Document Coversheet

Study Title: Comparison of Every 3 Week Versus Weekly Cisplatin Concurrent With Radiation in Squamous Cell Carcinoma of the Head and Neck (SCCHN) and Correlation With Oxidative Stress Markers

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TITLE: Randomized phase II comparison of every 3 week versus weekly cisplatin concurrent with radiation in Squamous Cell Carcinoma of the Head and Neck (SCCHN) and correlation with oxidative stress markers.

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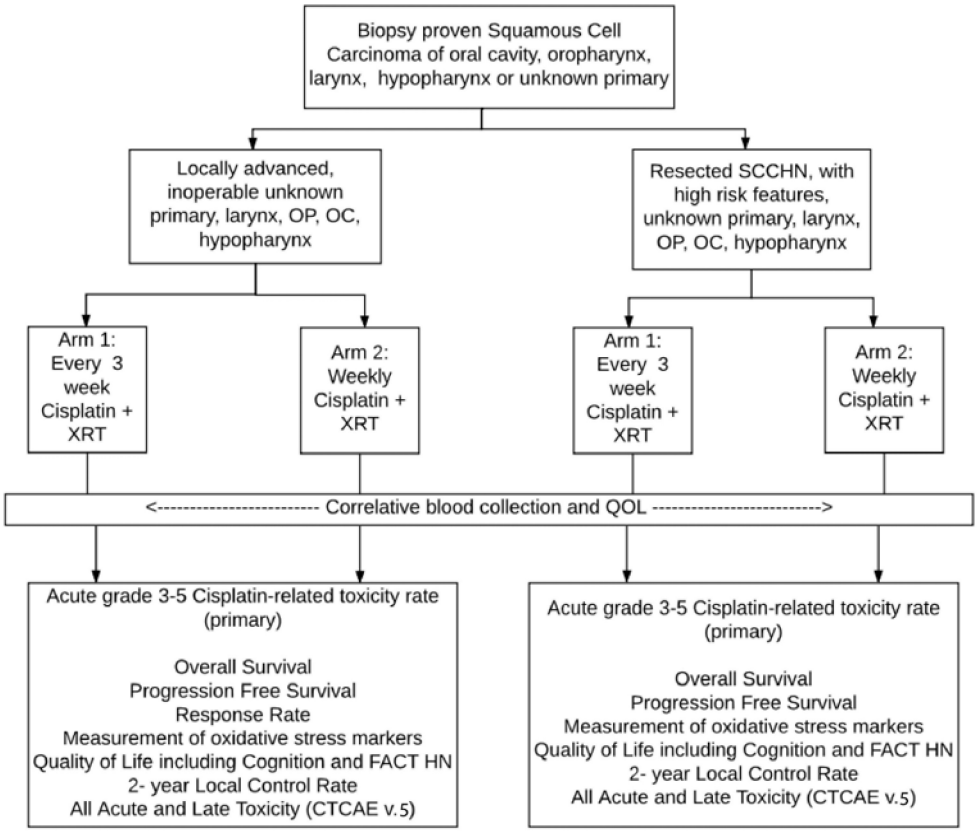
Other Agent(s): Cisplatin

Study Exempt from IND Requirements per 21 CFR 312.2(b).

SCHEMA


Biopsy proven Squamous Cell Carcinoma of oral cavity, oropharynx, larynx, hypopharynx or unknown primary
Locally advanced, inoperable unknown primary, larynx, OP, OC, hypopharynx
Resected SCCHN, with high risk features, unknown primary, larynx, OP, OC, hypopharynx
Arm 1: Every 3 week Cisplatin + XRT
Arm 2: Weekly Cisplatin + XRT
Arm 1: Every 3 week Cisplatin + XRT
Arm 2: Weekly Cisplatin + XRT
<---------- Correlative blood collection and QOL ---------->
Acute grade 3-5 Cisplatin-related toxicity rate (primary)
Overall Survival
Progression Free Survival
Response Rate
Measurement of oxidative stress markers
Quality of Life including Cognition and FACT HN
2- year Local Control Rate
All Acute and Late Toxicity (CTCAE v.5)
Acute grade 3-5 Cisplatin-related toxicity rate (primary)
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Quality of Life including Cognition and FACT HN
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All Acute and Late Toxicity (CTCAE v.5)

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1. OBJECTIVES

1.1 Primary Objectives

1.1.1 Rate of grade 3-5 cisplatin-related adverse events occurring within 90 days of initiation of concurrent radiation and chemotherapy including:

- nausea/vomiting
- ototoxicity
- nephrotoxicity
- neutropenia
- thrombocytopenia

1.1.2 Hypothesis: Patients with locally advanced non-nasopharyngeal SCCHN treated with weekly cisplatin (40 mg/m2 weekly for 7 doses) with radiation (RT) will have fewer cisplatin-related acute toxicities as compared to those receiving every three-week cisplatin (100 mg/m^2 for 3 doses) with radiation in the following cohorts:

1.1.2.1 Cohort 1: Unresectable locally advanced non-nasopharyngeal SCCHN

1.1.2.2 Cohort 2: Resected non-nasopharyngeal SCCHN at high risk of recurrence as defined by the following criteria:

- extracapsular nodal extension
- invasive cancer at the primary tumor resection margin (positive margin)
- lymphovascular invasion
- perineural invasion
- pT3 or pT4 primary
- presence of multilevel nodal disease

1.2 Secondary Objectives

1.2.1 To compare the following therapeutic endpoints in both populations:

- 2-year local control rates
- Overall survival (OS)
- Progression free survival (PFS)
- Response Rate (Cohort 1 only, as Cohort 2 is completely resected)

1.2.2 To compare and contrast the development of oxidative stress markers which occur as a result of exposure to weekly or every 3-week doses of cisplatin in this population

1.2.3 Rates of radiation related CTCAE adverse events, specifically: mucositis, dysphagia, dry mouth, and skin and their relationships with patient reported outcomes at 3 months and 12 months

1.2.4 CTCAE acute (< 90 days from start of chemoradiation) adverse events related (possibly, probably or definitely) to cisplatin or radiation

1.2.5 CTCAE late (> 90 days from start of chemoradiation) adverse events related (possibly, probably or definitely) to cisplatin or radiation.

1.2.6 Quality of life as measured by Functional Assessment of Cancer Therapy-Head & Neck (FACTHN) and Functional Assessment of Cancer Therapy Cognition (FACTCOG) at baseline, 3, and 12 months from end of RT

2. BACKGROUND

2.1 Squamous Cell Carcinoma of the Head and Neck Cancer (SCCHN)

SCCHN is a lethal disease that often presents in a locally advanced state. Surgery and radiation are the mainstays of treatment and provide a long-term survival of approximately 40-50% in inoperable subjects [1-3], and 40-60% in operable subjects [4-6], depending on stage and other risk factors, while 5-year PFS is often reported between 50 and 75% [2]. Defined criteria have evolved to delineate high-risk individuals in the postoperative setting: positive margins, lymphovascular or perineural invasion, extracapsular extension of lymph nodes, or multilevel nodal disease all increase the risk of local recurrence in this disease, a major cause of recurrence and death from SCCHN. Several biologic features predict sensitivity to cisplatin (HPV-driven cancer [7, 8], intact DNA repair mechanisms, and adequate renal and marrow function to allow full dose delivery); however a full understanding of individual sensitivity to cisplatin is needed to further refine the treatment of SCCHN.

2.2 Cisplatin in SCCHN

Concurrent chemoradiation using every 3-week cisplatin is the standard of care treatment for locally advanced (stage III and IV) squamous cell carcinoma of the head and neck (SCCHN). It is used as definitive treatment in inoperable patients and as adjuvant treatment after surgery in high risk patients [2-5, 8-18]. Multivariate analysis of over 16,000 patients (MACH–NC) revealed an overall survival benefit of 4.5% at 5 years in patients undergoing concomitant chemotherapy and radiotherapy, with platinum-based regimens significantly more effective than other types of chemotherapy. Multiple groups have published data regarding small randomized and nonrandomized trials comparing weekly versus every 3-weeks cisplatin but no large-scale phase 3 studies have been reported to date comparing lower to higher dose cisplatin delivery.

2.3 Oxidative Stress in Cancer

Reactive oxygen species (ROS) lead to oxidation of amino acid residue side chains, formation of protein-protein cross-linkages, and oxidation of the protein backbone resulting in inactivation of protein functions. As an example, HNE (a highly toxic form of ROS-induced lipid peroxidation products) may yield similar products and that heavy metal ions can promote formation of $^{\cdot}OH$ and $O^{\cdot-}_2$ in some of the reactions [19]. The ROS generated *in vivo* by some cancer therapies result in cancer cell killing, but also side effects in normal tissues. Toxic side effects of anti-cancer therapy lead to a loss of quality of life and acute and chronic damage to humans. Convincing mechanisms of action regarding normal tissue damage have been elucidated for the effect of

DNA damaging agents such as cisplatin, doxorubicin and others on normal tissues during human cancer treatment [20-25]. Critical to expanding this knowledge is the need for studies that focus on the generation of ROS or other markers of oxidative stress *immediately following* cisplatin infusion, and the degree of oxidative stress that occurs at various doses of cisplatin concurrent with radiation. Generation of ROS has been implicated in the toxicity of nearly 50% of the current FDA approved cancer therapeutic drugs. Formation of ROS is thought to lead to direct DNA damage by cisplatin via protein-protein cross-linkages and oxidation of the protein backbone resulting in inactivation of the protein function. The toxic side effects of cisplatin can lead not only to cognitive impairment, but renal, cutaneous, and other toxicities due to this phenomenon of ROS generation. While there is an understanding of high risk clinical features that predict survival in SCCHN, full knowledge of how an individual reacts to the oxidative stress caused by platinum compounds is not clear. This avenue of exploration will help to predict sensitivity to cisplatin, as well as to provide causative links to changes in cognition, toxicity and interaction with radiation. Further investigation of normal tissue response to injury resulting from drug-induced ROS generation and comparing ROS formation in response to various doses of platinum concurrent with radiation will provide an increased understanding of treatment response in SCCHN. This study is designed to gather that information, and to compare the efficacy of low and high dose cisplatin in the treatment of SCCHN, both in the inoperable and operable setting.

2.4 Tests to Assess Cognitive Function

Choosing an appropriate test for cognition is critical to be able to assess subtle changes in cognition as they occur in SCCHN. Well-established cognitive difficulties have been reported in other types of cancer, including breast and brain cancers [26, 27]. The FACTCOG [28] was chosen based on its reliability and validity, in addition to its demonstrated utility in assessing cognitive domains of interest in CICI, including attention and concentration, verbal and visual memory, and information processing speed as recommended by Vardy et al. and the Venice cognitive workshop [29, 30].

2.5 Overall Hypothesis

We hypothesize that weekly cisplatin will lead to a 1-year local control rate comparable to every 3-week (high dose) cisplatin in locally advanced SCCHN; however, there will be significantly fewer cisplatin-related acute toxicities for those treated weekly. We will also explore the relationship between cisplatin toxicity and the level of reactive oxygen species generated by the drug in subjects with squamous cell carcinoma of the head and neck treated on this trial.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have pathologically (histologically or cytologically) proven diagnosis of head and neck squamous cell carcinoma (HNSCC) involving the oral cavity, oropharynx, larynx, hypopharynx, paranasal sinuses or unknown primary squamous carcinoma limited to the head and neck region;

- Cohort 1: Unresectable locally advanced non-nasopharyngeal SCCHN without evidence of distant metastases

- Cohort 2: Patients with non-nasopharyngeal SCCHN who have undergone gross total surgical resection within 63 days prior to registration. Patients must have at least 1 of the following high-risk pathologic features: extracapsular nodal extension, invasive cancer at the primary tumor resection margin (positive margin), lymphovascular invasion or perineural invasion, or the presence of multilevel nodal disease. Patients must be without evidence of distant metastases.

3.1.2 Women of childbearing potential and male participants who are sexually active must agree to use a medically effective means of birth control.

3.1.3 Cohort 1: Patients in Cohort 1 must have either (a) measurable disease, defined as at least one lesion that can be accurately measured in at least one dimension (longest diameter to be recorded for non-nodal lesions and short axis for nodal lesions) as ≥20 mm (≥2 cm) with conventional techniques or as ≥10 mm (≥1 cm) for non-nodal lesions, and > 15 mm (> 1.5 cm) for nodal lesions with spiral CT scan, MRI, or calipers by clinical exam or (b) evaluable disease based on evaluable non-target lesions (< 1.5 cm - >1.0 cm) as specified in protocol section 11.1.1. See Section 11 for the evaluation of measurable disease.

Cohort 2: Subjects in the post-operative setting (Cohort 2) are not required to have measurable disease and response rate will not be assessed in cohort 2.
Date of resection:_____

3.1.4 Patients may have a history of prior head and neck malignancy, but must be able to tolerate full dose radiation and chemotherapy for the current head and neck cancer, as determined by the treating oncologist.

3.1.5 Age ≥18 years.

3.1.6 ECOG performance status 0, 1 or 2 (see Appendix A).

3.1.7 Life expectancy of greater than 12 weeks.

3.1.8 Patients must have normal organ and marrow function assessed within 14 days prior to registration as defined below:

• absolute neutrophil count	≥1,000/mcL
• platelets	≥100,000/mcL
• creatinine	within normal institutional limits
	OR
• creatinine clearance	≥60 mL/min/1.73 m2 for patients with creatinine levels above institutional normal

3.1.9 No prior chemotherapy for the **current** locally advanced SCCHN is allowed. Prior radiation or chemotherapy for a previous head and neck cancer is allowed provided full dose cisplatin and radiation can be delivered to the patient in this clinical trial and provided the patient is in remission from the prior head and neck cancer, and can undergo full dose radiation and chemotherapy for the current primary head and neck cancer.

3.1.10 Cisplatin and radiation are known teratogens. For this reason, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, throughout the duration of active treatment and for 4 months after completion of chemotherapy and radiation. Should a woman become pregnant or suspect she is pregnant while she or her partner is participating in this study, she should inform her treating physician immediately. Men treated or enrolled on this protocol must also agree to use adequate contraception prior to the study, for the duration of active study treatment, and for 4 months after completion of chemotherapy and radiation (both induction and definitive) administration.

3.1.11 Ability to understand and the willingness to sign a written informed consent document.

3.2 Exclusion Criteria

3.2.1 Patients who have had chemotherapy or radiotherapy within 4 weeks (6 weeks for nitrosoureas or mitomycin C) prior to entering the study or those who have not recovered from adverse events due to agents administered more than 4 weeks earlier.

3.2.2 Patients who are receiving any other investigational agents.

3.2.3 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cisplatin.

3.2.4 Patients with greater than grade 2 hearing loss.

3.2.5 No other prior malignancy is allowed except for the following: head and neck cancer in remission, adequately treated basal cell or squamous cell skin cancer, in situ cervical cancer, adequately treated previous Stage I or II cancer from which the patient is currently in complete remission or other cancer from which the patient has been disease-free for 2 years.

3.2.6 Patients with nasopharynx or salivary gland primary site.

3.2.7 Patients with distant metastatic disease (M1c) from the current head and neck cancer including brain metastasis.

3.2.8 Uncontrolled intercurrent illness including, but not limited to, ongoing or active infection (grade 3 or greater), symptomatic congestive heart failure, unstable angina pectoris, symptomatic cardiac arrhythmia, or psychiatric illness/social situations that would limit compliance with study requirements. Subjects with significant symptoms of congestive

heart failure who would not be expected to tolerate the IV hydration for cisplatin are excluded.

3.2.9 Pregnant women are excluded from this study because cisplatin and radiation are agents with the potential for teratogenic or abortifacient effects. Because there is an unknown but potential risk for adverse events in nursing infants secondary to treatment of the mother with cisplatin and radiation, breastfeeding should be discontinued if the mother is treated with cisplatin or radiation on this trial.

3.2.10 HIV-positive patients with uncontrolled HIV despite combination antiretroviral therapy are ineligible because of the potential for increased risk of lethal infections when treated with marrow-suppressive therapy. Appropriate studies will be undertaken in patients receiving combination antiretroviral therapy when indicated.

3.3 Inclusion of Women and Minorities

This trial will not exclude potential subjects from participating in this or any study solely on the basis of ethnic origin, gender or socioeconomic status. Every attempt will be made to enter all eligible patients into this protocol and therefore address the study objectives in a patient population representative of the head and neck cancer population of the catchment area of the MCC.

4. REGISTRATION PROCEDURES

4.1 Protocol Review and Monitoring Committee and Institutional Review Board Review

Before implementing this study, the protocol must be reviewed by Markey Cancer Center's Protocol Review and Monitoring Committee and the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the University of Kentucky Institutional Review Board (IRB). A signed and dated UK IRB initial review approval memo must be maintained in the Markey Cancer Center Clinical Research Office (MCC CRO) regulatory binder. Any amendments to the protocol, other than administrative ones, must be reviewed and approved by the PRMC, study sponsor and the UK IRB.

4.2 Enrollment Guidelines

Eligible patients will be identified by the principal investigator (PI) and co-investigators of this study. Potentially eligible patients will be screened in the University of Kentucky Markey Cancer Center clinics by the investigators, study personnel, and the PI. Upon obtaining proper consent, patients will be enrolled into the study.

4.3 Informed Consent

The goal of the informed consent process is to provide people with sufficient information so they can make informed choices about whether to begin or continue participation in clinical research. The process involves a dynamic and continuing exchange of information between the research

team and the participant throughout the research experience. It includes discussion of the study's purpose, research procedures, risks and potential benefits, and the voluntary nature of participation.

The informed consent document provides a summary of the clinical study and the individual's rights as a research participant. The document acts as a starting point for the necessary exchange of information between the investigator and potential research participant. Also, research participants and their families may use the consent document as an information resource and reference throughout participation in the trial. The informed consent document is often considered the foundation of the informed consent process; it does not, however, represent the entirety of the process. Nor is the informed consent document a risk-management tool for the investigator and/or institution.

The investigator must explain to each subject (or legally authorized representative) the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved and any discomfort it may entail. Each subject must be informed that participation in the study is voluntary and that he/she may withdraw from the study at any time and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in non-technical language. The subject should read and consider the statement before signing and dating it, and should be given a copy of the signed document. If the subject cannot read or sign the documents, oral presentation may be made or signature given by the subject's legally appointed representative, if witnessed by a person not involved in the study, with documentation that the patient could not read or sign the documents. No patient can enter the study before his/her informed consent has been obtained. The informed consent form is considered to be part of the protocol, and must be submitted by the investigator with the protocol at the time of IRB review.

4.4 Compliance with Laws and Regulations

The study will be conducted in accordance with U.S. Food and Drug Administration (FDA) and International Conference on Harmonization (ICH) Guidelines for Good Clinical Practice (GCP), the Declaration of Helsinki, any applicable local health authority, and IRB requirements. The PI or designee will be responsible for obtaining continuing and not less than annual IRB re-approval throughout the duration of the study. Copies of the PI's annual report to the IRB and copies of the IRB continuance of approval must be maintained by the MCC CRO. The PI or designee is also responsible for notifying the Data and Safety Monitoring Committee of the MCC and the UK IRB of any significant adverse events that are serious and/or unexpected, as per SOP's of those entities. The MCC DSMC will review all adverse events of this IIT as per its SOP.

5. TREATMENT PLAN

5.1 Enrollment and Screening Process

Prior to any study-required tests, subjects must first provide written informed consent to participate in this study. All lab tests should be completed within 3 weeks prior to registration: Complete history, physical examination, and evaluation of ECOG Performance Status. CBC; serum chemistry tests to include alkaline phosphatase, creatinine, electrolytes, AST (SGOT), and total bilirubin. All radiographic studies (CT with contrast or MRI of the head and neck region, CT of chest or chest x-ray) should be completed within: a) Cohort 1: 6 weeks prior to registration, OR b) Cohort 2: within 8 weeks prior to registration.

5.2 Cisplatin Administration

Treatment will be administered on an inpatient or outpatient basis. Reported adverse events and potential risks are described in Section 7. Appropriate dose modifications are described in Section 6. No investigational or commercial agents or therapies other than those described below may be administered with the intent to treat the patient's malignancy.

5.2.1 Planned Treatment

Treatment will consist of standard of care radiation therapy to the primary tumor of the head and neck and involved nodal metastasis and draining nodal basin, as determined by treating radiation oncologist. Patients will be randomized to receive cisplatin at 100 mg/m^2 every 3 weeks (3 doses) during radiation versus cisplatin at 40 mg/m^2 once weekly (7 doses) during radiation. This will provide similar cumulative doses of cisplatin in all arms of the study.

Cisplatin Arm	Maximum Cumulative Dose
Every 3 weeks	300 mg/m^2
Weekly	280 mg/m^2

According to a recent review, total doses above 200 mg/m^2 during radiation lead to higher overall survival [17], and every attempt will be made to reach at least 200 mg/m^2. Because of the significant differences in response to therapy in oropharyngeal carcinoma (OPC) due to human papilloma virus (HPV) infection, HPV status will be recorded at baseline and adjusted during final analyses where appropriate.

Patients will first be designated by the enrolling CRA, in conjunction with the enrolling physician, as either: a) Cohort 1 (locally advanced non-nasopharyngeal SCCHN that is unresectable) OR b) Cohort 2 (resected and at high risk of recurrence with at least one of the following criteria: extracapsular nodal extension, or invasive cancer at the primary tumor resection margin (positive margin), lymphovascular invasion or perineural invasion, pT3 or pT4 primary, or the presence of multilevel nodal disease. Subjects will then be randomized to receive either Arm 1 or Arm 2 cisplatin as below.

Radiation and Cisplatin will be given concurrently and should start on the same day, ±1 day. Radiation will continue without interruption whenever possible. Radiation delays or interruptions will be the decision of the treating radiation oncologist, as outlined in section 5.3.

5.2.2 Cisplatin Dosing

Use the actual body weight as long as the BSA is ≤ 2.3. If the BSA is > 2.3, recalculate using the adjusted body weight, and use the recalculated BSA to determine the dose with no cap.

Estimate Ideal body weight in (kg)
Males: IBW = 50 kg + 2.3 kg for each inch over 5 feet
Females: IBW = 45.5 kg + 2.3 kg for each inch over 5 feet

Adjusted body weight
AjBW = IBW + 0.4(ABW - IBW)

Arm 1 – Conventional fractionation plus every 3-week cisplatin
Patients will receive cisplatin (100 mg/m^2) administered intravenously over 1 hour on days 1, 22, and 43 of the treatment course, relative to the initiation of radiation.

Arm 2 – Conventional fractionation plus weekly cisplatin
Patients will receive cisplatin (40 mg/m^2) administered intravenously over 1 hour on days 1, 8, 15, 22, 29, 36, and 43 of the treatment course, relative to the initiation of radiation.

Premedication: Arms 1 & 2
Suggested premedication: include aprepitant (intravenous or oral), ondansetron, dexamethasone and either promethazine or prochlorperazine, per institutional standard. This trial endorses the NCCN guidelines for anti-emetic prophylaxis.

Pre- and Post-hydration: Arms 1 & 2
Patients must receive vigorous hydration and diuresis. A suggested regimen is: pre-hydration with a 1 liter of normal saline with electrolyte supplementation (e.g. potassium, magnesium) per standard of care, over 2 hours i.v. immediately prior to cisplatin. Then cisplatin 100 mg/m^2 in 500 ml normal saline is administered over 1 hour. Following cisplatin infusion, an additional 1 liter of normal saline with electrolyte supplementation (e.g. potassium, magnesium) per standard of care, given post-hydration over 2 hours.

Please see Section 6.0 for all dose modifications of cisplatin.

5.3 Radiation Therapy

All radiation therapy is considered standard of care, and toxicities and dose modifications will be made by the treating physician based on institutional standards. The guidelines below are recommended practice but may be modified at the discretion of the treating radiation oncologist.

5.3.1 Dose Specifications

IMRT has been a standard of care in the U.S. beginning in 2005 and is now widely used in practice. Use of H&N IMRT in RTOG protocols (and associated QA) was begun in 2005 in RTOG 0522, as an optional technique. At the close of the accrual phase, approximately 90% of cases enrolled on 0522 (>800 patients) were treated with IMRT. Oropharynx cases comprised 70% of the study population.

IMRT will be delivered in 30-35 fractions over 6-7 weeks, 5 fractions weekly. The primary tumor and involved nodes (CTV1) will typically consist of a 0.5-1.5 cm expansion of the gross tumor volume (GTV) to cover potential local invasion and will be prescribed 2 Gy/fraction, total 55-70Gy. High-risk sub-clinical disease sites, which include possible local subclinical infiltration at the primary site (primary site CTV2) and first echelon nodes, which are not clinically or radiographically involved (nodal CTV2), should be expanded by 3-5 mm to create PTV2. PTV2 should receive 1.6 Gy/fraction to a total dose of 52.8 Gy to 56 Gy. Lower-risk targets (PTV3) (such as neck nodal levels which are not first echelon nodes and are not adjacent to levels containing grossly involved nodes) will be prescribed 50-52.5 Gy. If the low neck is treated, the preferred technique is to treat with isocentric matching AP or AP-PA fields with larynx block, matched to the IMRT portals just above the arytenoids. The dose will be 2 Gy per fraction prescribed to 3 cm depth to a total dose of 50 Gy in 25 daily fractions. Whole-neck IMRT is allowed. This can be achieved by either boosting the low neck field with an additional 16 Gy in 8 fractions, by an AP or AP-PA fields, or by planning the whole neck using IMRT. In cases of gross involvement of the vallecula or low neck, whole-neck IMRT should be considered. Whole-neck IMRT may also be considered if level VI is considered to be at risk due to gross involvement of level IV nodes. All plans must be normalized such that 95% of the volume of the PTV is covered with prescription dose.

In cases of weight loss >10% or significant shrinkage of lymphadenopathy during therapy, it is recommended that the immobilization mask will be adjusted or re-made in order to preserve adequate immobilization, and that a repeated simulation CT be performed to assess the dose distributions in the current anatomy. Whether or not a new IMRT plan will be generated is at the discretion of the treating physician. If a new plan is made, the targets should be the same as those used for the initial plan. The new CT dataset should be used for IGRT image registration when the patient's shape changes significantly.

5.3.2 Compliance Criteria

Treatment breaks must be clearly indicated in the treatment record along with the reason(s) for the treatment break(s). Treatment breaks, if necessary, ideally should not exceed 5 treatment days at time and 10 treatment days total. Treatment breaks should be allowed only for resolution of severe acute toxicity and/or for intercurrent illness and not for social or logistical reasons. Any treatment break(s) exceeding 2 treatment days for reasons other than toxicity/illness will be considered a protocol deviation. The following define compliance:

Overall RT treatment time:

- ≤ 52 days (compliant)
- > 52 days (non-compliant)
- Up to 57 days for non-medical reasons (such as holiday, machine breakdown) as determined by the treating radiotherapy physician

Missed treatments due to holidays or logistic reasons can be compensated for by delivering an additional BID treatment during the week, OR treating on the Saturday or Sunday of that week, OR adding to the end of treatment. These additions will not be considered non-compliance.

5.3.3 Radiation Therapy Toxicity/Adverse Events

Grade 3-4 (CTCAE, v. 4.0) therapy-induced mucositis and/or dysphagia, which are enhanced by cisplatin, are expected to develop in about two-thirds of patients. Nutritional evaluation prior to the initiation of therapy for a prophylactic gastrostomy (PEG) tube placement is highly recommended. Placement of a feeding tube should be recorded, as should use of a feeding tube during and after treatment (e.g. greater than or less than 50% of nutrition by tube). Other common radiation adverse events include: fatigue, weight loss, regional alopecia, xerostomia, hoarseness, transient ear discomfort, dysgeusia, and skin erythema and desquamation within the treatment fields. Less common long-term treatment adverse events include: hypothyroidism, loss of hearing, chronic swallowing dysfunction requiring permanent feeding tube, and cervical fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis, and cervical myelopathy (< 1% with restriction of spinal cord dose to ≤ 45 Gy).

5.3.4 R.T. Quality Assurance Reviews

We will use several approaches to ensure H&N IMRT quality assurance (QA) including H&N anatomic atlases, site and machine certification of H&N IMRT, and individual case reviews. The department performs routine radiation review and QA as part of standard of care.

5.3.5 Technical Factors, Localization, Simulation, and Immobilization

Patients must have an immobilization device (e.g. Aquaplast mask) made prior to treatment planning CT scan. The treatment planning CT scan should be performed with IV contrast so that the major vessels of the neck are easily visualized. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be 0.3 cm.

5.3.6 Treatment Planning/Target Volume

Planning Target Volumes (PTVs): In general, the PTV should not go outside of the skin surface; if it does exceed the skin surface, the application of bolus material over this portion of the PTV may be considered if it is judged clinically that the skin is at risk but

is generally not recommended. In general, the CTV-to-PTV expansion (without IGRT) should not exceed 10 mm. In general, the CTV-to-PTV expansion (with IGRT) should not exceed 5 mm.

5.3.7 Definition of Normal Tissues/Organs at Risk (OARs)

NOTE: Only the parts of the normal tissues/organs at risk outside the PTVs will be considered for dose optimization purposes.

Spinal Cord: The cord begins at the cranial-cervical junction (i.e. the top of the C1 vertebral body). Superior to this is brainstem and inferior to this is cord. The inferior border of the spinal cord is at approximately T3-4 (i.e., just below the lowest slice level that has PTV on it). The spinal cord shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) spinal cord shall be defined. The PRVcord = cord + 5 mm in each dimension. This is irrespective of whether or not IGRT is used.

Brainstem: The inferior most portion of the brainstem is at the cranial-cervical junction where it meets the spinal cord. For the purposes of this study, the superior most portion of the brainstem is approximately at the level of the top of the posterior clinoid. The brainstem shall be defined based on the treatment planning CT scan. In addition, however, a Planning Risk Volume (PRV) brainstem shall be defined. The PRVbrainstem = brainstem + 3 mm in each dimension.

Lips and Oral Cavity: These should be contoured as 2 separate structures as the goal is to keep the lip dose much lower than the oral cavity dose. The oral cavity will be defined as a composite structure consisting of the anterior ½ to 2/3 of the oral tongue/floor of mouth, buccal mucosa, and palate.

Parotid Glands: Parotid glands will be defined based on the treatment planning CT scan.

Cervical Esophagus: This will be defined as a tubular structure that starts at the bottom of the oropharynx and extends to the thoracic inlet.

Glottic/Supraglottic Larynx (GSL): This will be defined as a “triangular prism shaped” 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 but not suprahyoid epiglottis.

Mandible: This includes the entire bony structure of the mandible from TMJ through the symphysis.

Unspecified Tissue Outside the Targets: This will be defined as tissue located between the skull base and thoracic inlet that is not included in either the target volumes or the normal tissues described above.

5.3.8 IMRT Dose Prescription to PTVs

The goal is for 95% of the planned PTV to receive ≥ 2 Gy with a minimum dose (cold spot). It is recognized that portions of the PTV close to the skin may receive significantly less. This is acceptable as long as cold spots within PTV1 do not exist at a depth deeper than 8 mm beneath the skin.

For planning prioritization and priorities in dose coverage, in the final plan, PTV1 will be the highest priority target structure. PTV2 and PTV3, if applicable, will be ranked in the IMRT planning as lower priority than PTV1m although usually at a higher priority than normal structures other than spinal cord and brain stem.

5.3.9 Doses to Normal Structures

Spinal Cord: The PRVcord should not exceed ≤ 50 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm).

Brainstem: The PRV brainstem (as defined in Section 6.4.2.2) should not exceed 52 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm).

Lips: Reduce the dose as much as possible. The mean dose should be < 20 Gy.

Oral Cavity: Reduce the dose as much as possible. The mean dose should be < 30 Gy for the non-involved oral cavity. Efforts should also be made to avoid hot spots (> 60 Gy) within the noninvolved oral cavity.

Parotid Glands: In most cases, it will be easier to spare one parotid than the other. The treatment planning goal will be for this individual parotid gland to receive a mean dose of < 26 Gy.

Contralateral submandibular gland: If contralateral level I is not a target, aim to reduce mean contralateral submandibular gland to < 39 Gy.

Mandible: Reduce the dose as much as possible. Hot spots within the mandible should be avoided. It is recommended that maximum dose within the mandible be < 66 Gy.

Unspecified Tissue Outside the Targets: No more than 1cc of unspecified tissue outside the targets can receive 74 Gy or more.

5.3.10 Prioritization for IMRT Planning

1. Spinal Cord
2. Brainstem
3. PTV1
4. PTV2 (if applicable)
5. PTV3 (if applicable)

6. a. Oropharynx, b. Parotid gland contralateral to primary tumor site
7. a. GSL, b. Esophagus
8. a. Lips, b. Oral Cavity
9. a. Parotid gland ipsilateral to primary tumor site, b. Mandible
10. Unspecified tissue outside the targets

5.4 General Concomitant Medication and Supportive Care Guidelines

Concomitant use of anti-emetics should follow institutional guidelines for highly emetogenic chemotherapeutic regimens. Additional guidance can be found at www.nccn.org. Additional supportive measures for toxicity from chemotherapy and radiation are at the investigators discretion, and not restricted.

Placement of a gastrostomy tube (PEG or PFG) before treatment begins is recommended to optimize nutrition and hydration during combined therapy.

Aggressive oral and skin care, and analgesics are recommended.

Use of G-CSF (Filgrastrim) or other growth factors is not anticipated for any treatment arm of this protocol. However, if the use of a growth factor is judged to be necessary in the supportive care of a patient by the treating physician, its use should be carefully documented on eCRFs, and should follow NCCN guidelines. Additional guidance can be found at www.nccn.org.

5.5 Duration of Therapy

In the absence of treatment delays due to adverse event(s), treatment will continue for 7 weeks or until one of the following criteria applies:

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

5.6 Duration of Follow Up

Patients will be followed for 2 years after completion of chemoradiation or until death, whichever occurs first, for toxicity and PFS. Following resolution of toxicity and completion of primary endpoint assessment by PI and study team, long-term follow-up of 5 years will be performed by the Kentucky Cancer Registry. Patients removed from study for unacceptable adverse event(s) will be followed until resolution or stabilization of the adverse event.

5.7 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.5 applies. The reason for study removal and the date the patient is removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

Dose Modifications for cisplatin, days 8 and beyond

Dose Level	Every 3-week Cisplatin	Weekly Cisplatin
-2	50 mg/m^2 every 3 weeks	20 mg/m^2 weekly
-1	75 mg/m^2 every 3 weeks	30 mg/m^2 weekly
0	100 mg/m^2 every 3 weeks	40 mg/m^2 weekly

No more than two dose reductions are allowed and no re-escalation of dosing is allowed, If a subject requires more than two dose reductions, cisplatin will be permanently discontinued. Every effort will be made to complete all planned doses of chemotherapy, with dose modifications listed below, however, no chemotherapy will be given after completion of radiation.

Neutropenia. If on the day of scheduled treatment with cisplatin the absolute neutrophil count (ANC) is < 1000, hold treatment until ANC ≥ 1000 then treat at 100% dose.

Neutropenic fever. If grade 3 or 4 neutropenic fever occurs, defined as temperature ≥38.5°C [101°F] sustained for more than one-hour concomitant with ANC <500/mm^3, hold cisplatin until ANC >1000, and reduce subsequent cisplatin doses by 1 dose level.

Thrombocytopenia. If on the day of scheduled treatment with cisplatin the platelet count is <75,000 hold treatment until platelets are >75,000 then treat at 100% dose.

Thrombocytopenia that results in significant bleeding. If grade 3 or 4 thrombocytopenia occurs with bleeding that is clinically significant, as determined by the treating physician, hold cisplatin until platelets are >75,000 and reduce subsequent cisplatin doses by 1 dose level.

Neurotoxicity. If grade 3 or greater neurotoxicity, including neuropathy occurs, hold cisplatin until resolution to less than or equal to grade 1. Resume cisplatin at one dose level lower. If grade 3 or greater neurotoxicity persist after two dose reductions or does not improve after 14 days, discontinue cisplatin.

Renal Toxicity. If a subject's creatinine clearance falls below 50 ml/min, cisplatin should be held for that dose and should only be restarted once the creatinine clearance improves to >50 ml/min. Subsequent doses should be dose reduced by one dose level. If Cr Cl does not recover to >50 ml/min after 14 days, discontinue cisplatin.

Mucositis: If grade 4 mucositis occurs, hold cisplatin until resolution to less than or equal to grade 2 and reduce subsequent cisplatin doses by 1 dose level.

Ototoxicity or tinnitus: If grade 3 or greater ototoxicity or tinnitus occurs, hold cisplatin until resolution to less than or equal to grade 2 and reduce subsequent cisplatin doses by 1 dose level. If grade 3 or greater hearing loss or tinnitus persist after two dose reductions or does not improve after 14 days, discontinue cisplatin.

Dose Modifications for Other Toxicity: In the event of any other (except nausea and vomiting) grade 3 or 4 non-hematologic toxicity not discussed above, hold all protocol treatment and discuss with the PI. For treatment or dose modification related questions, please contact the PI.

7. ADVERSE EVENTS: LIST AND REPORTING REQUIREMENTS

Adverse event (AE) monitoring and reporting is a routine part of every clinical trial. The following list of AEs (Section 7.1) and the characteristics of an observed AE (Section 7.2) will determine whether the event requires expedited reporting via Medwatch Forms **in addition** to routine reporting.

7.1 Expected Toxicities

7.1.1 Adverse Events List(s)

7.1.1.1 Adverse Event List(s) for Cisplatin

Please see the package insert for all toxicities associated with CISPLATIN. Below is a listing of the most commonly seen toxicities.

Nephrotoxicity: Dose-related and cumulative renal insufficiency, including acute renal failure, is the major dose-limiting toxicity of PLATINOL. Renal toxicity has been noted in 28% to 36% of patients treated with a single dose of 50 mg/m^2. It is first noted during the second week after a dose and is manifested by elevations in BUN and creatinine, serum uric acid and/or a decrease in creatinine clearance. Renal toxicity becomes more prolonged and severe with repeated courses of the drug. Elderly patients may be more susceptible to nephrotoxicity. Impairment of renal function has been associated with renal tubular damage. The administration of CISPLATIN using a 6-8-hour infusion with intravenous hydration, and mannitol has been used to reduce nephrotoxicity. However, renal toxicity still can occur after utilization of these procedures.

Ototoxicity: Ototoxicity has been observed in up to 31% of patients treated with a single dose of CISPLATIN 50 mg/m^2 and is manifested by tinnitus and/or hearing loss in the high frequency range (4000 to 8000 Hz). Decreased ability to hear normal conversational tones may occur. Deafness after the initial dose of CISPLATIN has been reported. Ototoxic effects may be more severe in children receiving CISPLATIN. Hearing loss can be unilateral or bilateral and tends to become more frequent and severe with repeated doses. Ototoxicity may be enhanced with prior or simultaneous cranial irradiation. It is unclear whether CISPLATIN-induced

ototoxicity is reversible. Ototoxic effects may be related to the peak plasma concentration of CISPLATIN. Careful monitoring of audiometry is recommended prior to initiation of therapy and prior to subsequent doses of CISPLATIN. Vestibular toxicity has also been reported. Ototoxicity may become more severe in patients being treated with other drugs with nephrotoxic potential.

Hematologic: Myelosuppression occurs in 25% to 30% of patients treated with CISPLATIN. The nadirs in circulating platelets and leukocytes occur between days 18 to 23 (range 7.5 to 45) with most patients recovering by day 39 (range 13 to 62). Leukopenia and thrombocytopenia are more pronounced at higher doses (>50 mg/m^2). Anemia (decrease of 2 g hemoglobin/100 mL) occurs at approximately the same frequency and with the same timing as leukopenia and thrombocytopenia. Fever and infection have also been reported in patients with neutropenia. Potential fatalities due to infection (secondary to myelosuppression) have been reported. Elderly patients may be more susceptible to myelosuppression. In addition to anemia secondary to myelosuppression, a Coombs' positive hemolytic anemia has been reported. In the presence of cisplatin hemolytic anemia, a further course of treatment may be accompanied by increased hemolysis and this risk should be weighed by the treating physician. The development of acute leukemia coincident with the use of CISPLATIN has been reported. In these reports, CISPLATIN was generally given in combination with other leukemogenic agents.

Gastrointestinal: Marked nausea and vomiting occur in almost all patients treated with CISPLATIN, and may be so severe that the drug must be discontinued. Nausea and vomiting may begin within 1 to 4 hours after treatment and last up to 24 hours. Various degrees of vomiting, nausea and/or anorexia may persist for up to 1 week after treatment. Delayed nausea and vomiting (begins or persists 24 hours or more after chemotherapy) has occurred in patients attaining complete emetic control on the day of CISPLATIN therapy. Diarrhea has also been reported.

OTHER TOXICITIES

Vascular toxicities: Vascular toxicities coincident with the use of CISPLATIN in combination with other antineoplastic agents have been reported. The events are clinically heterogeneous and may include myocardial infarction, cerebrovascular accident, thrombotic microangiopathy (hemolytic-uremic syndrome [HUS]), or cerebral arteritis. Various mechanisms have been proposed for these vascular complications. There are also reports of Raynaud's phenomenon occurring in patients treated with the combination of bleomycin, vinblastine with or without CISPLATIN. It has been suggested that hypomagnesemia developing coincident with the use of CISPLATIN may be an added, although not essential, factor associated with this event. However, it is currently unknown if the cause of Raynaud's phenomenon in these cases is the disease, underlying vascular compromise, bleomycin, vinblastine, hypomagnesemia, or a combination of any of these factors.

Serum Electrolyte Disturbances: Hypomagnesemia, hypocalcemia, hyponatremia, hypokalemia, and hypophosphatemia have been reported to occur in patients treated with CISPLATIN and are probably related to renal tubular damage. Tetany has been reported in patients with hypocalcemia and hypomagnesemia. Generally, normal serum electrolyte levels are restored by administering supplemental electrolytes and discontinuing CISPLATIN. Inappropriate antidiuretic hormone syndrome has also been reported.

Hyperuricemia: Hyperuricemia has been reported to occur at approximately the same frequency as the increases in BUN and serum creatinine. It is more pronounced after doses >50 mg/m^2, and peak levels of uric acid generally occur between 3 to 5 days after the dose. Allopurinol therapy for hyperuricemia effectively reduces uric acid levels.

Neurotoxicity: Neurotoxicity, usually characterized by peripheral neuropathies, has been reported. The neuropathies usually occur after prolonged therapy (4 to 7 months); however, neurologic symptoms have been reported to occur after a single dose. Although symptoms and signs of CISPLATIN neuropathy usually develop during treatment, symptoms of neuropathy may begin 3 to 8 weeks after the last dose of CISPLATIN. CISPLATIN therapy should be discontinued when the symptoms are first observed. The neuropathy, however, may progress further even after stopping treatment. Preliminary evidence suggests peripheral neuropathy may be irreversible in some patients. Elderly patients may be more susceptible to peripheral neuropathy. Lhermitte's sign, dorsal column myelopathy, and autonomic neuropathy have also been reported. Loss of taste, seizures, leukoencephalopathy, and reversible posterior leukoencephalopathy syndrome (RPLS) have also been reported.

Muscle cramps: Muscle cramps, defined as localized, painful, involuntary skeletal muscle contractions of sudden onset and short duration, have been reported and were usually associated with patients receiving a relatively high cumulative dose of CISPLATIN and with a relatively advanced symptomatic stage of peripheral neuropathy.

Ocular Toxicity: Optic neuritis, papilledema, and cerebral blindness have been reported in patients receiving standard recommended doses of CISPLATIN. Improvement and/or total recovery usually occurs after discontinuing CISPLATIN. Steroids with or without mannitol have been used; however, efficacy has not been established. Blurred vision and altered color perception have been reported after the use of regimens with higher doses of CISPLATIN or greater dose frequencies than recommended in the package insert. The altered color perception manifests as a loss of color discrimination, particularly in the blue-yellow axis. The only finding on funduscopic exam is irregular retinal pigmentation of the macular area.

Anaphylactic-Like Reactions: Anaphylactic-like reactions have been reported in patients previously exposed to CISPLATIN. The reactions consist of facial edema, wheezing, tachycardia, and hypotension within a few minutes of drug administration.

Reactions may be controlled by intravenous epinephrine with corticosteroids and/or antihistamines as indicated. Patients receiving CISPLATIN should be observed carefully for possible anaphylactic-like reactions and supportive equipment and medication should be available to treat such a complication.

Transient liver function test abnormalities, cardiac abnormalities, hiccups, elevated serum amylase, rash, alopecia, malaise, asthenia, and dehydration have been reported.

Local soft tissue toxicity has been reported following extravasation of CISPLATIN. Severity of the local tissue toxicity appears to be related to the concentration of the CISPLATIN solution.

Infusion of solutions with a CISPLATIN concentration >0.5 mg/mL may result in tissue cellulitis, fibrosis, necrosis, pain, edema, and erythema.

7.2 Adverse Event Characteristics

- **CTCAE term (AE description) and grade:** The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 will be utilized for AE reporting. All appropriate treatment areas should have access to a copy of the CTCAE version 4.0. A copy of the CTCAE version 4.0 can be downloaded from the CTEP web site: http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm.

- **For expedited reporting purposes only:**
  - AEs for the agent(s) that are listed above should be reported only if the adverse event varies in nature, intensity or frequency from the expected toxicity information which is provided.
  - Other AEs for the protocol that do not require expedited reporting are outlined in the next section (Expedited Adverse Event Reporting) under the sub-heading of Protocol-Specific Expedited Adverse Event Reporting Exclusions.

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

7.3 Expedited Adverse Event Reporting

7.3.1 For MCC Investigator-Initiated Trials (IITs), investigators **must** report to the Overall PI any serious adverse event (SAE) that occurs after the initial dose of study treatment, during treatment, or within 30 days of the last dose of treatment on the local institutional SAE form. This applies to the following categories:

- **Grade 3 (severe) *Medical* Events –** Only events that are Unexpected and Possibly, Probably or Definitely Related / Associated with the Intervention.
- **ALL Grade 4 (life threatening or disabling) *Medical* Events –** Unless expected AND specifically listed in protocol as not requiring reporting.
- **ALL Grade 5 (fatal) Events** regardless of study phase or attribution.

Note: If subject is in Long Term Follow Up, death is reported at continuing review.
Note: Abnormal laboratory values are not considered medical events, unless determined to be causative of SAE by the investigator or grade 5.

7.3.2 Required Forms and Reporting Structure for Clinical Trials

The following table outlines the required forms and reporting structure for clinical trials.

Study type	Expedited reporting to MCC	Expedited reporting to External Agency	Non-expedited AE	Form	IRB
IIT by MCC investigator of commercially available agent (non-IND and non-IDE)	• Grade 3 – Unexpected AE PLUS Possibly, Probably or Definitely Related • ALL Grade 4 Unless expected AND listed in protocol as not requiring reporting. • ALL Grade 5 (fatal) Events	FDA: Suspected AE that is serious and Unanticipated (not listed in IDB or consent)	OnCore and DSMC reporting only	Voluntary Medwatch 3500 for Serious and unanticipated OnCore for all AEs, including SAEs	Per IRB regulations

7.3.3 MCC Expedited Reporting Guidelines for MCC IITs

Investigators within MCC will report SAEs directly to the MCC DSMC per the MCC DSMC SOP and the University of Kentucky IRB reporting policy.

	MCC Reportable AEs				
Attribution	**Gr. 2 & 3 AE Expected**	**Gr. 2 & 3 AE Unexpected**	**Gr. 4 AE Expected**	**Gr. 4 AE Unexpected**	**Gr. 5 AE Expected or Unexpected**
Unrelated Unlikely	Not required	Not required	5 calendar days#	5 calendar days	24 hours*
Possible Probable Definite	Not required	5 calendar days	5 calendar days#	5 calendar days	24 hours*

If listed in protocol as expected and not requiring expedited reporting, event does not need to be reported.
* For participants enrolled and actively participating in the study ***or*** for AEs occurring within 30 days of the last intervention, the AE should be reported within 24 business hours of learning of the event.

7.3.4 **Protocol-Specific Expedited Adverse Event Reporting Exclusions**

For this protocol only, lymphopenia Grade 3 and Grade 4 does not require expedited reporting to the Overall PI or the MCC DSMC. It will not be recorded on the OnCore case report forms but will be recorded in the source documents.

7.4 Expedited Reporting to External Agencies

The Overall PI will comply with the policies of all external funding agencies and the UK IRB regarding expedited reporting, as per the UK IRB's SOP: http://www.research.uky.edu/ori/SOPs_Policies/C4-0150-Mandated_Reporting_to_External_Agencies_SOP.pdf.

7.5 Expedited Reporting to Hospital Risk Management

Participating investigators will report to the UK Office of Risk Management any participant safety reports or sentinel events that require reporting according to institutional policy.

7.6 Routine Adverse Event Reporting

All Adverse Events **must** be reported in routine study data submissions to the Overall PI on the OnCore case report forms, except exclusions listed in the table below:

Adverse Event	Grade	Attribution
Alopecia	All	All causes
Lymphopenia	1-4	All causes
Laboratory abnormalities	1-2	Deemed not clinically significant by treating MD

AEs reported through expedited processes (e.g., reported to the IRB, FDA, etc.) must also be reported in routine study data submissions.

7.4 Second Malignancy

A second malignancy is one unrelated to the treatment of a prior malignancy (and is **NOT** a metastasis from the initial malignancy). Second malignancies require **ONLY** routine AE reporting unless otherwise specified.

8. PHARMACEUTICAL INFORMATION

A list of the adverse events and potential risks associated with cisplatin administered in this study can be found in Section 7.1.

8.1 Cisplatin

Refer to the package insert for detailed pharmacologic and safety information. Formulation: Each vial contains 10 mg of DDP, 19 mg of sodium chloride, 100 mg of mannitol, and hydrochloric acid for pH adjustment. One vial is reconstituted with 10 ml of sterile water. The pH range will be 3.5 to 4.5. Cisplatin injection also is available from the manufacturer in aqueous solution, each ml containing 1 mg cisplatin and 9 mg NaCl and HCL or NaOH to adjust pH.

Storage and Preparation: The dry, unopened vials should be stored at refrigeration temperature (+4°C to +8°C). Reconstitution results in a solution stable for not more than one hour at room temperature when exposed to normal room illumination, and not more than 8 hours at room temperature when protected from light.

Mechanism of Action: The dominant mode of action of cisplatin appears to be inhibition of the incorporation of DNA precursors, although protein and RNA synthesis are also inhibited. Although this drug seems to act as an alkylating agent, there are data to indicate that its mode and sites of action are different from those of nitrogen mustard and the standard alkylating agents.

Administration: After administering appropriate antiemetics, cisplatin will be infused over 1 hour according to institutional guidelines along with vigorous hydration of normal saline of 1 liter before and after cisplatin infusion.

Storage and Stability: Reconstituted solution of cisplatin is stable for 20 hours when stored at 27°C and should be protected from light if not used within 6 hours. The vials and injection should not be refrigerated. Cisplatin has been shown to react with aluminum needles, producing a black precipitate within 30 minutes.

Supply: Cisplatin is commercially available. The use of drug(s) or combination of drugs in this protocol meets the criteria described under Title 21 CFR 312.2(b) for IND exemption.

Chemotherapy Pharmaceutical Data: Cisplatin (Cis-Diaminedichloroplatinum, DDP)

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

9.1 Correlative Studies: Functional Assessment of Cancer Therapy

Cognitive Function (FACT-Cog)[28] is a self-report questionnaire designed to assess perceived cognitive impairments (20 items), impact on quality of life (4 items), comments from others (4 items), and perceived cognitive abilities (9 items). Estimated time for administration is approximately 12 minutes.

9.2 Biologic Correlates

Serum studies in the proposed project will include measurement of the serum cytokine TNF-α, protein carbonyls, nitric oxide and 4-hydroxynonenal protein adducts. Additionally, we will also collect PK samples on a small cohort of these patients for cisplatin pharmacokinetics. Please refer to the Lab Manual for all instructions for correlative collection and processing.

10. STUDY CALENDAR

Baseline evaluations are to be conducted as follows:

- Within 3 weeks prior to registration: Complete history, physical examination, and evaluation of ECOG Performance Status, CBC; serum chemistry tests to include alkaline phosphatase, creatinine, electrolytes, AST (SGOT), and total bilirubin.
- All radiographic studies should be completed within:
    a. Cohort 1: 6 weeks prior to registration
    b. Cohort 2: 8 weeks prior to registration
- In the event that the patient's condition is deteriorating, laboratory evaluations should be repeated within 48 hours prior to initiation of the next cycle of therapy.

	Pre-Study	**Wk 1**	**Wk 2**	**Wk 3**	**Wk 4**	**Wk 5**	**Wk 6**	**Wk 7**	**Post Treatment Follow up**	**Long term Follow up[h]**
Cisplatin Arm 1		A			A			A		
Cisplatin Arm 2		B	B	B	B	B	B	B		
Informed consent	X									
Demographics, medical history	X									
Concurrent meds		X[i]								
Physical exam	X	X			X			X	X	X[h]
Pulse, blood pressure	X	X			X			X	X	
Height	X									
Weight [a]	X	X	X [a]	X [a]	X	X [a]	X [a]	X		
Performance status	X	X							X	
CBC w/diff, plts [a]	X	X	X [a]	X [a]	X	X [a]	X [a]	X	X	
Serum basic chemistry[b]			X [a]	X [a]		X [a]	X [a]			
Serum comprehensive chemistry [c]	X	X			X			X	X	
Adverse event evaluation		X----------								----X
Tumor measurements	X[d]								X[e]	X[e]
B-HCG	X[f]									
Correlative studies		X								
FACTHN and FACT-COG [g]	X [g]								X [g]	X [g]

A: Arm 1: Cisplatin 100 mg/m^2 every 3 weeks for 3 total doses
B: Arm 2: Cisplatin 40 mg/m^2 every week for 7 total doses
a: Every 3 weeks for Arm 1 during radiation, weekly for Arm 2 during radiation, and then as scheduled.
b: Weeks 2,3,5, 6 of Arm 2 only: creatinine, glucose, potassium, sodium.
c: Every three weeks for both arms: Albumin, alkaline phosphatase, total bilirubin, calcium, creatinine, potassium, SGOT [AST], SGPT [ALT], sodium.

d: Baseline scans can include either: 1) CT with contrast or MRI of the head and neck region, CT of chest or chest x-ray. Response assessment should include assessment of all sites of disease and use the same imaging method as was used at baseline.
e: Restaging scans must be repeated after the end of protocol treatment within 8 weeks of completion of radiation. Thereafter, scans of the head and neck will be repeated as clinically indicated, but at a minimum of every 6 months (±6 weeks) for the first two years. Following this, all scans are at the treating physician's discretion.
f: Serum pregnancy test (women of childbearing potential).
g: Pre-study, at 3 months (±6 weeks) and 12 months (±12 weeks) following initiation of treatment.
h: Physical exams will be repeated as clinically indicated, but at a minimum of every 6 months (±6 weeks) for the first two years. Following this, all follow-up is at the treating physician's discretion.
i: Only on Days 1 and 2 of cycle 1

11. MEASUREMENT OF EFFECT

11.1 Antitumor Effect – Solid Tumors

For the purposes of this study, patients should be re-evaluated for response at the end of radiation within 8 weeks of the completion of radiation.

Response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [31]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.1.1 Definitions

Evaluable for toxicity. All patients will be evaluable for toxicity from the time of their first treatment with cisplatin.

Evaluable for objective response. Only patients who have measurable disease present at baseline, have received at least one cycle of therapy, and have had their disease re-evaluated will be considered evaluable for response. These patients will have their response classified according to the definitions stated below. (Note: Patients who exhibit objective disease progression prior to the end of cycle 1 will also be considered evaluable.)

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

11.1.2 Disease Parameters

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 (≥2 cm) by chest x-ray or as ≥10 mm (≥1 cm) with CT scan, MRI, or calipers by clinical exam.

All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters).

Note: Tumor lesions that are situated in a previously irradiated area might or might not be considered measurable. *If the investigator thinks it appropriate to include them, the conditions under which such lesions should be considered must be defined in the protocol*.

Malignant lymph nodes. To be considered pathologically enlarged and measurable, a lymph node must be ≥15 mm (≥1.5 cm) in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm [0.5 cm]). At baseline and in follow-up, only the short axis will be measured and followed.

Non-measurable disease. All other lesions (or sites of disease), including small lesions (longest diameter <10 mm [<1 cm] or pathological lymph nodes with ≥10 to <15 mm [≥1 to <1.5 cm] short axis), are considered non-measurable disease. Bone lesions, leptomeningeal disease, ascites, pleural/pericardial effusions, lymphangitis cutis/pulmonitis, inflammatory breast disease, and abdominal masses (not followed by CT or MRI), are considered as non-measurable.

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

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

Target lesions. All measurable lesions up to a maximum of 2 lesions per organ and 5 lesions in total, representative of all involved organs, should be identified as **target lesions** and recorded and measured at baseline. Target lesions should be selected on the basis of their size (lesions with the longest diameter), be representative of all involved organs, but in addition should be those that lend themselves to reproducible repeated measurements. It may be the case that, on occasion, the largest lesion does not lend itself to reproducible measurement in which circumstance the next largest lesion which can be measured reproducibly should be selected. A sum of the diameters (longest for non-nodal lesions, short axis for nodal lesions) for all target lesions will be calculated and reported as the baseline sum diameters. If lymph nodes are to be included in the sum, then only the short axis is added into the sum. The baseline sum diameters will be used as reference to further characterize any objective tumor regression in the measurable dimension of the disease.

Non-target lesions. All other lesions (or sites of disease) including any measurable lesions over and above the 5 target lesions should be identified as **non-target lesions** and should also be recorded at baseline. Measurements of these lesions are not required, but

the presence, absence, or in rare cases unequivocal progression of each should be noted throughout follow-up.

11.1.3 Methods for Evaluation of Measurable Disease

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.

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

Clinical lesions: Clinical lesions will only be considered measurable when they are superficial (*e.g.*, skin nodules and palpable lymph nodes) and ≥10 mm (≥1 cm) diameter as assessed using calipers (*e.g.*, skin nodules). In the case of skin lesions, documentation by color photography, including a ruler to estimate the size of the lesion, is recommended.

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: This guideline has defined measurability of lesions on CT scan based on the assumption that CT slice thickness is 5 mm (0.5 cm) or less. If CT scans have slice thickness greater than 5 mm (0.5 cm), the minimum size for a measurable lesion should be twice the slice thickness. MRI is also acceptable in certain situations (*e.g.* for body scans).

Use of MRI remains a complex issue. MRI has excellent contrast, spatial, and temporal resolution; however, there are many image acquisition variables involved in MRI, which greatly impact image quality, lesion conspicuity, and measurement. Furthermore, the availability of MRI is variable globally. As with CT, if an MRI is performed, the technical specifications of the scanning sequences used should be optimized for the evaluation of the type and site of disease. Furthermore, as with CT, the modality used at follow-up should be the same as was used at baseline and the lesions should be measured/assessed on the same pulse sequence. It is beyond the scope of the RECIST guidelines to prescribe specific MRI pulse sequence parameters for all scanners, body parts, and diseases. Ideally, the same type of scanner should be used and the image acquisition protocol should be followed as closely as possible to prior scans. Body scans should be performed with breath-hold scanning techniques, if possible.

PET-CT. At present, the low dose or attenuation correction CT portion of a combined PET-CT is not always of optimal diagnostic CT quality for use with RECIST measurements. However, if the site can document that the CT performed as part of a

PET-CT is of identical diagnostic quality to a diagnostic CT (with IV and oral contrast), then the CT portion of the PET-CT can be used for RECIST measurements and can be used interchangeably with conventional CT in accurately measuring cancer lesions over time. Note, however, that the PET portion of the CT introduces additional data which may bias an investigator if it is not routinely or serially performed.

Ultrasound: Ultrasound is not useful in assessment of lesion size and should not be used as a method of measurement. Ultrasound examinations cannot be reproduced in their entirety for independent review at a later date and, because they are operator dependent, it cannot be guaranteed that the same technique and measurements will be taken from one assessment to the next. If new lesions are identified by ultrasound in the course of the study, confirmation by CT or MRI is advised. If there is concern about radiation exposure at CT, MRI may be used instead of CT in selected instances.

Endoscopy, Laparoscopy: The utilization of these techniques for objective tumor evaluation is not advised. However, such techniques may be useful to confirm complete pathological response when biopsies are obtained or to determine relapse in trials where recurrence following complete response (CR) or surgical resection is an endpoint.

Tumor markers: Tumor markers alone cannot be used to assess response. If markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response. Specific guidelines for both CA-125 response (in recurrent ovarian cancer) and PSA response (in recurrent prostate cancer) have been published [*JNCI* 96:487-488, 2004; *J Clin Oncol* 17, 3461-3467, 1999; *J Clin Oncol* 26:1148-1159, 2008]. In addition, the Gynecologic Cancer Intergroup has developed CA-125 progression criteria which are to be integrated with objective tumor assessment for use in first-line trials in ovarian cancer [*JNCI* 92:1534-1535, 2000].

Cytology, Histology: These techniques can be used to differentiate between partial responses (PR) and complete responses (CR) in rare cases (*e.g.*, residual lesions in tumor types, such as germ cell tumors, where known residual benign tumors can remain).

The cytological confirmation of the neoplastic origin of any effusion that appears or worsens during treatment when the measurable tumor has met criteria for response or stable disease is mandatory to differentiate between response or stable disease (an effusion may be a side effect of the treatment) and progressive disease.

FDG-PET: While FDG-PET response assessments need additional study, it is sometimes reasonable to incorporate the use of FDG-PET scanning to complement CT scanning in assessment of progression (particularly possible 'new' disease). New lesions on the basis of FDG-PET imaging can be identified according to the following algorithm:

a. Negative FDG-PET at baseline, with a positive FDG-PET at follow-up is a sign of PD based on a new lesion.
b. No FDG-PET at baseline and a positive FDG-PET at follow-up: If the positive FDG-PET at follow-up corresponds to a new site of disease confirmed by CT, this is PD. If

the positive FDG-PET at follow-up is not confirmed as a new site of disease on CT, additional follow-up CT scans are needed to determine if there is truly progression occurring at that site (if so, the date of PD will be the date of the initial abnormal FDG-PET scan). If the positive FDG-PET at follow-up corresponds to a pre-existing site of disease on CT that is not progressing on the basis of the anatomic images, this is not PD.

c. FDG-PET may be used to upgrade a response to a CR in a manner similar to a biopsy in cases where a residual radiographic abnormality is thought to represent fibrosis or scarring. The use of FDG-PET in this circumstance should be prospectively described in the protocol and supported by disease-specific medical literature for the indication. However, it must be acknowledged that both approaches may lead to false positive CR due to limitations of FDG-PET and biopsy resolution/sensitivity.

Note: A 'positive' FDG-PET scan lesion means one which is FDG avid with an uptake greater than twice that of the surrounding tissue on the attenuation corrected image.

11.1.4 Response Criteria

11.1.4.1 Evaluation of Target Lesions

Complete Response (CR): Disappearance of all target lesions. Any pathological lymph nodes (whether target or non-target) must have reduction in short axis to <10 mm (<1 cm).

Partial Response (PR): At least a 30% decrease in the sum of the diameters of target lesions, taking as reference the baseline sum diameters.

Progressive Disease (PD): At least a 20% increase in the sum of the diameters of target lesions, taking as reference the smallest sum on study (this includes the baseline sum if that is the smallest on study). In addition to the relative increase of 20%, the sum must also demonstrate an absolute increase of at least 5 mm (0.5 cm). (Note: the appearance of one or more new lesions is also considered progression.)

Stable Disease (SD): Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum diameters while on study.

11.1.4.2 Evaluation of Non-Target Lesions

Complete Response (CR): Disappearance of all non-target lesions and normalization of tumor marker level. All lymph nodes must be non-pathological in size (<10 mm [<1 cm] short axis).

Note: If tumor markers are initially above the upper normal limit, they must normalize for a patient to be considered in complete clinical response.

Non-CR/Non-PD: Persistence of one or more non-target lesion(s) and/or maintenance of tumor marker level above the normal limits.

Progressive Disease (PD): Appearance of one or more new lesions and/or *unequivocal progression* of existing non-target lesions. *Unequivocal progression* should not normally trump target lesion status. It must be representative of overall disease status change, not a single lesion increase.

Although a clear progression of "non-target" lesions only is exceptional, the opinion of the treating physician should prevail in such circumstances, and the progression status should be confirmed at a later time by the review panel (or PI).

11.1.4.3 Evaluation of Best Overall Response

The best overall response is the best response recorded from the start of the treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

For Patients with Measurable Disease (*i.e.*, Target Disease)

Target Lesions	Non-Target Lesions	New Lesions	Overall Response	Best Overall Response when Confirmation is Required*
CR	CR	No	CR	≥4 wks Confirmation**
CR	Non-CR/Non-PD	No	PR	≥4 wks Confirmation**
CR	Not evaluated	No	PR	
PR	Non-CR/Non-PD/not evaluated	No	PR	
SD	Non-CR/Non-PD/not evaluated	No	SD	Documented at least once ≥4 wks from baseline**
PD	Any	Yes or No	PD	no prior SD, PR or CR
Any	PD***	Yes or No	PD	
Any	Any	Yes	PD	

* See RECIST 1.1 manuscript for further details on what is evidence of a new lesion.
** Only for non-randomized trials with response as primary endpoint.
*** In exceptional circumstances, unequivocal progression in non-target lesions may be accepted as disease progression.
Note: Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time should be reported as "*symptomatic deterioration.*" Every effort should be made to document the objective progression even after discontinuation of treatment.

For Patients with Non-Measurable Disease (*i.e.*, Non-Target Disease)Non-Target Lesions	New Lesions	Overall Response

CR	No	CR
Non-CR/non-PD	No	Non-CR/non-PD*
Not all evaluated	No	not evaluated
Unequivocal PD	Yes or No	PD
Any	Yes	PD

* 'Non-CR/non-PD' is preferred over 'stable disease' for non-target disease since SD is increasingly used as an endpoint for assessment of efficacy in some trials so to assign this category when no lesions can be measured is not advised.

11.1.5 Duration of Response

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

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

Duration of stable disease: Stable disease is measured from the start of the treatment until the criteria for progression are met, taking as reference the smallest measurements recorded since the treatment started, including the baseline measurements.

11.1.6 Progression-Free Survival

PFS is defined as the duration of time from start of treatment to time of progression or death, whichever occurs first.

12. DATA REPORTING / REGULATORY REQUIREMENTS

Adverse event lists, guidelines, and instructions for AE reporting can be found in Section 7.0 (Adverse Events: List and Reporting Requirements).

12.1 Data Reporting

12.1.1 Method

This study will require data submission and reporting via the OnCore Database, which is the official database of the Markey Cancer Center Clinical Research Office (CRO). Instructions for submitting data are listed in Study-Specific Data Management Plans created by Data Management Specialist Senior housed in the Cancer Research Informatics (CRI) Shared Research Facility (SRF). **Please refer to the study calendar for all data reporting requirements.**

12.1.2 Responsibility for Data Submission

Study staff are responsible for submitting study data and/or data forms to OnCore as per the Markey Cancer Center CRO SOP's. This trial will be monitored by the MCC Data and Safety Monitoring Committee (DSMC) on a schedule determined by the Protocol Review and Monitoring Committee (PRMC) at the initial PRMC review. The CRO staff is responsible for compiling and submitting data for all participants and for providing the data to the Principal Investigator for review.

12.1.3 Responsibility for Data Monitoring

The MCC Quality Assurance Office will be responsible for creation and implementation of a clinical Data Monitoring Plan in collaboration with the PI and study team, as per QA Office SOPs.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This is a 1:1 randomized, unblinded phase II trial of radiation with cisplatin weekly versus every three weeks for patients with locally advanced non-nasopharyngeal SCCHN. The primary endpoint is cisplatin-related acute toxicities (within the first 90 days after the start of radiation). These include all grade 3-5 events of nausea/vomiting, ototoxicity, nephrotoxicity, and neutropenia and thrombocytopenia. Secondary objectives include clinical outcomes (2-year local control rates, OS, PFS, response), additional toxicity outcomes (rates of dysphagia, dry mouth, and skin, other acute and late events according to CTCAE), correlatives (oxidative stress markers), and quality of life outcomes (FACTHN, FACTCOG).

13.2 Sample Size/Accrual Rate

The primary objective of this study is to see if cisplatin delivered weekly results in fewer cisplatin-related toxicities and improved tolerability compared to cisplatin administered every 3 weeks. Both groups will still receive standard of care radiation therapy in addition to cisplatin. Assuming historical rates of 80% toxicities for patients receiving XRT + cisplatin every 3 weeks [10, 32-34], with 36 patients per arm we will have 80% power based on a Fisher's exact test to detect a decrease in toxicity rate to 50%, assuming a one-sided level of significance equal to 0.05. Conservatively assuming a 10% loss to follow-up, we will recruit 80 total patients for at least 72 analyzable.

Based on the Cancer Research Informatics SRF incidence tables for SCCHN from 2010-2014, **there were an average of 125 patients seen per year at MCC** that would be eligible for this trial based on tumor stage and tumor site. If even 33% of these subjects met all criteria and agreed to participate, we anticipate this study would be completed in 2 years. Our HN CCART has an excellent track record of accrual to clinical trials in this subset of SCCHN, thus we feel that this estimate is conservative and that it is possible that we could accrue faster than predicted.

13.3 Stratification Factors

13.3.1 Randomization will be stratified by type of SCCHN: Cohort (1) is unresectable and Cohort (2) is resected and at high risk of recurrence as defined by the presence of one of the following criteria:

- extracapsular nodal extension
- invasive cancer at the primary tumor resection margin (positive margin)
- lymphovascular invasion
- perineural invasion
- pT3 or pT4 primary
- presence of multilevel nodal disease

13.4 **Analysis Plan**

Following study completion, the percentage of subjects experiencing cisplatin-related actual toxicities in each group will be estimated along with exact 95% binomial confidence intervals. A Fisher's exact test will also be employed to test for differences between toxicity rates.

For all toxicity outcomes, incidence tables will be generated to summarize incidence of patients reporting at least one episode of each adverse event, incidence of adverse events causing withdrawals and incidence of serious adverse events. Listing of adverse events by patients will include the time to onset, the duration of each event, the severity of each event, and the relationship of the event to study therapy, whether it was a serious event, and whether it caused withdrawal.

All correlative and secondary endpoints are exploratory in nature and will be primarily descriptive; however, response and 2-year local control rates will be estimated with corresponding 95% confidence intervals and assessed for differences using Fisher's exact tests. PFS and OS will be displayed using Kaplan-Meier curves with estimated median times, and differences will be assessed using log rank tests. Repeated measures mixed models will be utilized to assess for differences in quality of life and correlative outcomes over time and between randomization groups.

In addition to those outlined above, subgroup analyses will also be run for each stratification cohort as numbers allow.

13.5 **Interim Analyses**

None planned.

13.6 **Data Management**

The study statistician and staff from the Biostatistics and Bioinformatics Core of the Markey Cancer Center will work closely with the study team, the Clinical Research Office (CRO) at MCC and the Cancer Research Informatics (CRI) Core at MCC to implement several aspects of Data Management for this trial. This will include development of eCRFs in the OnCore system, trial-specific processes for data entry, generation of reports, data management and statistical

analysis. Specifically, the statistician will attend several meetings including the eCRF development meeting, the data management process meeting and the protocol initiation meeting. Appropriate and accurate collection of primary and secondary study endpoints and inclusion of valid values and range checks for data fields will be designed for the eCRFs. The OnCore clinical trial management system, managed by Markey's CRO and CRI, will be the primary database repository of clinical data from all patients enrolled into this trial. Data will be accessed by the study statistician on a regularly scheduled basis to perform statistical programming for conduct of data quality control, data management, generation of interim reports and statistical analysis. In collaboration with the study team, procedures will be developed for timelines for data quality control, resolution of data queries, interim reporting and final data analysis.

A protocol specific Data Management Plan (DMP) will be authored by a senior data manager in collaboration with the biostatistician and CRO, each team will be expected to review and sign off on the DMP prior to finalization. In order to maintain best clinical practices in data management, the DMP may include, but not be limited to CRF/eCRF design, database build and design, database training, edit check/validation specifications, study database testing/release, data and paper workflow, report, metrics, query/discrepancy management, management of external (including lab) data, medical coding, SAE handling/reconciliation, data transfers and database lock. The protocol specific DMP will additionally define the schedule at which data will be accessed by study statisticians to perform statistical programming for conduct of data quality, data control, data management, generation of interim reports and statistical analysis. Cross-team members will collaborate to establish procedures and timelines for quality control, audits, query resolution, interim and final data analysis.

13.7 **Reporting and Exclusions**

13.7.1 Evaluation of Toxicity

All patients will be evaluable for toxicity from the time of their first treatment with cisplatin or radiation.

13.7.2 Evaluation of Response

All patients included in the study must be assessed for response to treatment, even if there are major protocol treatment deviations or if they are ineligible. Each patient will be assigned one of the following categories: 1) complete response, 2) partial response, 3) stable disease, 4) progressive disease, 5) early death from malignant disease, 6) early death from toxicity, 7) early death because of other cause, or 9) unknown (not assessable, insufficient data). [Note: By arbitrary convention, category 9 usually designates the "unknown" status of any type of data in a clinical database.]

All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) should be included in the main analysis of the response rate. Patients in response categories 4-9 should be considered to have a treatment failure (disease progression). Thus, an incorrect treatment schedule or drug

administration does not result in exclusion from the analysis of the response rate. Precise definitions for categories 4-9 will be protocol specific.

All conclusions should be based on all eligible patients. Subanalyses may then be performed on the basis of a subset of patients, excluding those for whom major protocol deviations have been identified (*e.g.*, early death due to other reasons, early discontinuation of treatment, major protocol violations, etc.). However, these subanalyses may not serve as the basis for drawing conclusions concerning treatment efficacy, and the reasons for excluding patients from the analysis should be clearly reported. The 95% confidence intervals should also be provided.

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APPENDIX A: PERFORMANCE STATUS CRITERIA

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

APPENDIX B: FACT-COGNITIVE FUNCTION (VERSION 3)

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

	<u>PERCEIVED COGNITIVE IMPAIRMENTS</u>	**Never**	**About once a week**	**Two to three times a week**	**Nearly every day**	**Several times a day**
CogA1	I have had trouble forming thoughts	0	1	2	3	4
CogA3	My thinking has been slow	0	1	2	3	4
CogC7	I have had trouble concentrating	0	1	2	3	4
CogM9	I have had trouble finding my way to a familiar place	0	1	2	3	4
CogM10	I have had trouble remembering where I put things, like my keys or my wallet	0	1	2	3	4
CogM12	I have had trouble remembering new information, like phone numbers or simple instructions	0	1	2	3	4
CogV13	I have had trouble recalling the name of an object while talking to someone	0	1	2	3	4
CogV15	I have had trouble finding the right word(s) to express myself.....	0	1	2	3	4
CogV16	I have used the wrong word when I referred to an object	0	1	2	3	4
CogV17b	I have had trouble saying what I mean in conversations with others	0	1	2	3	4
CogF19	I have walked into a room and forgotten what I meant to get or do there	0	1	2	3	4
CogF23	I have had to work really hard to pay attention or I would make a mistake	0	1	2	3	4
CogF24	I have forgotten names of people soon after being introduced	0	1	2	3	4

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

		Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogF25	My reactions in everyday situations have been slow	0	1	2	3	4
CogC31	I have had to work harder than usual to keep track of what I was doing	0	1	2	3	4
CogC32	My thinking has been slower than usual	0	1	2	3	4
CogC33a	I have had to work harder than usual to express myself clearly	0	1	2	3	4
CogC33c	I have had to use written lists more often than usual so I would not forget things	0	1	2	3	4
CogMT1	I have trouble keeping track of what I am doing if I am interrupted	0	1	2	3	4
CogMT2	I have trouble shifting back and forth between different activities that require thinking	0	1	2	3	4

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

	<u>COMMENTS FROM OTHERS</u>	Never	About once a week	Two to three times a week	Nearly every day	Several times a day
CogO1	Other people have told me I seemed to have trouble <u>remembering information</u>	0	1	2	3	4
CogO2	Other people have told me I seemed to have trouble <u>speaking clearly</u>	0	1	2	3	4
CogO3	Other people have told me I seemed to have trouble <u>thinking clearly</u>.....	0	1	2	3	4
CogO4	Other people have told me I seemed <u>confused</u>	0	1	2	3	4

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

	PERCEIVED COGNITIVE ABILITIES	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
Cog PC1	I have been able to concentrate	0	1	2	3	4
Cog PV1	I have been able to bring to mind words that I wanted to use while talking to someone	0	1	2	3	4
Cog PM 1	I have been able to remember things, like where I left my keys or wallet	0	1	2	3	4
Cog PM 2	I have been able to remember to do things, like take medicine or buy something I needed	0	1	2	3	4
Cog PF1	I am able to pay attention and keep track of what I am doing without extra effort	0	1	2	3	4
Cog PC H1	My mind is as sharp as it has always been	0	1	2	3	4
Cog PC H2	My memory is as good as it has always been	0	1	2	3	4
Cog PM T1	I am able to shift back and forth between two activities that require thinking	0	1	2	3	4
Cog PM T2	I am able to keep track of what I am doing, even if I am interrupted	0	1	2	3	4

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

	IMPACT ON QUALITY OF LIFE	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
Cog Q35	I have been upset about these problems	0	1	2	3	4
Cog Q37	These problems have interfered with my ability to work	0	1	2	3	4
Cog Q38	These problems have interfered with my ability to do things I enjoy	0	1	2	3	4
Cog Q41	These problems have interfered with the quality of my life	0	1	2	3	4

APPENDIX C: FACT/NCCN HNSI

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

		Not at all	A little bit	Some-what	Quite a bit	Very much
GP4	I have pain.....	0	1	2	3	4
GP1	I have a lack of energy.....	0	1	2	3	4
H&N7	I can swallow naturally and easily.....	0	1	2	3	4
H&N 12	I have pain in my mouth, throat, or neck.....	0	1	2	3	4
H&N3	I have trouble breathing.....	0	1	2	3	4
H&N10	I am able to communicate with others.....	0	1	2	3	4
GP2	I have nausea.....	0	1	2	3	4
H&N11	I can eat solid foods.....	0	1	2	3	4
GE6	I worry that my condition will get worse.....	0	1	2	3	4
GF7	I am content with the quality of my life right now.....	0	1	2	3	4