13-HN-23-MCC: A Pilot study of Concentrated Beet Root in participants being treated for locally advanced unresectable, previously untreated squamous cell cancer of the head and neck:
A University of Kentucky Markey Cancer Center Clinical Trial

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SCHEMA

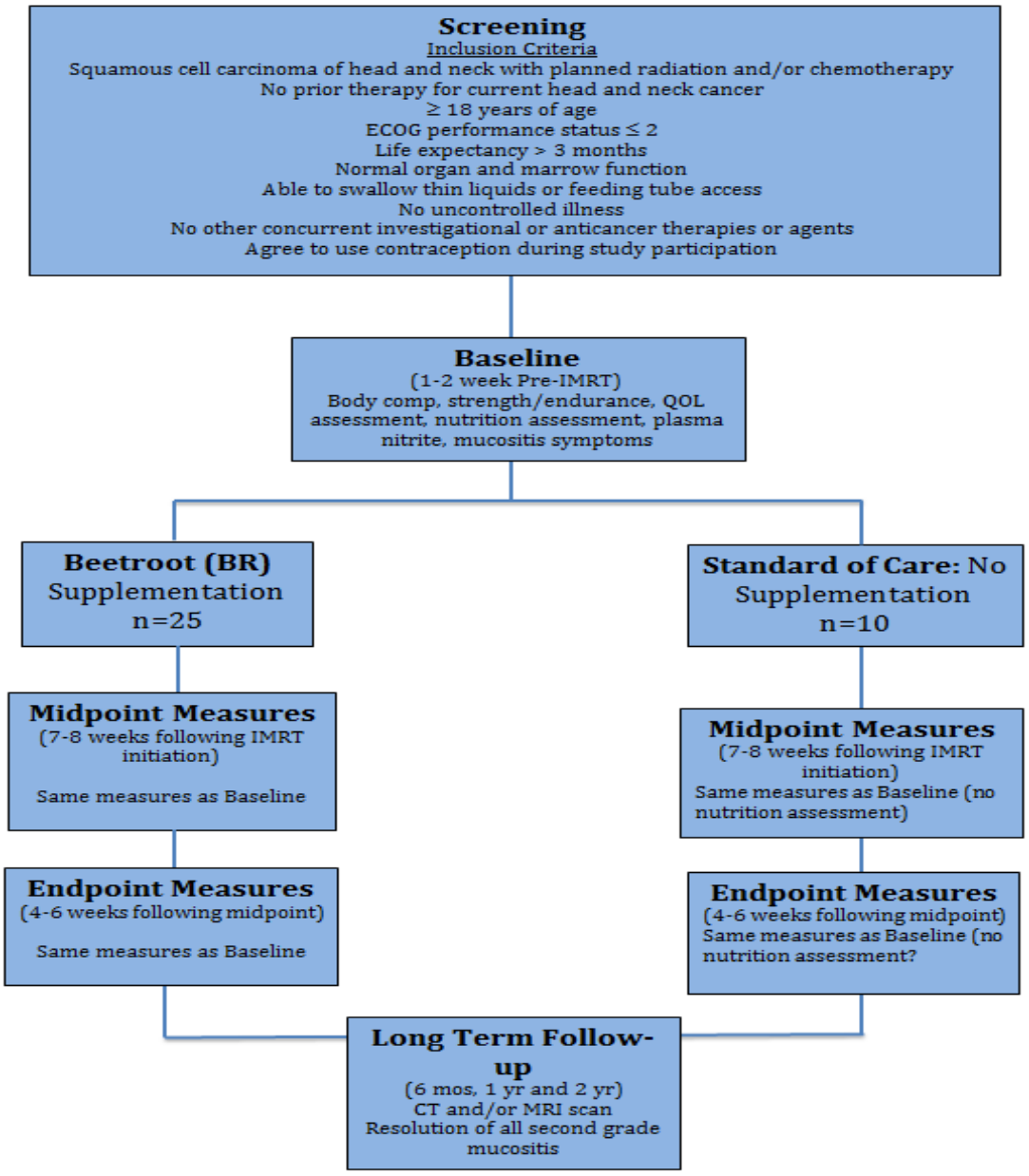
Screening
Inclusion Criteria
Squamous cell carcinoma of head and neck with planned radiation and/or chemotherapy
No prior therapy for current head and neck cancer
≥ 18 years of age
ECOG performance status ≤ 2
Life expectancy > 3 months
Normal organ and marrow function
Able to swallow thin liquids or feeding tube access
No uncontrolled illness
No other concurrent investigational or anticancer therapies or agents
Agree to use contraception during study participation
Baseline
(1-2 week Pre-IMRT)
Body comp, strength/endurance, QOL assessment, nutrition assessment, plasma nitrite, mucositis symptoms
Beetroot (BR) Supplementation n=25
Standard of Care: No Supplementation n=10
Midpoint Measures
(7-8 weeks following IMRT initiation)
Same measures as Baseline
Midpoint Measures
(7-8 weeks following IMRT initiation)
Same measures as Baseline (no nutrition assessment)
Endpoint Measures
(4-6 weeks following midpoint)
Same measures as Baseline
Endpoint Measures
(4-6 weeks following midpoint)
Same measures as Baseline (no nutrition assessment?
Long Term Follow-up
(6 mos, 1 yr and 2 yr)
CT and/or MRI scan
Resolution of all second grade mucositis

TABLE OF CONTENTS

1. OBJECTIVES

1.1 Primary Objectives

Obtain preliminary data estimates of treatment compliance of radiation alone or chemoradiation (as defined by completion of initially prescribed radiotherapy and chemotherapy) in patients receiving beetroot (dietary nitrate/nitrite supplementation) and treatment for head and neck cancer

1.2 Secondary Objectives

- Quantify changes in strength, and body composition, before and following supplementation
- Determine feasibility of beetroot supplementation in head and neck cancer patients defined for each patient as the proportion of days successfully consumed supplement during treatment schedule
- Determine the toxicity of concentrated beetroot given in conjunction with radiation or chemo-radiation in SCCHN as measured by CTCAE v. 4.0
- Evaluate the trend in grade of mucositis during radiotherapy or chemoradiotherapy as measured weekly by CTCAE v 4.0
- Determine 1- and 2-year locoregional control rate and progression-free survival of subjects enrolled on this clinical trial.

2. BACKGROUND

2.1 Squamous Cell Carcinoma of the Head and Neck

Head and neck cancers are a group of geographically and biologically similar malignancies that originate in the upper aerodigestive tract, including the lip, oral cavity, nasal cavities, pharynx and larynx. The majority of these derives from the squamous mucosa, and often spread to regional lymph nodes of the neck, and subsequently to other distant sites. Head and neck cancer is strongly associated with tobacco exposure (both as smoking and chewing), alcohol consumption, and the human papillomavirus. Additional environmental exposures to various chemicals and dusts also predispose to head and neck cancer development, but are less common etiologies. These cancers are frequently aggressive in their biologic behavior, and some areas tend to present with more advanced disease, such as tumors which originate in the hypopharynx, as opposed to tonsillar or true vocal cord lesions, which tend to cause symptoms earlier in their course. Early-stage head and neck cancers have high cure rates with, though up to 50% of head and neck cancer patients present with advanced disease. As expected, cure rates decrease with more advanced disease cases, though patients with locally advanced disease, including those with regional nodal involvement, can still be cured with multimodality therapy. The most common regimen used in the setting of advanced disease is radiation 180 cGy of radiation given daily to a total dose of 6600 cGy to 7200 cGy with Cisplatin 100 mg/m2 every three weeks although cetuximab weekly is also given in the setting. Multimodality chemoradiation is toxic and approximately 50% of subjects in multiple clinical trials by the RTOG complete the prescribed radiation within 50 days. In addition, only 67% of subjects receive all three planned doses of chemotherapy and this has been shown to impact overall survival and local control. Similarly patients receiving significant dose of radiotherapy to the oral mucosa suffers similar delays and compliance issues. Improving the tolerance of radiotherapy and chemoradiotherapy in head and neck cancer is an important avenue of investigation. Data from the American Cancer Society indicate that in 2012, an estimated 52,510 new cases of head and neck cancer will be diagnosed, of whom 10,500 patients will succumb to their disease (1).

2.2 Reducing Toxicity to Therapy

In head and neck cancer patients, compliance with combined modality treatment is essential to improve clinical outcomes. It is well known that compliance to treatment ranges from 50-70% and that the use of PEG tubes supports improved treatment compliance and outcomes by improving nutrient intake. Despite these findings, improved effectiveness has plateaued secondary to mucositis and side effects of multi-modal therapy including chronic fatigue, loss of muscle mass, and body fat. Various interventions have attempted to ameliorate the side effects of therapy in an effort to improve compliance. Medical therapies such as amifostine for radioprotection of normal tissue, and bezydamine, palifermin, and GCSF to reduce mucositis have not shown significant benefit.

2.3 Concentrated Beetroot

Novel dietary supplementation strategies, proven helpful in other human studies, coupled with enteral support may serve as an inexpensive method to improve medical compliance, physical function/body composition, and quality of life. Looking beyond standard macronutrient supplementation, beet root may offer an innovative solution to improve compliance because it has been implicated as an effective ergogenic aid by improving endurance and strength. Moreover, due to the metabolism of its bioactive components, may interrupt the pathogenesis of mucositis. Beet root is gaining attention in the sport performance arena due to recent reports that supplementation improves exercise capacity, increases muscle contractile efficiency, and may elicit other cardiovascular benefits secondary to mediating the nitrate-nitric oxide metabolic pathway. Dietary nitrate from beetroot has been shown to reduce the oxygen cost of exercise and enhance muscle contractile efficiency by reducing the use of phosphocreatine and ATP utilization (2). Improved exercise capacity has been demonstrated through delayed time to exhaustion (3, 4), improved time trial performance (5-7), and reduced oxygen cost of exercise (3, 5, 8-11). Enhanced mitochondrial efficiency has been shown as well (8, 12, 13). Due to these significant muscle-related physiological changes observed in healthy/nitrate-sufficient subjects, it is plausible that improvements in physical function in a sick population that is nitrate (exogenous) deplete will be observed and that the active ingredients may have a significant impact on lean tissue preservation directly and indirectly (via increased mobility/QOL). Concentrated beet root also contains a unique class of strong antioxidants, known as betalains, which have been shown to inhibit lipid peroxidation and heme decomposition. Recently, beetroot has shown some promising results in head and neck cancer patients. Roszkowski, 2012 (14) recently supplemented beetroot chips to patients undergoing radiotherapy in an effort to learn if antioxidants from beets would influence parameters of oxidative stress and DNA damage. Their results indicated that beetroot did not worsen survival time and reduced intensification of acute radiation reactions while not influencing markers of oxidative stress/DNA damage. The authors suggested that beetroot supplementation may be a safe method for assisting medical therapy.

Due to a direct correlation between compliance with medical therapy and improved clinical outcomes, there is a need to investigate promising interventions that may increase patient compliance with combined modality treatment, while concomitantly preserving muscle function and fat-free mass to further augment therapeutic gains.

2.4 Nitric Oxide Pathway and Cancer Risk

In the past, there has been concern of the effect of exposure to dietary nitrates and nitrites and an increased risk of cancer. Indeed, the presence of nitrates and nitrites in food has been associated with an increased risk of gastrointestinal cancer in studies, predominantly the consumption of cured and processed meats (15). While associations of general dietary nitrite and nitrate consumption and cancer have guided the World Health Organization and others to recommend caution in ingestion, direct evidence of the negative effect on human carcinogenesis is lacking, despite extensive epidemiologic study (16). In addition, animal toxicological studies (17) have not conclusively established a relationship between nitrite exposure and the risk of cancer (18). The permissible concentration of nitrate in drinking water is 44 mg/L in the United States following World Health Organization recommendations 1970 and reaffirmed in 2004. More recent reviews have suggested a difference in nitrite and nitrate exposure from fruits and vegetables which are generally reported as beneficial to cardiovascular health and exercise tolerance. (19-21) In one recent review, Bryan et al, concluded that there is no significant correlation between nitrite or nitrate ingestion and gastric cancer risk (20, 22).

2.5 Rationale

The *objective* of the current proposal is to obtain pilot data to determine if concentrated beet root could potentially improve medical treatment compliance as defined by completion of radiotherapy or radiotherapy plus chemotherapy without dose reduction (primary outcome), and preserve fat-free mass, and strength while reducing mucositis (secondary outcomes). Our *central hypothesis* is that dietary nitrate/nitrite supplementation in head and neck cancer patients receiving aggressive medical care will improve compliance with medical treatment by attenuating the loss of muscle mass and strength and reducing symptoms (mucositis) associated with treatment compared to patients who do not receive dietary nitrate/nitrite supplementation. The rationale for this hypothesis is based on recent evidence that dietary nitrate supplementation improves measures of muscle strength, endurance, and performance capacity and the role nitrate may play in interrupting mucositis pathogenesis. Our *long-term goal* is to identify novel, nutrition intervention strategies to effectively reduce the negative side effects associated with chemotherapy and radiation that often impact therapeutic outcomes. Improvements in these outcomes will have a significant impact on augmenting the delivery of combined modal therapy and will contribute to improved quality of life.

Our working hypothesis is that beetroot supplementation will enable head and neck cancer patients to improve treatment compliance as defined by completion of radiotherapy or radiotherapy plus concurrent chemotherapy without dose reduction as compared to historic controls. The rationale for improved treatment compliance is based on expected improvements in strength, endurance and mucositis symptoms following beetroot treatment. These improvements are hypothesized to be greater in a head and neck cancer patient population presumed to be nitrate deficient.

3. PATIENT SELECTION

3.1 Eligibility Criteria

3.1.1 Patients must have a histologically confirmed malignancy of the head and neck (nasopharynx, oral cavity, oropharynx, hypopharynx, larynx, sinuses, skin or salivary gland) without distant metastatic disease and be planned to receive a continuous course of conventional external beam irradiation to at least 55 Gy of radiation to at least 2 mucosal sites with or without chemotherapy. Patients may have received induction therapy prior to definitive therapy for the current head and neck cancer.

3.1.2 Patients may have a history of prior 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.

3.1.3 Age ≥18 years.

3.1.4 ECOG performance status ≤2, see Appendix A.

3.1.5 Life expectancy of greater than 3 months

3.1.6 Patients must have normal organ and marrow function as defined below:

– leukocytes	≥3,000/mcL
– absolute neutrophil count	≥1,500/mcL
– platelets	≥100,000/mcL
– total bilirubin	≤ 1.5 times ULN (upper limit of normal)
– ALT and AST	≤ 2.5 times the ULN
– Creatinine	≤ 1.5 times ULN
OR	
– Measured creatinine clearance	> 60 mL/min

3.1.7 Able to swallow thin liquids or have a feeding tube for delivery of nutrition.

3.1.8 No uncontrolled illness including, but not limited to, any of the following:
- ― Ongoing or active serious infection
- ― Symptomatic congestive heart failure
- ― Unstable angina pectoris
- ― Uncontrolled cardiac arrhythmia
- ― Uncontrolled hypertension
- ― Psychiatric illness or social situation that would preclude compliance with study requirements

3.1.9 No other concurrent anticancer therapies or agents.

3.1.10 The effects of beet root on the developing human fetus are unknown. For this reason and because the subjects will be undergoing radiation and chemotherapy, women of child-bearing potential and men must agree to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry and for the duration of study participation. Should a woman become pregnant or suspect she is pregnant while 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 study participation, and 4 months after completion of beet root administration.

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

3.2 Exclusion Criteria

3.2.1 Active infection > CTCAE Grade 2, that is considered clinically serious by the treating physician.

3.2.2 Pregnant women are excluded from this study because chemo-radiation has 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 chemo-radiation, breastfeeding should be discontinued.

3.2.3 While there are no well documented drug-beet root juice interactions, HIV-positive patients on combination antiretroviral therapy are ineligible because of the potential for pharmacokinetic interactions with these drugs and beet root juice.

3.2.4 Subjects with a history of calcium oxalate nephrolithiasis are excluded.

3.2.5 Subjects with a significant history of malabsorption (e.g. celiac sprue, short bowel syndrome, or other, as determined by the treating physician) are excluded.

3.3 Inclusion of Women and Minorities

Both men and women of all races and ethnic groups are eligible for this trial. This study was designed to include women and minorities, but was not designed to measure differences of intervention effects. Men and women will be recruited with no preference to gender. No exclusion to this study will be based on race. Minorities will be actively recruited to participate.

Accrual Targets					
Ethnic Category	**Sex/Gender**				
	Females		**Males**		**Total**
Hispanic or Latino	0	+	1	=	1
Not Hispanic or Latino	8	+	26	=	34
Ethnic Category: Total of all subjects	8 (A1)	+	27	=	35 (C1)

Racial Category					
American Indian or Alaskan Native	0	+	0	=	0
Asian	0	+	1	=	1
Black or African American	1	+	2	=	3
Native Hawaiian or other Pacific Islander	0	+	0	=	0
White	7	+	24	=	31
Racial Category: Total of all subjects	8 (A2)	+	27 (B2)	=	35

4. REGISTRATION PROCEDURES

4.1 Protocol Review and Monitoring Committee and Institutional Review Board Review

Before implementing this study, the protocol, the proposed informed consent form and other information to subjects, must be reviewed by the Markey Cancer Center's Protocol Review and Monitoring Committee and the University of Kentucky Institutional Review Board (IRB). A signed and dated statement that the protocol and informed consent have been approved by the IRB must be maintained in the Markey Cancer Center Clinical Research Organization (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 and co-investigators of this study. Potentially eligible patients will be screened in the University of Kentucky Markey Cancer Center clinics by the investigators and study personnel. 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, mentioning 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 Institutional Review Board (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 Investigator's annual report to the IRB and copies of the IRB continuance of approval must 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

This is a non-randomized, pilot Phase II clinical trial that will determine the safety of concentrated beet root given in conjunction with radiation or radiation plus chemotherapy for locally advanced head and neck cancer. This trial will enroll 25 subjects taking beetroot supplement with up to an additional 10 standard of care subjects that refuse participation in the beetroot supplementation but are willing to obtain strength outcomes during their cancer treatment for a maximum of 35 patients.

5.1 Standard of Care Treatment Administration

All treatment will be administered on an outpatient basis. Adult subjects with head and neck cancer who are planned to receive a continuous course of conventional external beam irradiation delivered by intensity-modulated radiotherapy
(IMRT) as single daily fractions of 2.0 to 2.2 Gy, to a minimum cumulative radiation dose of 55 Gy to at least 2 mucosal will be recruited through Markey Cancer Center to undergo screening and testing. Approximately a 3:1 ratio of males to females will be recruited based on reported cases of head and neck cancer, although no preference will be given to either sex. Based on Kentucky's ethnicity statistics, we expect to have a Caucasian: African American ratio of 9:1, as ethnicity and race are not exclusion criteria. The population is readily accessible from this resource. We plan to

enroll patients who are primarily fed enterally by a percutaneous endoscopic gastrostomy (PEG) tube. Patients on "po" diets with thin (standard consistency) liquids are also eligible. Dr. Kudrimoti will initially identify patients who are eligible based on the aforementioned criteria. A research associate will then explain the study to eligible participants and provide a research flier. Interested volunteers will then complete the formal consenting process prior to participation with the research associate under the direction of Drs. Kudrimoti and Thomas.

5.1.1 **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.

5.1.1.1 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 55-70 Gy. 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.

5.1.1.2 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 a 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.

5.1.1.3 Radiation Therapy 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).

5.1.1.4 R.T. Quality Assurance Reviews

RTOG uses 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 QA committee will perform RT Quality Assurance Reviews for this trial.
Technical Factors, Localization, Simulation, and ImmobilizationPatients 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.

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.

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 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.

5.1.1.5 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.

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 non-involved 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.

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

5.1.2 Drug therapy

All systemic therapies are considered standard of care, and toxicities and dose modifications will be made by the treating physician based on institutional standards. Drugs are commercially available and are not considered investigational.

Patients Receiving Cisplatin or Cetuximab with Concurrent Radiation Therapy (RT)

Patients who receive cisplatin, will receive 100 mg/m2, administered intravenously every three weeks (with a three day window) as per institutional standard. Patients who receive cetuximab will receive a loading dose of 400 mg/m² given at least 5 days prior to radiation initiation and 250 mg/m² given weekly during radiation. Chemotherapy can be given either before or after the radiation therapy fraction that is given on the same day. If radiation is held for more than 2 days (for any reason), cisplatin may be held as well until radiation resumes. High dose cisplatin is a highly emetogenic regimen with significant incidence of delayed nausea and vomiting whereas cetuximab is less than that at Gen.. Institutional guidelines for anti-emetic regimens should be followed per physician preference and institutional guidelines. Supportive care guidelines will vary by drug type but are standardized at the Markey Cancer Center via standardized chemotherapy order sets and electronic medical record order entry for all patients.

5.1.3 Beetroot Administration

Study Supplements:
Subjects will be given 10 grams of concentrated organic beetroot crystals to mix with 120ml of water (BEETELITE™). Beetelite study supplement readily dissolve in water and may be given via gastrostomy tube or orally.

Daily Supplement Administration:
Subjects will begin daily supplementation following baseline measures (1-2 weeks before 7-week IMRT and for a minimum of 4 days) and will continue supplementation 4-6 weeks after treatment. Patients will be taught to self-administer their assigned study beverage by mouth and via PEG (as needed) by study staff during the baseline measurement period for the entirety of the trial. Patients requiring enteral support will be taught how to self-administer their assigned study beverage by a CRA or CRN. Compliance will be monitored by verbal assessment at clinic visits and by collection of written logs. Written instructions (Appendices E and F) for proper mixing of study beverage powders with water will be provided to both study volunteers and MCC staff involved in supplement administration and supervision. MCC staff will supervise the initial self-administration to ensure uniformity of ingestion. Subjects will be required to record the supplement intake in a dietary log which will be reviewed frequently at clinic visits.

Beetroot will be self-administered daily (M-F) at the same time each day during the afternoon hours (12pm-5pm) and if possible, should be dosed after radiation to promote a consistent administration/habit. IDS will provide pre-measured 10g portions of the supplement powder each week during the IMRT period. The patient will mix and administer, and will record that they took the product daily in the compliance log that will be brought back and assessed at clinic. If at any point during the 7-week IMRT treatment the patient is unable to self-administer, the patient's family or study personnel who are recognized as clinical providers (such as a CRN) will mix the water and powder and will aid in supplement administration if the patient wishes to continue with the study. Subjects will then be discharged with beetroot for daily dosage (M-F) throughout the post IMRT follow-up period. Standard PEG tube care guidelines will be followed and the tube will be flushed with 30 to 50mL of water before and after every supplement dose. For patients requiring supplement administration assistance at IMRT discharge, a family member or caregiver of the patient will be identified and taught to provide assistance during the MP-EP follow-up period. An additional copy of the written mixing/administration instructions will be provided at this time and study staff will offer additional instructional assistance as needed.

Subjects who vomit the beetroot within the first 15 minutes after administration may repeat the administration once that same day. If vomiting occurs greater than 15 minutes after administration, the dose should not be repeated. Vomiting will be closely monitored and additional supplement packets will be provided at discharge in case of vomiting.

Study volunteers will be asked to retain all used and unused study packaging on a weekly basis to turn in to study staff at the end of the week. Study packaging will be compared to the patient generated compliance log to document weekly compliance data. Subjects who are deemed "non-compliant" with the beetroot protocol (less than 3 consumed supplements during any 1 week period between baseline and midpoint measures) will be excluded in the per protocol analysis. Compliance to beet root consumption between midpoint and endpoint measure will be encouraged with weekly phone calls by nutrition graduate students supervised by Dr. Thomas. Dr. Thomas will oversee all aspects of the supplementation protocol. The Investigational Drug Service (IDS) at the University of Kentucky will assist with storage, supply management, quality control, and transfer of all beet root.

Bulleted supplementation administration guidelines for each study period are provided below:
Baseline and prior to IMRT enrollment (supplement initiation period):

- Following randomization, participants will be taught to self-administer their supplement by study personnel.

- The CRA or nutrition student will then distribute the supplement needed for the 1-2 weeks prior to IMRT to the participant.
- The supplement powder will be packaged in 10g portions by the IDS. Packaging will only be identified by the letter "A" or "B" and only IDS staff will be unmasked to supplement assignment.
- Participants will begin daily, single dose supplementation (M-F during the afternoon hours) on the first day of receiving their supplement from study personnel.
- Participants will be taught to mix their assigned powder with 120mL of water and self-administer within 30 minutes of mixing**.**
- Compliance during this time period will be encouraged by phone calls, a supplement "count," and with a patient generated supplement log sheet.

7-8 week IMRT treatment period (daily supplement observation period):

- Participants will be asked to continue daily (M-F) self-administration of the supplement. The pre-measured supplement powder will be provided to the participant on a weekly basis and patients will be asked to consume the supplement during the afternoon hours (M-F).
- At the beginning of treatment and throughout the IMRT period, study personnel will assess the need to provide additional education on proper self-administration of the study supplement (ex. Transitioning from PO feeding to enteral feeds).
- CRNs serving as study personnel may offer observation or administration assistance if patient requests this and may document supplement compliance.
- Patients will be instructed to make up any missed doses by taking up to 1 additional dose per day on the weekend days. Patients will receive 5 doses per week (for M-F) and will be instructed to never exceed 1 dose per day.

4-6 weeks post-IMRT (discharge period):

- After completion of IMRT the participant will be instructed to continue daily (M-F) self-administration (PO or PEG) until completion of endpoint measures.
- For patients requiring supplement administration assistance at discharge, a family member or caregiver will be identified and taught to provide assistance.
- On the day of discharge and during scheduled follow-up visits, the CRA will distribute the pre-measured supplement packets needed for daily administration.
- Participants will continue to follow the supplement mixing protocol and be reminded to consume their assigned supplement within 30-minutes of mixing.
- Supplement compliance will continue to be encouraged by weekly phone calls by study personnel and compliance logs/supplement counts will occur at least twice per month.

Supplementation on Testing Days

On testing days, The BEETELITE™ solution (beet root) will be administered on-campus 20-45 minutes before subjects undergo the baseline, midpoint (following IMRT), and endpoint (4-6 weeks following midpoint) strength/endurance measures. Prior to testing, subjects will not have to refrain from standard oral care, using antibacterial mouth wash, or chewing gum 48 hours before testing sessions because the BEETELITE™ product does not rely on salivation/oral bacteria to convert dietary nitrate to nitrite (23). Previous studies have administered up to 500mL of beet root per day with nitrate concentrations of 5.5 mMol (24), 6.2mMol (7, 25), 5.2mMol (26), and 5.1mMol (27). Plasma nitrite ($NO2^{-}$) levels in these aforementioned studies also increased following dietary nitrate supplementation.

5.1.4 Subjects will elect not to participate in beet root supplementation study

Subjects to elect not to participate in the beet root supplementation study will be asked to consider participation in an observational study of muscle strength testing that matches the muscle strength testing of those receiving beet root supplementation during their cancer treatment. These subjects will be performing cohort of non-therapeutic interventional subjects who will provide baseline information in a preliminary manner as a comparator to those subjects receiving beet root supplementation. This is not a randomization but rather utilization of subjects who would otherwise not be participating in the clinical trial. These subjects will be compensated for their time in a similar manner to subjects who are on the beat root supplementation study. A separate consent form will be used and a separate registration will be used for these patients.

5.1.5 Testing procedures at Baseline, Midpoint and Endpoint of therapy

All testing procedures, unless otherwise indicated, will be performed at the Markey Cancer Center (MCC) and the Center for Clinical and Translational Science (CCTS). Testing will occur at Baseline (Pre-IMRT), Midpoint (week number 7-8 following IMRT initiation), and Endpoint (4-6 weeks following Midpoint testing). A range of testing times at midpoint and endpoint are provided for subject convenience and flexibility with medical follow-up appointments. Primary outcome measure: 1) IMRT treatment compliance- No delays in treatment of radiation and/or chemotherapy (Cycles: Namely 35 fraction of daily radiation therapy (Monday-Friday) with 100 mg/m^2 cisplatin on days 1, 21, & 43. Total duration of therapy = 50 days). Treatment compliance will be defined as completion of all radiotherapy or completion of all radiotherapy plus prescribed chemotherapy without dose reduction or delay of radiation therapy that would extend treatment beyond 50 days.; Secondary outcome measures: 1) muscle strength/function, 2) serum/salivary nitrate/nitrite, 3) preservation of fat-free mass (CT/DXA), 4) mucositis symptoms, 5) nutrition assessment, 6) quality of life g. Details of each test are provided in section 9.0.

5.1.6 General Testing Procedures and Blinding

A trained CCTS exercise physiologist will complete DXA, Biodex strength/endurance measures, and handgrip dynamometry under the direction of Drs. Thomas and Clasey. CT measures will be performed by trained MCC staff at baseline, midpoint and endpoint, and will be overseen by Dr. Clasey. Quality of life (FACT H/N version 4) assessment will be administered by the study exercise physiologist. Assessment for toxicity to radiotherapy or chemoradiotherapy and mucositis assessment will be completed on a weekly basis by Dr. Kudrimoti and will serve as a safety measure. Nutrition intake will be collected during clinical status checks by a trained clinical nutrition graduate student under the direction of Dr. Thomas.

5.1.7 Testing Order

As part of a scheduled medical visit, computed tomography (CT) scans at the MCC will be the first measurement completed on testing days unless a medical scheduling conflict requires rescheduling (within 7 days of other time point measures). Following CT measures, subjects will be transported via wheelchair by the CRA to the CCTS for QOL assessment and total body dual energy x-ray absorptiometry (DXA) scanning. The study supplement will then be self- administered at a discrete location. At 25 minutes post supplementation, plasma will be collected to measure nitrate/nitrite content. At 30 minutes post supplementation, saliva will be collected to measure salivary

nitrate/nitrite content. At approximately 35 minutes post supplementation, Biodex strength and endurance assessments will be initiated (knee extensors) followed by hand-grip dynamometry approximately 60 minutes post supplementation in the Multidisciplinary Science Building (MDS). All secondary outcome measurements (with the exception of CT) will be completed at the 3 aforementioned time points.

Management and dose modifications associated with the above adverse events are outlined in Section 6.

5.2 General Concomitant Medication and Supportive Care Guidelines

Patients will undergo clinical toxicity assessment on a weekly basis in the clinic. Toxicity assessment will be made as per the CTCAE version 4.0 as assessed by medical and radiation oncology physicians. All toxicities and their attribution will be recorded, regardless of attribution. Of particular interest will be toxicities that are possible, probable or definitely related to administration of beet root, as determined by the treating physician or related to acute radiation toxicities of: mucositis, radiation skin reaction, radiation pneumonitis, or dry mouth. Staging of tumors will be done as per the multidisciplinary head/neck team using AJCC staging manual version 7. The response to treatment will be made by repeating clinical and radiological studies as per standard of care (6- 12 weeks) and repeated during follow up as per NCCN guidelines. Patients will be followed until resolution of all grade 2 or greater toxicities.

Supportive Care:

Mucositis:

If patients require supporting care for mucositis-related pain during concurrent chemotherapy and radiation treatment, the following regimen is recommended, but the local standard of care is permitted.

- A compound containing viscous lidocaine and magnesium aluminum oxide (Maalox®) or sucralfate;
- Liquid or solid oxycodone, 5-10 mg, every 3-4 hours as needed.

Nutritional Support:

Patients may take nutritional supplements (i.e. protein/kcal), such as Ensure®, but should refrain from other nutritional supplements (i.e. nutraceuticals). Patients may take appetite stimulants as prescribed by treating physicians. Feeding tubes are encouraged to prevent malnutrition.

Febrile neutropenia will be managed according to accepted guidelines. Measures may include appropriate laboratory testing, including blood and urine cultures. If a source for the fever is not identified or the fever resolves when the neutrophil count recovers, antibiotics may be discontinued and the patient observed.

Antiemetics: Antiemetics may be necessary. The use of antiemetics is encouraged to prevent dehydration. The specific drugs will be left to the treating physician's discretion.

Other Concomitant Medications: Therapies considered necessary for the wellbeing of the patient might be given at the discretion of the investigator. Other concomitant medications should be avoided except for analgesics, chronic treatments for concomitant medical conditions, or agents required for life-threatening medical problems. All concomitant medications, including over-the-counter and/or alternative medications, must be recorded.

Other Anticancer or Experimental Therapies: No other anticancer therapy (including chemotherapy, radiation, hormonal treatment or immunotherapy) of any kind is permitted during the study period. No other drug under investigation may be used concomitantly with the study drug.

Treatment For Diarrhea: Diarrhea should be treated promptly with appropriate supportive care, including loperamide. Instruct patients to begin taking loperamide at the first signs of: 1) poorly formed or loose stool, 2) occurrence of more bowel movements than usual in one day, or 3) unusually high volume of stool. Loperamide should be prescribed in the following manner: 4 mg at first onset of diarrhea, then 2 mg after each unformed stool. Daily dose should not exceed 16 mg/day. Loperamide should not be taken prophylactically. Advise patients to drink plenty of clear fluids to help prevent dehydration caused by diarrhea. Avoid loperamide if there is blood or mucus in the stool or if diarrhea is accompanied by fever. If grade 3 or 4 diarrhea develops, discontinue further treatment until the diarrhea has recovered to grade 1 or less. Although unlikely, in the event that fatigue is encountered, medications such as modafinil and methylphenidate may be used at the investigator's discretion.

5.3 Duration of Therapy

Subjects will be removed from study if one of the following occurs:

- Subjects who do not complete at least 50% of the planned medical therapy
- Intercurrent illness that prevents further administration of medical 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.

5.4 Duration of Follow Up

The response to treatment will be made by repeating clinical and radiological studies as per standard of care (at 6-12 weeks) and repeated during follow up as per NCCN guidelines. Patients will be followed until resolution of all grade 2 or greater toxicities.

5.5 Criteria for Removal from Study

Patients will be removed from study when any of the criteria listed in Section 5.4 applies. The reason for study removal and the date the patient was removed must be documented in the Case Report Form.

6. DOSING DELAYS/DOSE MODIFICATIONS

The following dosing delays and dose modifications refers only to adverse events which are **at least possibly related** to beetroot juice. When grade 3 and 4 toxicities are encountered and are possibly, probably or definitely related to beetroot juice, please use the following dose reduction table.

Event	**Management/Next Dose for *Beet Root***
≤ Grade 1	*No change.*
Grade 2	No change

Event	**Management/Next Dose for *Beet Root***
Grade 3 or 4	Hold until recovery to grade 2 or less, then decrease to Monday-Wednesday-Friday dosing

Exceptions to this procedure include: any grade alopecia and grade 3 or 4 fatigue.

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 Mandatory Medwatch Forms 3500a) **in addition** to routine reporting in OnCore.

7.1 Adverse Event List(s) for Concentrated Beet Root

BEET ELITE™ is an oral concentrated beet root dietary supplement and not specifically FDA approved. Since BEET ELITE™ is not a drug, there is no Investigator Brochure. This supplement will be obtained from Neogenis® Labs, Inc., Austin, Texas. The BEET ELITE™ product is made from organic beet root crystals, natural flavors, malic acid, and stevia extract and is manufactured in a GMP certified facility. The concentration of the shot is equivalent to 6 beets in one shot.

Beet Root Toxicities:
Potential adverse effects of beet root are rare and include: stomach cramping/diarrhea, pink coloration of urine and stools, and allergic reactions. These side effects are consistent with events that may occur with normal beet consumption (as a food). There have been no reports of mucosal injury in the head and neck, or irritating effect on the oral mucosa.

Methemoglobinemia has been reported in infants who have consumed high levels of nitrate, but these findings have largely been discredited due to confounding cases of gastroenteritis and co-ingestion of sodium nitrite (from contaminated well water). Methemoglobinemia has not been documented in adults consuming nitrates at the level proposed in this trial. Given the oxalate content of beet root (28), caution should be taken for individuals with a history of nephrolithiasis or gall bladder dysfunction.

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 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 where MCC investigator holds the IDE or IND	• 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 consent)	OnCore and DSMC reporting only	Mandatory Medwatch 3500a for Serious and unanticipated OnCore for all AEs, including SAEs	Yes if it meets the IRB reporting requirements: Unanticipated Problem and/or Serious AE (use IRB AE reporting form for all correspondence with IRB)

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.

Attribution	MCC Reportable AEs				
	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

N/A

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.

7.4.1 **Expedited Reporting to the Food and Drug Administration (FDA)**

The Overall PI, as study sponsor, will be responsible for all communications with the FDA. The Overall PI will report to the FDA, regardless of the site of occurrence, any serious adverse event that meets the FDA's criteria for expedited reporting following the reporting requirements and timelines set by the FDA.

7.4.2 **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.

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

8. PHARMACEUTICAL INFORMATION

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

8.1 Beet Root Juice

8.1.1 List of Supplement Ingredients

- Ingredient List: Organic Beetroot Crystals, Natural Flavors, Malic Acid and Stevia Leaf Extract
- Neogenis® Labs is not able to release proprietary information that describes the specific formulation because of product competitors and privacy issues.

8.1.2 Beet Root Juice (BEET ELITE™) Product Description

Product description: BEET ELITE™ is an oral concentrated beet root dietary supplement. One 10g packet contains both nitrate and nitrite. Typically, only about 5% of beet nitrates are metabolized to active intermediates taking at least 90 minutes. BEET ELITE™ is a revolutionary formula that includes a natural form of nitrite, thus bypassing the inefficient nitrate reduction process. BEET ELITE™ begins working in 15 minutes and has the Nitric Oxide content of 6 beets in one shot. The recommended dose is typically one shot per day. Product is available through Neogenis® Labs, inc., and is available online as a dietary supplement.

8.1.3 Solution preparation:

BEET ELITE™ products are individually packaged in 10g packets and must be mixed with 120ml of water and consumed within 30 minutes of mixing. Participants will be taught to prepare and self-administer their assigned study supplement and IDS will provide participants with the water and powder packet during the IMRT treatment period.

8.1.4 **Route of administration:**

BEET ELITE™ products will be self-administered throughout the entire study period via enteral

tube (PEG) or by mouth as a thin liquid (PO). Participants will be asked to take this product mixed with water (120ml) daily (M-F) without supervision. Participants will be instructed to administer BEET ELITE™ in the afternoon hours by mouth or by using their PEG tube in accordance with standard PEG feeding tube guidelines. Participants should flush their feeding tube with 30-50mL of water before and after supplementation. This supplement can be served cold or at room temperature within 30 minutes of mixing and may be tolerated best at room temperature if given enterally.

8.2 Labeling:

8.2.1 **BEETELITE Labeling**

Below is a copy of the container label for a single dose NEoShot product.

Nutrition Facts

Serving Size: 1 pack (10g)
Servings Per Container: 10

Amount Per Serving		% Daily Value*
Calories 30	Calories from Fat 0	
Total Fat	0 g	0%
Sodium	15 mg	0%
Potassium	170 mg	2%
Carbohydrates	8 g	1%
Sugars	7 g	
Protein	0 g	

Not a significant source of saturated fat, trans fat, cholesterol, dietary fiber, Vitamin A, Vitamin C, Iron and Magnesium.

*Percent Daily Values are based on a 2,000 calorie diet.

8.2.2 **The following label will be used for the study medication**

NAME: PATIENT NO:
PI: Dr. D. THOMAS DATE:

Mix with 120mls of water and take by mouth
or via PEG daily as directed. PROTOCOL:13–HN–23–MCC
NEoShot or PLACEBO POWDER 10GM
(Store between 59–86 F) Sponsor:Markey Cancer Center
Caution: New Drug–limited by Federal Law
to investigational use

9. BIOMARKER, CORRELATIVE, AND SPECIAL STUDIES

CCTS testing procedures are described below in the planned order of occurrence on testing days:

9.1 Assessment of Body Composition and Quality of Life

9.1.1 Computed Tomography (CT)

Immediately following or preceding radiation simulation (Correlative Day 1) radiation treatment (Correlative Day 2) and follow-up period (Correlative Day 3) at the Markey Cancer Center, subjects will be transported to the ground level of Markey by MCC staff for CT measures. Computed tomography (CT) images (GE large bore 16 slice) will be used to quantify skeletal muscle and fat area of the right and left thighs, and the right and left forearms of each subject using 100mA with a scanning time of 3 s and a 512 X 512 matrix. With the subject supine, one 10 mm thick cross-section scan of both legs will be taken corresponding to the midpoint between the inguinal crease and the proximal border of the patella, and one 10 mm thick cross-section scan will be taken corresponding to 2/3 the distance from the styloid process of the radius to the olecranon. Tissue area quantification will be determined using corresponding attenuation values of ≥200 HU; -190 to -30 HU; and 0-100 HU for bone, adipose tissue, and skeletal muscle, respectively using available software (NIH ImageJ; http://rsbweb.nih.gov/ij/). Total thigh fat will be further subdivided into two compartments including the fat above the fascia late (subcutaneous thigh fat) and below the fascia lata (deep thigh fat). In addition, the skeletal muscle will be subdivided into areas of low attenuation (0-34 HU) representing “fat-rich” muscle, and high attenuation values (35-100 HU) representing muscle with normal fat content. While the forearm scan methodology is unique and has been developed specifically for this study, the method of analyzing thigh composition has been previously described (9). All CT scans will be assessed under the direction of Dr. Jody Clasey.

9.1.2 Quality of Life

Following CT measures at Markey, subjects will be transported to the CCTS for Quality of Life and DXA measures. Quality of life (FACT H/N version 4) assessment will be administered by the CCTS exercise physiologist (Mr. Long) during set-up for the DXA scan. This is a 5 minute survey that can easily be administered by the technician while the DXA scan is calibrated. This survey will be completed at baseline, midpoint, and endpoint by the same DXA technician prior to the DXA scan.

9.1.3 Dual-Energy X-ray Absorptiometry (DXA)

Total body DXA scans will be performed using a GE Healthcare Lunar iDXA (Lunar Inc., Madison, WI) bone densitometer. The subjects will be instructed to remove all objects such as jewelry or eyeglasses and will wear only a standard hospital gown or t-shirt and shorts containing no metal during the scanning procedure. All scans will be analyzed by a trained investigator using the GE Healthcare Lunar Encore software version 14.10. Total body and regional DXA bone mineral content (g), DXA bone mineral density (g/cm2), DXA fat-free mass (FFM; kg), DXA fat mass (kg), and DXA mineral-free lean mass (kg), and DXA percent fat (DXA %Fat) will be assessed.

9.2 Blood and Saliva Collection for Plasma Nitrate, Nitrite and 25(OH)D, and Saliva Nitrate and Nitrite Measures

Following the DXA scan, participants will remain in the CCTS for blood and saliva collection by trained CCTS phlebotomists (will occur between25-30 minutes post supplement administration on all testing days). Venous blood samples (~8mL) will be drawn into lithium-heparin tubes (low nitrate/nitrite). Within 3 minutes of collection, samples are centrifuged at 4,000rpm at 4C for 10 minutes. Plasma will be extracted and immediately frozen at -80C for later analysis of plasma nitrate (NO_3^-) and nitrite (NO_2^-) at the end of the study period.

Saliva will be collected by study personnel at 30 minutes post supplement administration. Subject will generate saliva and place in a collection tube. Sample saliva (200µL) will be taken from the tube and placed in a separate tube. Sample will be vortexed and centrifuged for 10 minutes. Supernatant will be removed and stored at -80C for shipment and later analysis.

9.3 Assessment of Muscle Strength and Endurance

Upper body muscle strength and endurance will be assessed by the CCTS exercise physiologist using a handgrip dynamometer (29) and overseen by Drs. Clasey and Thomas at all three study time points. Strength and endurance measures will be collected after the blood draw and will not occur more than one hour following testing day beet root administration or at the time of arrival in the unit for the observational cohort. Strength will be determined for both the dominant and non-dominant hands using peak force determination from 3 trials. Determining the absolute and relative decline in contractile force at 30, 60, and 90 sec of sustained contraction will assess muscular endurance. Lower body strength and endurance will be assessed by completing a one-legged MVC using a Biodex isokinetic machine.

9.3.1 Isokinetic Strength and Endurance Testing

Before the start of maximal isokinetic force (strength) testing, the participant will be instructed on proper lifting and breathing techniques. Isokinetic strength at 60^0 per second will be determined in the subject's dominant leg in a seated position with knee and hip angulation of 60^0 and 120^0 degrees respectively. During this time, subjects will be provided with strong verbal encouragement and provided with visual feedback of torque on a computer monitor to help with achievement of their best effort. To minimize the use of muscles other than the knee extensors, participants will be stabilized with two shoulder straps, and a waist strap. Strength will be recorded as the highest force generated during one set of 3-4 trials starting at a knee angle of 90^0. Before recording the maximal effort, 3 trials will be given at a moderate intensity to provide for further muscle warm-up. A two minute rest period will be given between each strength trial. Following isokinetic strength testing of the dominant leg, endurance and fatigability will be assessed by having the participant complete 25 reps at an angular velocity of 240^0 per second followed by another strength trial. The fall in peak torque and power will be used to calculate fatigability and endurance capacity of the muscle.

9.3.2 Handgrip Strength

Subjects will use a handgrip dynamometer for the assessment of handgrip strength in their dominant and non-dominant arm. The participant will be in a standing position, arms at their side, not touching their body, and elbow bent slightly. The participant will squeeze the dynamometer with as much force as possible, being careful to squeeze only once for each measurement. Three trials will be made with a pause of about 10-20 seconds between each trial to avoid the effects of muscle fatigue. Each trial will be recorded to the nearest pound or kilogram. If the difference in scores is within 6.6 lbs. or 3 kgs., the test is complete. If the difference between any two measures is more than 6.6 lbs. or 3 kgs., then the test will be repeated once more after a rest period.

9.4 Diet and nutrition status monitoring

Nutrition intake data will be collected randomly within a two week period at baseline and midpoint and will not be scheduled on CCTS testing days. All nutrition data collection and management procedures will be overseen by Dr. Thomas in collaboration with the MCC registered dietitian.

Twenty four hour dietary recalls will be collected in-person twice at baseline and midpoint (4 total 24-hr recalls per subject) by a nutrition graduate student trained in dietary assessment. During clinical status checks/chemo visits at the MCC, participants will be asked to report their food and beverage intake (enteral and/or by mouth) over the previous 24-hours. The Nutrition Data System for Research software (NDSR version 2012, Minneapolis, MN) will be used to organize and assess all dietary data collected. NDSR uses the multiple-pass method to help improve the validity of dietary data. This method is a standardized recall strategy that refers to the number of times a participant's food intake is reviewed during the interview in - an effort to improve recall accuracy (10, 11). Enteral feeding regimens during the 7 week IMRT period will also be monitored closely with clinical progress notes and communication with the MCC registered dietitian to document feeding interruptions, change in formula type, volume, and tolerance. Subjects will also provide a daily beet root juice intake diary (Appendices C and D) and side effect profile. A comprehensive summary of nutrient analysis reports will be generated for all participants.

9.5 Other Study Measures Occurring Weekly

9.5.1 Mucositis

Severity of mucositis will also be evaluated and documented by the treating radiation oncologist, who will be blinded to the group assignment, according to the CTCAE v. 4.0 (Appendix B).

10. STUDY CALENDAR

10.1 Baseline Evaluations/Assessments

Baseline evaluations must be done ≤ two weeks prior to protocol therapy, except for radiologic assessments, which must be performed < 21 days prior to the initiation of therapy. The "on-study" tumor assessment can be from archival material.

10.2 Calendar for Beetroot Supplementation Cohort

Timepoints	Baseline	Weekly during Concurrent Radiation and Cisplatin	Midpoint (After IMRT)	Endpoint (4-6 weeks following Midpoint testing)	Off-treatment	Off study
Studies:						
H&P[1] VS	X	X	X	X	X	X
TOX	X	X	X	X		
Pregnancy Testing	X					
Muscle Strength and Endurance Testing	X		X	X		
Body Composition (DXA)	X		X	X		
Plasma/Salivary Nitrate/Nitrite	X		X	X		
QOL and Mucositis	X		X	X		
Diet	X		X			
Ct SCAN (body comp)	X		X	X		
Routine Cancer Imaging[2]	X			X		X
Treatments:						
Beet Root (daily) [3]	X	X	X	X		

1) Abbreviations: H&P=History and Physical examination; PS=ECOG performance status; VS=vital signs (blood pressure, temperature, pulse and respiratory rates, weight and height); TOX=toxicity assessment

2) Routine cancer imaging will be standard of care CT or MRI scans to document disease and response to therapy. These will be required pre-treatment, post-chemoradiation and at 1- and 2-year follow-up (+/- 6 weeks), as per standard of care.

3)Beet root will be self-administered each day (M-F in afternoon)

4)Toxicity will be followed for all patients until (endpoint) testing. Any beetroot related toxicity > grade 2 will be followed until resolution to grade 1 or less.

10.3 Calendar for Observational Cohort

Timepoints	Baseline	Weekly during Concurrent Radiation and Cisplatin	Midpoint (After IMRT)	Endpoint (4-6 weeks following Midpoint testing)	Off-treatment	Off study
Studies:						
Muscle Strength and Endurance Testing	X		X	X		
Body Composition (DXA)	X		X	X		
Plasma/Salivary Nitrate/Nitrite	X		X	X		
QOL and Mucositis	X		X	X		
Ct SCAN (body comp)	X		X	X		

11. MEASUREMENT OF EFFECT

11.1 Toxicity

For the purposes of this study, patients receiving beetroot supplement will be re-evaluated for toxicity as listed above and weekly during radiation as per institutional standard. All subjects receiving beetroot supplement will be evaluated for toxicity from the time of their first treatment with beet root to the end of study. Subjects will also be required to record each dose of beet root juice, including date and time, and subjective side effects (i.e. nausea, diarrhea, allergic reactions) noted after each dose. Subjects receiving only muscle strength testing will not be followed for toxicity as they receive standard of care and supportive medications as per routine. These subjects are not considered to be part of the interventional study but certainly serve as a baseline observational cohort.

11.2 Antitumor Effect – Solid Tumors

Response and progression are not the primary endpoints of this study, however, response and progression will be evaluated in this study using the new international criteria proposed by the revised Response Evaluation Criteria in Solid Tumors (RECIST) guideline (version 1.1) [*Eur J Ca* 45:228-247, 2009]. Changes in the largest diameter (unidimensional measurement) of the tumor lesions and the shortest diameter in the case of malignant lymph nodes are used in the RECIST criteria.

11.2.1 Definitions

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

Evaluable for objective response. Only those 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.

11.2.2 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 by chest x-ray or as ≥10 mm 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 in short axis when assessed by CT scan (CT scan slice thickness recommended to be no greater than 5 mm). At baseline and in follow-up, only the short axis will be measured and followed.

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

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

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

11.2.3 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 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 or less. If CT scans have slice thickness greater than 5 mm, 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.

11.2.4 Response Criteria

11.2.4.1 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.

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

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

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

11.2.4.2 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 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 Principal Investigator).

11.2.4.3 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

11.2.5 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.

11.2.6 Progression-Free Survival

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).

12.1.1 Method

This study will be monitored by the Markey Cancer Center Data and Safety Monitoring Committee. Adverse event and quality assessment will be submitted to DSMC using electronic case report form in OnCore.

12.1.2 Responsibility for Data Submission

Study CRA's and investigators are responsible for submitting data and/or data forms to OnCore. The date for submission to OnCore will be set by the CRDM SRF. The OnCore Management staff is responsible for compiling and submitting study data to DSMC for all participants and for providing the data to the Principal Investigator for review.

13. STATISTICAL CONSIDERATIONS

13.1 Study Design/Endpoints

This non-randomized, pilot study plans to enroll 35 total patients with previously untreated squamous cell cancer of the head and neck. As the goal of this study is to obtain preliminary data regarding current standard therapy compliance rates for this patient population at the University of Kentucky Markey Cancer Center and assess feasibility of an additional beet juice supplementation during therapy, the primary objective is to estimate treatment compliance defined as completion of radiation alone or radiation and chemotherapy with beet root supplementation during primary treatment. Treatment compliance is defined in more detail in section 5. Secondary objectives to obtain pilot estimates for cancer specific outcomes such as response rate, adverse events, mucositis rates, and 1 and 2 year locoregional control rates and progression-free rates Additional secondary

measures will include strength measures, CT scans, quality of life surveys, nitrate/nitrite levels, endurance testing, handgrip strength, and Body Composition DXA variables of interest (Bone Mineral Density, Bone Mineral Content, Area, % fat). Beet juice rates of completion will also be estimated to assess feasibility of this product.

13.2 Sample Size/Accrual Rate

The primary endpoint of this study is treatment compliance, for the chemoradiation strata defined as completion of radiotherapy and 3 cycles of chemotherapy with no treatment delay with published historical rates average around 52.1% (30). For those receiving radiation alone, we predict higher compliance rates closer to 70% as these patients tend to experience less mucositis and adverse events during treatment. We anticipate 60% of patients will receive radiation alone versus 40% receiving chemoradiation. 25 total patients (10 – chemoradiation, 15 – radiation alone) receiving beet root supplementation, will result in 90% confidence intervals around each estimated compliance rate with a maximum widths of +/- 27.75% and 22.85% for chemoradiation and radiation alone respectively. The combined estimate of compliance will still have a 90% confidence interval estimate with a maximum width of +/- 17.7% as previously designed. For the 10 subjects in the observational cohort not receiving beet root supplementation, we will still be able to estimate compliance rates +/- 27.75% and obtain pilot data regarding strength outcomes during standard of care therapy. This design is not powered to compared compliance rates between treatment strata or beet root versus standard of care; instead it allows us to gain preliminary information about these rates with a certain amount of precision as pilot data for a larger, more definitive study. We plan to accrue patients over a 2 year period.

There will be a pre-specified safety consideration after half of the planned enrollment in the beet root supplementation (interim after 13) to verify acceptable treatment completion rates as compared to a published historical rate of 52.1%. Two prior beta distributions (non-informative and null-hypothesis based) will be considered with patient information collected from the first 13 enrolled in beet root arm to calculate the posterior probability that the mean proportion of successful completion is less than or equal to historical rates of 52.17% with corresponding 90% credible intervals. The study team will reconsider continuation of the protocol due to safety and feasibility concerns if either arm has a high probability of experiencing a success rate lower than published rates.

13.3 Data Analysis

Following study completion, primary data analysis will include estimation of subjects achieving treatment compliance along with corresponding exact 90% binomial confidence intervals.

Other secondary endpoints listed in section 13.1 will be primarily descriptive as they are exploratory in nature; however means and standard deviations (or N and percentages where appropriate) will be estimated and summarized for each time point to gain more information of expected effect size differences between standard therapy and BR arms. Repeated measures ANOVA will be utilized to test for exploratory differences in these various measures over time points between BR and standard therapy arms. Kaplan-Meier curves will be presented for locoregional control and progression-free survival along with 90% confidence interval bounds. Exploratory log rank tests will be performed to assess for any preliminary differences in these survival outcomes by treatment arm.

13.4 Reporting and Exclusions

13.4.1 Evaluation of Toxicity

All subjects on beet root supplementation will be included in the safety analysis, with toxicities graded according to NCI CTCAE v4.0. Incidence tables will be generated to summarize incidence of patients reporting at least one episode of each specific 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. This will also capture all incidence and severity of mucositis during the duration of this study.

13.4.2 Evaluation of Outcomes

All patients included in the study will be assessed for treatment compliance, even if there are major protocol treatment deviations or if they are ineligible. All of the patients who met the eligibility criteria (with the possible exception of those who received no study medication) will be included in the intent to treat analysis for the primary completion endpoint as well as all secondary outcomes.

Due to concerns of potential non-compliance of taking all beet supplements over the course of primary treatment, a per protocol analysis will also be performed for all patients that consume at least 3 servings of the required beet supplements per week. Percentage of beet supplements taken will also be reported as part of this subgroup analysis.

13.5 Data Management

All cancer treatment related data, adverse events, and compliance with BR supplementation will be stored in the OnCore Data Management System of the Markey Cancer Center, as well as all strength measurements, body composition (CT and DXA), and quality of life surveys. Case report forms will record all study endpoints and data will be accessed in a secure manner using this password protected, encrypted software. The study statistician, along with staff from the Biostatistics Shared Resource Facility (BSRF), will work closely with the study PI and the MCC CRO staff on the development of eCRFs for the study. Instructions for data entry will be listed in Study-Specific Data Management Plan created by CRO staff in conjunction with the study statistician. The OnCore database is housed on secure servers maintained by the Cancer Research Informatics Shared Resource Facility (CRISRF) of Markey Cancer Center. The database is backed up daily.

Each subject will be assigned a sequence number at time of study entry through the OnCore system. This same sequence number will be distributed to study personnel at CCTS and utilized for all data. Data will be accessed by the study statistician via OnCore on a regularly scheduled basis to perform statistical programming to assess data quality control, study recruitment and to generate interim reports and analyses. In collaboration with the study team, procedures and timelines will be developed for data quality control, resolution of data queries, interim reporting and final data analysis.

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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

CTCAE version 4.0:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.ht

APPENDIX C

Patient Name:_____
Patient ID#:_____
Date Range:___/___/_____ to ___/___/_____

Weekly Supplement Log

Instructions for the participant: This is a weekly log on which you are to record each supplement dose you take. For each dose write down the day, time and amount consumed (only fill out if supplement is mixed with water). Bring the log and all supplement packaging with you to your next scheduled supply pick-up.

Dose Number	Day (Example: Monday)	Time (Example: 12:00pm)	Amount Consumed (percent drank: 50%, 100%)	How was it taken (mouth or tube)
1				
2				
3				
4				
5				

Did you vomit up your supplement within 15 minutes of taking it on any day? If yes, how many days? _____
Did you retake the supplement each time? If yes, how many times did you retake it? _____
_____

Patient Initials:_____ Date:_____

Section to be completed by research personnel:
Distribution Date:___/___/_____ Return Date:___/___/_____
Total Bags Returned:_____ Number of Empty Bags:_____
Comments:_____
_____
_____

_____ _____
Signature (Research Personnel) Date

APPENDIX D

Patient Name:________________
Patient ID#:________________
Date Range:___/___/_____ to ___/___/_____

Monthly Supplement Log

Instructions for the participant: This is a monthly log on which you are to record each supplement dose you take. For each dose write down the dose number, time and amount consumed as a percent (only write down if supplement is mixed with water) under the day you had it. For example, write down: Dose 1, 12pm and 50% if you drank half of the supplement. Bring the log and all supplement packaging with you to your next scheduled supply pick-up.

Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube
☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube
☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube
☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube
☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube	☐ Mouth ☐ Tube

Did you vomit up your supplement within 15 minutes of taking it on any day? If so, how many days? ________________

Did you retake the supplement each time? If not, how many times did you retake it? __________ _______________

Patient Initials:________________ Date:______________

Section to be completed by research personnel:
Distribution Date:___/___/_____ Return Date:___/___/_____
Total Bags Returned:__________ Number of Empty Bags:__________
Comments:____
____

____________________________ ____________________
Signature (Research Personnel) Date

Beetroot Juice Supplement Instruction Sheet (by stomach tube)

1. Mix the supplement powder with 4-8 oz of water only.

2. Do not mix the powder with anything other than water or more than 8 oz of water.

3. You may pour water into a glass and add in the powder or place the powder in a small bottle of water to pour in the tube.

4. Flush the tube with a small amount of water before and after administration of the supplement according to your physician's guidelines.

5. Pour the entire supplement within 2-3 minutes so it is all in the stomach at the same time.

6. On your supplement log write down the day (example: Monday), dose number (example: 1), approximate time you mixed the powder (example: 9:00am), and how much you administered (as a percent, example: 100%).

7. Administer the supplement between afternoon hours of 12-5pm.

8. The supplement is meant to be taken on weekdays (Monday-Friday).

9. If a dose is forgotten, take as soon as you remember that day. Then resume the supplement schedule the next day.

10. Do not consume more than 1 dose in 1 day. However, if you vomit the dose within 15 minutes of putting it in your PEG tube, you may repeat the dose once that day (after recovering from vomiting and nausea).

11. If 1 dose is missed during the week, you can take the missed dose on Saturday.

12. If 2 doses are missed, you can take them on Saturday and Sunday.

Beetroot Juice Supplement Instruction Sheet (by mouth)

1. Mix the supplement powder with 4-8 oz of water only.
2. Do not mix the powder with anything other than water or more than 8 oz of water.
3. You may pour water into a glass and add in the powder or place the powder in a small bottle of water to drink.
4. Swallow as fast as possible within 2-3 minutes so it is all in the stomach at the same time.
5. On your supplement log write down the day (example: Monday), dose number (example: 1), approximate time you mixed the powder (example: 9:00am), and how much you drank (as a percent, example: 100%).
6. Consume the supplement between the afternoon hours of 12 and 5pm.
7. The supplement is meant to be taken on weekdays (Monday-Friday).
8. If a dose is forgotten, take as soon as you remember that day. Then resume the supplement schedule the next day.
9. Do not consume more than 1 dose in 1 day. However, if you vomit the dose within 15 minutes of swallowing it, you may repeat the dose once that day (after recovering from vomiting and nausea).
10. If 1 dose is missed during the week, you can take the missed dose on Saturday.
11. If 2 doses are missed, you can take them on Saturday and Sunday.

APENDIX G

Mucositis scoring

PROTOCOL ID: IDR-OM-01

Site Number: ___ ___ Subject ID Number: ___ ___ ___ Assessment Date: ___ ___ / ___ ___ ___ / ___ ___ (D D / M M M / Y Y)

Assessment Type *(mark only one)*: ☐ Baseline ☐ IMRT Visit, Week ____ Visit ____ ☐ End of Treatment (EOT)

☐ Post-IMRT Week ____ ☐ Initial Follow-up (IFU)

Oral Evaluator Initials: ___ ___ ___ Oral Evaluator Signature: _____

☐ **Missed Visit** **Reason:** _____

MUCOSITIS ASSESSMENT WORKSHEET

YES ☐ NO ☐ **Confirm that all PROs were completed prior to conducting this clinical exam.**

DIET ASSESSMENT

DIET 1:
What has the subject been able to eat within the past 24 hours *(mark only one)*:
☐ Solids
☐ Liquids
☐ Nothing by mouth

If Solids is marked above, proceed to the Mouth Pain Assessment.

If Liquids or Nothing by Mouth is marked above, continue to DIET 2.

DIET 2:
If the subject has been unable to eat Solid food, mark the reason(s) why *(mark **all** that apply)*:
☐ Nausea/Vomiting ☐ Oral Discomfort
☐ Loss of Appetite ☐ Dry Mouth
☐ Throat Discomfort ☐ No teeth
☐ Difficulty swallowing
☐ Other: _____

If Oral Discomfort is marked above, proceed to the Mouth Pain Assessment.

If Oral Discomfort is NOT marked, continue to DIET 3.

DIET 3:
Based solely on how the mouth feels, what does the subject feel (s)he could try to eat if (s)he did not have to swallow *(mark only one)*:
☐ Solids
☐ Liquids
☐ Nothing by mouth

Proceed to the Mouth Pain Assessment.

MOUTH PAIN ASSESSMENT

Please indicate if the subject is experiencing any mouth pain or oral discomfort **at this time:** ☐ Yes *OR* ☐ No

ORAL ASSESSMENT

Oral Site	Ulceration/ Pseudomembrane Formation	Other Ulceration (e.g., tumor or surgical)	Erythema
Upper Lip	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐
Lower Lip	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐
Right Cheek	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐
Left Cheek	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐
Right Ventral & Lateral Tongue	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐
Left Ventral & Lateral Tongue	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐
Floor of the Mouth	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐
Soft Palate	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐	Yes ☐ No ☐ NE ☐

WHO Score *(mark only one)*: **Note: The Other Ulceration column will not be used when deriving the WHO Score**

☐ WHO = 0 – None
☐ WHO = 1 – Erythema and Mouth Pain
☐ WHO = 2 – Ulceration/Pseudomembrane Formation; Able to eat Solids or could try to eat Solids if swallowing were not required.
☐ WHO = 3 – Ulceration/Pseudomembrane Formation; Able to eat Liquids or could try to eat Liquids if swallowing were not required.
☐ WHO = 4 – Ulceration/Pseudomembrane Formation; Unable to eat Solids or Liquids

Version Date 17-Oct-13 **EMAIL TO CAP at SGX@CAPTRIALS.COM** Page 1 of 1
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