographics	X											
Medical history	X											
Concomitant medication review[17]	X						X	X	X	X		X
Physical exam	X						X	X	X	X	X	X
Vital signs[1]	X	X[15]	X[15]	X[15]			X	X	X	X		X
Height	X											
Weight	X						X	X	X	X		X
ECOG Performance Status	X						X	X	X	X		X
CBC with diff[2]	X[11]		X[12]	X[12]	X[12]	X[12]	X[12]	X				
Serum chemistries[3]	X[11]		X[12]	X[12]	X[12]	X[12]	X[12]	X				
Pregnancy test for WOCP[4]		X	X	X								
Electrocardiogram	X[16]				X[16]							
Serum TSH, free T4	X							X	X	X	X	
Administration of thyroid-protection	X	X	X	X			X[13]					

Assessment	Screening Period		Treatment Period				Post Treatment					With-drawal
	D-42 to D-1	*Dosimetry Test Dose*	*Treatment dose 1*	*Treatment dose 2*	*EBRT*	*Safety Monitoring Visits*[12]	*1 mo post CLR 131 Infusion (± 2 wks)*	*3 mo post EBRT (± 4 wks)*	*6 mo post EBRT (± 4 wks)*	*12 mo post EBRT (± 6 wks)*	*24 mo post EBRT (± 6 wks)*[17]	*With-drawal*[14]
medication (start D-1)[5]												
Adverse event evaluation[6]	X		X	X	weekly	X	X	X	X	X	X	X
QOL Surveys	X							X	X	X		
Oral swab and saliva collection	X							X	X	X		
Research oral profile exam and SOC Modified barium swallow study	X							X	X			
SPECT/CT Imaging		X[7]	X[8]	X								
Disease Assessment												
SOC Diagnostic imaging[9]	X							X		X	X	
Treatment												
Administration of CLR 131[10]		X[15]	X[15]	X[15]								
SOC EBRT					X							

Notes

1. Vital signs include blood pressure, pulse, respiratory rate, and temperature.
2. CBC to include red blood cell count, hemoglobin, hematocrit, white blood cell count with differential including % neutrophils, lymphocytes, monocytes, eosinophils and basophils, absolute neutrophil count, and platelet count.
3. Serum chemistries to include sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, AST, ALT, alkaline phosphatase, total bilirubin, calcium, protein, albumin, and phosphorus.

Assessment	Screening Period		Treatment Period				Post Treatment					With-drawal
	D-42 to D-1	*Dosimetry Test Dose*	*Treatment dose 1*	*Treatment dose 2*	*EBRT*	*Safety Monitoring Visits*[12]	*1 mo post CLR 131 Infusion (± 2 wks)*	*3 mo post EBRT (± 4 wks)*	*6 mo post EBRT (± 4 wks)*	*12 mo post EBRT (± 6 wks)*	*24 mo post EBRT (± 6 wks)*[17]	*With-drawal*[14]

4. A negative urine pregnancy test is required within 24 hours prior to each CLR 131 dose.
5. Thyroid protection medication to begin 1 day prior to dosimetry test dose and continue until 14 days post last treatment dose of CLR 131.
6. For subjects with unresolved treatment-related toxicity, follow as medically appropriate until resolution or stabilization. AEs will be recorded from time of informed consent until 28 days after last EBRT treatment or 85 days after first treatment dose of CLR 131, whichever is later.
7. SPECT/CT imaging will be performed approximately approximately 3 days after CLR 131 dosimetry test dose to confirm tumor uptake. If uptake is not seen at that timepoint, an additional SPECT/CT scan will be performed 7 days post CLR 131 test dose. Uptake in the specified site of recurrent/metastatic disease that is to be treated with radiation therapy will be determined by the study radiologist.
8. SPECT/CT imaging will be performed on days 2, 3, 4-6, and 7-8 of the treatment period to visualize and quantitate the biodistribution of CLR 131.
9. Imaging may consist of any combination of CT, MR or PET-MR scans as clinically indicated.
10. Time between dosimetry test dose and first treatment dose: approximately 14 days, but can be permitted up to 4 weeks. Dosing dates for treatment can be scheduled to start -1 or +3 days to accommodate clinic scheduling (for example: holidays, weekends, treating physician schedules, etc.).
11. Screening laboratory tests are to be collected within two weeks of dosimetry test dose to determine eligibility
12. CBC with differential and serum chemistries to be done weekly beginning with D1 treatment dose and continue for 12 weeks. Approximately 6 visits will coincide with CLR 131 administration and/or SOC EBRT visits, and ~6 visits may fall outside of SOC EBRT visits.
13. Duration of thyroid protection medication: 32-38 days; must take for 14 days post last CLR 131 dose.
14. If a subject withdraws or the investigator terminates subject participation prior to the 12 month post EBRT visit, the withdrawal visit procedures will be completed.
15. Vital signs are to be collected prior to and 1 hr post infusion of CLR 131.
16. Electrocardiograms will be performed at the baseline visit and the first day of treatment with external beam radiation therapy.
17. Follow-up assessment will not be completed if the subject has initiated a new, anti-cancer therapy prior to the 24 month visit.
18. All concomitant medications and treatments will be documented appropriately and recorded until 28 days after last EBRT treatment or 85 days after first treatment dose of CLR 131, whichever is later. Anti-cancer therapy drugs will be continue to be captured at all study timepoints

APPENDIX B: ECOG EASTERN COOPERATIVE ONCOLOGY GROUP PERFORMANCE STATUS

Grade	Performance Status
0	Fully active, able to carry on all pre-disease performance without restriction
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
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50 % of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

As published:
Oken MM, Creech RH, Tormey DC, *et al*. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982;5(6):649-655.
http://www.ecog-acrin.org [homepage on the Internet]. Eastern Cooperative Oncology Group and American College of Radiology Imaging Network, Robert Comis MD and Mitchell Schnall, MD PhD, Group Co-Chairs. [cited 2016 September 12]. Available from: http://www.ecog-acrin.org/resources/ecog-performance-status

SUPPLEMENTAL MATERIALS

These documents are relevant to the protocol, but they are not considered part of the protocol. They are stored and modified separately. As such, modifications to these documents do not require protocol amendments.

- Videofluoroscopy Study Manual
- CLR 131 Radiopharmaceutical Manual
- CLR 131 Investigational Brochure
- CLR 131 Patient Pamphlet