SUMMARY OF CHANGES – Protocol

For Protocol Amendment # to: **Phase II Trial of Post-operative Concurrent Radiation and Cetuximab for Locally Advanced Cutaneous Squamous Cell Carcinoma of the Head and Neck**

UCCI Protocol #: UCHN-12-001
IRB Protocol #: 2013-3193 (UC)

UCCI Version Date: 03APR2018
Original Protocol Date: 21NOV2013

I. Brief Table of Changes:

#	Section	Change
1.	1.6	Added that tissue may be collected from pathology
2.	2.3	Added tertiary objective to match protocol
3.	4.2.2	Deleted unnecessary test/EKG
4.	5.0	Changed registration into OnCore
5.	7.2	Clarification in subsequent dosing
6.	7.2.1	Change in premedication wording
7.	8.1	Added pathology as source and added Univ of Mich
8.	11	Changed reporting requirements as well as data collection
9.	12	Added Study Calendar
10.	All	Update font and layout; update investigators

II. Detailed Table of Changes:

Section	Old Language	New Language	Rationale for Change
1.6	We plan to harvest and store tissue samples at the time of surgery through the Head and Neck Tumor Bank already in place	We plan to harvest and store tissue samples at the time of surgery through the Head and Neck Tumor Bank already in place when possible. Otherwise, tissues may be requested from pathology.	Adding that tissue may be collected from pathology allows for the use of pre-existing tissue samples.
2.3		To quantify EGFR phosphorylation patterns and immune	The process for buccal swabs was already within the

		markers in the tumor-adjacent normal tissue from buccal swabs obtained pre-treatment, post-loading dose of cetuximab and during RT.	protocol. Here we clarified the tertiary objective
4.2.2	EKG within 8 weeks prior to start of treatment	deleted	Unnecessary per Hemonc (Dr Worden)
5.0	Patients are registered by contacting the University of Cincinnati Clinical Trials Office at 513-584-7698.	Patients are registered and enrolled in OnCore at the University of Cincinnati by the clinical coordinators. For University of Michigan patients, a unique number will be assigned by the University of Michigan team who will notify the University of Cincinnati Clinical Trials Office at 513-584-7698 so that the patient may be entered into OnCore.	Added clarity that OnCore will be used for patient registration and enrollment which is in-line with current practices at UCCI.
7.2	Cetuximab weeks 2 through 7 or 8 (concurrent with RT depending on standard of care RT): Patients will receive cetuximab, 250 mg/m2, intravenously (i.v.) over 60 minutes on a weekly schedule. The infusion rate of cetuximab must never exceed 5 mL/min. Cetuximab will be given once a week prior to RT for a total of 6-7 doses concurrent with radiation therapy. In cases of delay in the completion of radiation therapy, then the concurrent doses of cetuximab may continue beyond week 8 without dose interruption until	Cetuximab weeks 2 through 7 or 8 (concurrent with RT depending on standard of care RT): Patients will receive cetuximab, 250 mg/m2, intravenously (i.v.) over 60-120 minutes on a weekly schedule. Cetuximab will be given ceconcurrent with radiation therapy. In cases of delay in the completion of radiation therapy, then the concurrent doses of cetuximab may continue beyond week 8 without dose interruption until radiation therapy is completed. The total of number of cetuximab doses should not exceed	Clarification in subsequent dosing

	radiation therapy is completed. The total of number of cetuximab doses should not exceed 11.	11.	
7.2.1	**All patients will be premedicated with diphenhydramine hydrochloride, 50 mg, (or an equivalent antihistamine) by *i.v.* 30-60 minutes prior to the first dose of cetuximab in an effort to prevent an infusion reaction.** At the discretion of the treating physician, dexamethasone, 20 mg, and an H2 blocker also may be administered i.v. Premedications are recommended prior to subsequent doses, but at the Investigator's discretion, the dose of diphenhydramine or dexamethasone may be reduced.	Premedications are recommended and per discretion of the treating physician.	Allowing for individual local standard between UC and UM
7.3.3		Updated table for clarification of cetuximab dosing modification	
8.1		Added pathology as source and added University of Michigan	
8.2		Added clarification regarding hypothesis for buccal swabs	
11		Changed reporting requirements as well as data collection	
12		Added Study Calendar	
All		Update font and layout; update investigators	

Phase II Trial of Post-operative Concurrent Radiation and Cetuximab for Locally Advanced Cutaneous Squamous Cell Carcinoma of the Head and Neck

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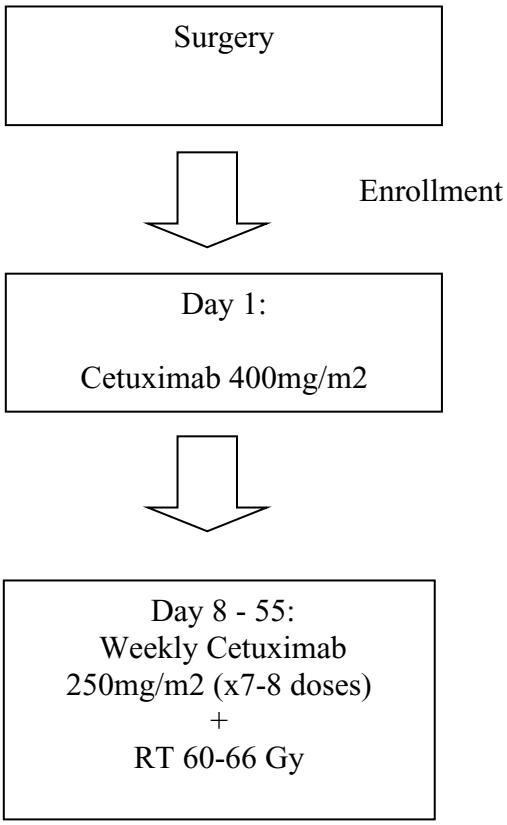
Roadmap

Eligibility: cutaneous squamous cell carcinoma with invasion of any skeletal muscle, cartilage, bone or lymph nodes of the head and neck after resection



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1.1 Locally Advanced Cutaneous Cancer

Cutaneous squamous cell carcinomas are very common malignant neoplasms in the United States, frequently associated with sun exposure and fair complexions. Other risk factors include advanced age and acquired immunosuppression after solid organ transplantation or treatment for leukemia/lymphoma.

Squamous cell carcinomas of the skin are considered aggressive non-melanoma skin cancers. Cutaneous squamous cell carcinomas of the head and neck (CSCCHN) occur commonly, and this is reflected in the AJCC seventh edition 2010 staging, which created new staging for non-melanoma skin cancer staging that correlates with the head and neck mucosal staging[1].

Within CSCCHN, poor prognosis has been associated with involvement of the parotid gland, advancing cervical nodal metastases, immunosuppression, and bony involvement. Overall survival at 2 years in retrospective studies[2]-[3], was 70-80% for N1 parotid and/or neck involvement, whereas it was 25-50% for N2-3 patients. It has been reported that immunocompromised patients have a 7.2 fold increased risk of local recurrence and a 5.3 fold increased risk of any recurrence after treatment for CSCCHN. Mortality is also increased with skin cancer; skin cancer was the fourth most common cause of death in a reported renal transplant cohort [4]. Additionally, single institution series have reported that histopathology of CSCC in immunocompromised patients is more aggressive, with tumor size being less important [5]. The 2010 AJCC staging manual documents increased local failure rates for tumors with invasion of skeletal muscle or cartilage.

CSCCHN is most commonly managed with primary surgery, although very locally advanced lesions can be palliated with primary radiotherapy. After radical resection, indications for post-operative radiotherapy include positive surgical margins, perineural invasion, positive lymph nodes, invasion of bone or cartilage and extensive skeletal muscle infiltration. Despite surgery and post-operative radiotherapy, approximately 25% patients will experience loco-regional failure, 25% will develop distant metastases and the 2 year overall survival is several large series is reported to be 40-55%[6] [7] [8]. In our experience at the University of Cincinnati, loco-regional control with surgery and post-operative radiotherapy alone has been 68% (unpublished).

While these numbers could certainly be improved upon, there have been no prospective trials to date looking at the addition of chemotherapy or targeted therapies to radiotherapy in this setting.

1.2 Study Design

Postoperative RT alone is the current standard of care for patients with locally advanced cutaneous malignancies of the head and neck, with suboptimal outcome. The goal of this trial is prospectively study the addition of concurrent cetuximab to radiotherapy for locally advanced CSCCHN in the post-operative setting for CSCCHN.

1.3 *Epidermal Growth Factor Receptor (EGFR)*

In mucosal SCCHN, a recent important area of advance has been the study of epidermal growth factor receptor (EGFR). EGFR is expressed at very high levels in the majority of human mucosal head and neck squamous cell carcinoma (SCCHN). Furthermore, pre-

clinical data indicate that it is not merely a 'bystander' but is intimately associated with the malignant phenotype of SCCHN. EGFR activation in response to a ligand (e.g., EGF or TGF-alpha) results in phosphorylation of its intracytoplasmic tyrosine kinase domain, leading to a cascade of signal transduction within the cell. This ultimately leads to DNA synthesis, cell proliferation, anti-apoptosis, and transcription of growth factors such as pro-angiogenic molecules. Blockade of this pathway is an effective anti-neoplastic strategy; furthermore, EGFR blockade appears to result in radiosensitization. This hypothesis was proven in a randomized trial by Bonner, et al. (2006)[9]. In that study, patients with locally advanced, non-operative mucosal SCCHN were randomized to RT alone or RT with weekly cetuximab. Local-regional control and survival were significantly improved with cetuximab. 2-year locoregional control was increased significantly with cetuximab by 9% (from 41 to 50%), and this translated into an overall survival advantage at 5 years. 5-year overall survival was 45% for RT/cetuximab, compared with 36% for RT alone. Interestingly, the development of $\geq$ grade 2 rash associated with cetuximab was associated with significantly improved overall survival.

1.4 Cetuximab

Cetuximab is a humanized monoclonal antibody against the EGFR receptor. In the Bonner study of cetuximab and radiotherapy for locally advanced non-operative mucosal SCCHN described above, cetuximab appeared to have little toxicity when given concurrently with radiotherapy for mucosal SCCHN and 93% of patients received the prescribed cetuximab dose [Bonner 2006]. Furthermore, the Bonner study showed no evidence that cetuximab increased the rate of ≥ Grade 3 mucositis or dysphagia, no evidence of an increased rate of late effects, and no evidence of a worsening of QOL relative to RT alone.

The Bonner study is not the only data in support of cetuximab as a valuable treatment against mucosal head and neck cancer. Cetuximab is currently under investigation in the post-operative setting for mucosal intermediate risk SCCHN in RTOG 0920. In platinum-refractory recurrent/metastatic mucosal SCCHN, single agent cetuximab has a response rate of approximately 11%[10], providing further clinical evidence that it is working via a pathway (or pathways) distinct from DNA damaging agents such as platins or RT. In first-line therapy for recurrent/metastatic SCCHN, the addition of cetuximab to 5- FU/platinum significantly improved overall survival [11].

In locally advanced unresectable CSCCHN, cetuximab has been investigated as a single agent, demonstrating 69% disease control rate at 6 weeks by RECIST criteria[12]. Seventy-eight percent of patients developed grade 2 acneiform rash, which was associated with prolonged disease free survival. To date, cetuximab has not been investigated concurrently with radiotherapy in the setting of cutaneous malignancy.

Based upon the data described above, we propose testing concurrent cetuximab with postoperative RT for those patients who have a high risk of recurrence as results with radiotherapy alone are suboptimal. We will compare the results of the current study with historical results using the current standard of care for these patients (RT alone).

1.5 Safety of Cetuximab in SCCHN Clinical Studies

Cetuximab has been evaluated in 208 patients with locally or regionally advanced SCCHN who received cetuximab in combination with radiation and as monotherapy in 103 patients with recurrent or metastatic SCCHN. Of the 103 patients receiving cetuximab monotherapy, 53 continued to a second phase with the combination of cetuximab plus

chemotherapy. Patients receiving cetuximab plus radiation therapy received a median of 8 doses (range 1-11 infusions). The population had a median age of 56; 81% were male and 84% Caucasian. Patients receiving cetuximab monotherapy, received a median of 11 doses (range 1-45 infusions). The population had a median age of 57; 82% were male and 100% Caucasian. The most serious adverse reactions associated with cetuximab in combination with radiation therapy in patients with head and neck cancer were: infusion reaction (3%); cardiopulmonary arrest (2%); dermatologic toxicity (2.5%); mucositis (6%); radiation dermatitis (3%);confusion (2%);diarrhea (2%).

Fourteen (7%) patients receiving cetuximab plus radiation therapy and 5 (5%) patients receiving cetuximab monotherapy, discontinued treatment primarily because of adverse events. The most common adverse events seen in 208 patients receiving cetuximab in combination with radiation therapy were acneiform rash (87%), mucositis (86%), radiation dermatitis (86%), weight loss (84%), xerostomia (72%), dysphagia (65%), asthenia (56%), nausea (49%), constipation (35%), and vomiting (29%).
The most common adverse events seen in 103 patients receiving cetuximab monotherapy were acneiform rash (76%), asthenia (45%), pain (28%), fever (27%), and weight loss (27%).

The data in the table below are based on the experience of 208 patients with locoregionally advanced SCCHN treated with cetuximab plus radiation therapy compared to 212 patients treated with radiation therapy alone (Cetuximab [Erbitux™] package insert, 2006).

Incidence of Selected Adverse Events (≥ 10%) in Patients with Locoregionally Advanced SCCHN

	Cetuximab plus Radiation (n=208)		Radiation Therapy Alone (n=212)	
Body System Preferred Term	Grades 1 – 4	Grades 3 and 4	Grades 1 – 4	Grades 3 and 4
	% of Patients			
Body as a Whole				
Asthenia/Malaise	56	4	48	5
Fever[1]	29	1	13	<1
Headache	19	<1	8	<1
Infusion Reaction[2]	15	3	2	0

Infection	13	1	9	1
Chills[1]	16	0	5	0
Digestive				
Mucositis/Stomatitis	93	56	94	52
Xerostomia	72	5	71	3
Dysphagia	65	26	63	30
Nausea	49	2	37	2
Constipation	35	5	30	5
Vomiting	29	2	23	4
Anorexia	27	2	23	2
Diarrhea	19	2	13	1
Dyspepsia	14	0	9	1
Metabolic/Nutritional				
Weight Loss	84	11	72	7
Dehydration	25	6	19	8
Respiratory				
Pharyngitis	26	3	19	4
Cough Increased	20	<1	19	0
Skin/Appendages				
Acneform Rash[3]	87	17	10	1
Radiation Dermatitis	86	23	90	18
Application Site Reaction	18	0	12	1
Pruritus	16	0	4	0

[1] Includes cases also reported as infusion reactions
[2] Infusion reaction is defined as any event described at any time during the clinical study as "allergic reaction" or "anaphylactoid reaction" or any event on the first day of dosing described as "allergic reaction", "anaphylactoid reaction", "fever", "chills", "chills and fever" or "dyspnea".
[3] Acneform rash as defined as any event described as "acne", "rash", "maculopapular rash", "pustular rash", "dry skin" or "exfoliative dermatitis".

Late Radiation Toxicity

The overall incidence of late radiation toxicities (any grade) was higher in cetuximab in combination with radiation therapy compared with radiation therapy alone. The following sites were affected: salivary glands (65% versus 56%), larynx (52% versus 36%), subcutaneous tissue (49% versus 45%), mucous membrane (48% versus 39%), esophagus (44% versus 35%), skin (42% versus 33%), brain (11% versus 9%), lung (11% versus 8%), spinal cord (4% versus 3%), and bone (4% versus 5%). The incidence of Grade 3 or 4 late radiation toxicities were generally similar between the radiation therapy alone and the cetuximab plus radiation treatment groups.

Clinically Relevant Adverse Events Related to Cetuximab

Pooled adverse event data are available for 2,127 patients treated with cetuximab alone or in combination with chemotherapy and/or radiation therapy (21 ImClone studies, 9 Merck KgaA, 2 BMS, and 1 ECOG study). A total of 90.3% of the patients reported adverse events (AEs). Approximately two-thirds (64.8%) of patients reported at least one Grade 3 or 4 event. Cetuximab-related AEs were observed in 1,817 patients (85.4%). The most common composite groupings of adverse events deemed related to cetuximab as reported by investigators in all cetuximab trials (N = 1,817) include acneiform rash (76.2%), acne-like rash (72.4 %), fatigue/malaise/lethargy (30.1%), nausea/vomiting (24%), mucositis/stomatitis (17.5 %), infusion-related symptoms (15.6%), diarrhea (15.4 %), and hypersensitivity reaction (5.3%).

Acne-Like Rash

In clinical studies of cetuximab, dermatologic toxicities, including acneiform rash, skin drying and fissuring, and inflammatory and infectious sequelae (e.g., blepharitis, cheilitis,

cellulitis, cyst) were reported. In patients with advanced colorectal cancer, acneiform rash was reported in 89% (686/774) of all treated patients, and was severe (grade 3 or 4) in 11% (84/774) of these patients. Subsequent to the development of severe dermatologic toxicities, complications including *S. aureus* sepsis and abscesses requiring incision and drainage were reported. Non-suppurative acneiform rash described as “acne”, “rash”, “maculopapular rash”, “pustular rash”, “dry skin”, or “exfoliative dermatitis” was observed in patients receiving cetuximab plus irinotecan or cetuximab monotherapy. One or more of the dermatological adverse events were reported in 88% (14% grade 3) of patients receiving cetuximab plus irinotecan and in 90% (8% grade 3) of patients receiving cetuximab monotherapy. Acneiform rash most commonly occurred on the face, upper chest, and back but could extend to the extremities and was characterized by multiple follicular- or pustular-appearing lesions. Skin drying and fissuring were common in some instances, and were associated with inflammatory and infectious sequelae (e.g., blepharitis, cellulitis, cyst). Two cases of *S. aureus* sepsis were reported. The onset of acneiform rash was generally within the first two weeks of therapy. Although in a majority of the patients the event resolved following cessation of treatment, in nearly half of the cases, the event continued beyond 28 days.

Nail Disorder
A related nail disorder, occurring in 14% of patients (0.4% Grade 3), is characterized as a paronychial inflammation with associated swelling of the lateral nail folds of the toes and fingers, with the great toes and thumbs as the most commonly affected digits.

Infusion Reactions
In clinical trials, severe, potentially fatal infusion reactions were reported, one leading to death. These events include the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension. In studies in advanced colorectal cancer, severe infusion reactions were observed in 3% of patients receiving cetuximab plus irinotecan and 2% of patients receiving cetuximab monotherapy. Grade 1 and 2 infusion reactions, including chills, fever, and dyspnea usually occurring on the first day of initial dosing, were observed in 16% of patients receiving cetuximab plus irinotecan and 19% of patients receiving cetuximab monotherapy. A 20-mg test dose was administered intravenously over 10 minutes prior to the initial dose to all patients in earlier studies. The test dose did not reliably identify patients at risk for severe allergic reactions. Severe infusion reactions occurred with the administration of cetuximab in approximately 3% of patients, rarely with fatal outcome (<1 in 1000). Approximately 90% of severe infusion reactions were associated with the first infusion of cetuximab despite the use of prophylactic antihistamines. These reactions were characterized by the rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), urticaria, and/or hypotension.

Pulmonary Toxicity
Interstitial lung disease (ILD) was reported in 3 of 774 (< 0.5%) patients with advanced colorectal cancer receiving cetuximab. Interstitial pneumonitis with non-cardiogenic pulmonary edema resulting in death was reported in one case. Two patients had pre-existing fibrotic lung disease and experienced an acute exacerbation of their disease while receiving cetuximab in combination with irinotecan. In the clinical investigational program, an additional case of interstitial pneumonitis was reported in a patient with head and neck cancer treated with cetuximab and cisplatin. The onset of symptoms occurred between the fourth and eleventh doses of treatment in all reported cases.

1.6 Translational Science

This study will aim to address future translational science questions related to EGFR and cetuximab in skin cancers. We plan to harvest and store tissue samples at the time of surgery through the Head and Neck Tumor Bank already in place when possible. Otherwise, tissues may be requested from pathology. These samples may be used for future exploratory analysis of other molecular factors in CSCCHN. Presently, while much has been learned about the relationships among EGFR, cetuximab, and SCCHN, there is marked uncertainty regarding if and how this biological information should be used clinically in mucosal or cutaneous SCCHN.

1.7 Quality of Life and Function Assessments

It is now well established that cancer of the head and neck often has profoundly debilitating effects on quality of life (QOL), function, and performance. In a recently reported phase III trial of cetuximab and radiation therapy (RT) for mucosal head and neck squamous cell carcinoma (HNSCC), cetuximab did not significantly increase acute RT-associated adverse effects (Bonner 2006). This study also found that addition of cetuximab to RT significantly improved locoregional control and increased overall survival without adversely affecting QOL (Curran 2007)[13].

1.7.1 *Quality of Life (QOL) Assessments*

Quality of life will be assessed using two validated, multidimensional patient reported QOL measures including: the FACT HN and the Dermatology Life Quality Index (DLQI). Both of these QOL validated tools are currently being used by the RTOG in SCCHN trials, and the FACT HN is being used in the UCCI Prospective Head and Neck Oncology Comprehensive Database that is set to go live 1/1/13.

The FACT-H&N is a multidimensional, patient self-report QOL instrument specifically designed and validated for use with head and neck cancer patients. The FACT-HN consists of a 27-item core scale (FACT-G) and is supplemented with a 12-item head and neck subscale targeting head and neck related symptoms and side effects[14].

The Dermatology Life Quality Index (DLQI) will be used to explore the impact of cetuximab induced rash on quality of life. It is expected that rash (acneiform; maculo-papular), pruritis, and other visible consequences associated with cetuximab-induced rash will have a significant negative impact quality of life[15,16]. The DLQI[17] is designed to assess the impact of a wide range of skin disease on patient quality of life [18,19], and it is currently being used in RTOG 0920 to assess the impact of cetuximab-induced rash on QOL in mucosal SCCHN. The DLQI consists of 10 items and covers 6 domains including symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. Response categories include "not at all," "a little,"a lot," and "very much," with corresponding scores of 0, 1, 2, and 3 respectively; the response "not relevant" (and unanswered items) are scored as "0". A total score is calculated by summing the score of all items, resulting in a maximum score of 30 and a minimum score of 0. Scale scores are calculated for each domain. Higher scores indicate poorer HRQL (i.e., more impairment). The FACT HN and DLQI will be administered a baseline and at 3, 12, and 24 months after the start of radiation therapy.

1.7.2 *Timeframe of Assessments*

These patient-reported QOL and function measures and the clinician-assessed measures will be administered at baseline and at 3, 12, and 24 months from the start of radiation.

The 3- month QOL assessment was chosen to coincide with usual practice of seeing a head and patient 2-3 weeks after completion of radiation therapy. This assessment will provide the immediate impact of radiation therapy +/- cetuximab on QOL. The 12-month QOL assessment was chosen to coincide with usual practice of seeing a head and patient 1 year after completion of radiation therapy. The Radiation Oncologists expect at this time that almost all acute toxicities related to radiation will be resolved, and they are interested in assessing the patient's QOL at that time. These 2 assessment time points for patient reported outcomes are routinely used in RTOG and other head and neck studies. PRO assessment has been added at 24 months from RT completion. That time point was chosen because 80 to 90% of the patients who will progress do so by 2 years. For patients who are disease free then, the issue, it is felt,
becomes the long-term sequelae of the treatments.

2.0 OBJECTIVES

2.1 Primary Objective

To assess the 2 – year locoregional control (LRC) of cetuximab and radiation therapy in high risk postoperative patients with cutaneous squamous cell carcinoma of the head and neck.

2.2 Secondary Objectives

To descriptively assess the impact of the addition of cetuximab to postoperative radiation therapy on the following:
2 year- disease-free survival (DFS) and 2 and 5 –year overall survival (OS);

2.3 Tertiary Objectives

To assess the impact of the addition of cetuximab to postoperative radiation therapy on the following:
Patient-reported quality of life (QOL), swallowing, xerostomia, and skin toxicity based on head and neck specific instruments, including the Functional Assessment of Cancer Therapy-Head & Neck (FACT-HN) and the Dermatology Life Quality Index (DLQI);

To quantify EGFR phosphorylation patterns and immune markers in the tumor-adjacent normal tissue from buccal swabs obtained pre-treatment, post-loading dose of cetuximab and during RT.

3.0 PATIENT SELECTION

3.1 Conditions for Patient Eligibility

3.1.1 Pathologically (histologically) proven diagnosis of cutaneous squamous cell carcinoma of the head and neck;

3.1.2 Pathologic invasion of skeletal muscle, cartilage, bone or lymph nodes (>N1), M0

including no distant metastases, based upon the following minimum diagnostic workup:

3.1.2.1 General history and physical examination by a Radiation Oncologist and/or Medical Oncologist within 2 weeks prior to registration;

3.1.2.2 Examination by an ENT or Head & Neck Surgeon, within 8 weeks prior to registration;

3.1.2.3 Chest CT scan (with or without contrast) or CT/PET of chest (with or without contrast) within 8 weeks prior to registration.

3.1.3 Gross total resection of the primary tumor with curative intent must be completed within 9 weeks of registration. This may be a recurrent cutaneous squamous cell carcinoma of the skin, and patient is still eligible as long as all gross disease is currently resected.

3.1.4 Zubrod performance status of 0-2 within 2 weeks prior to registration

3.1.5 Age $\geq$ 18;

3.1.6 CBC/differential obtained within 4 weeks prior to registration on study, with adequate bone marrow function defined as follows:

3.1.6.1 Absolute granulocyte count (AGC) $\geq$ 1,500 cells/mm3;

3.1.6.2 Platelets $\geq$ 100,000 cells/mm3;

3.1.6.3 Hemoglobin > 8.0 g/dl (Note: The use of transfusion or other intervention to achieve Hgb > 8.0 g/dl is acceptable).

3.1.7 Adequate hepatic function, defined as follows:

3.1.7.1 Total bilirubin < 2 x institutional ULN within 2 weeks prior to registration;

3.1.7.2 AST or ALT < 3 x institutional ULN within 2 weeks prior to registration.

3.1.8 Negative serum pregnancy test within 2 weeks prior to registration for women of childbearing potential;

3.1.9 The following assessments are required within 2 weeks prior to the start of registration: Na, K, Cl, glucose, Ca, Mg, and albumin. Note: Patients with an initial magnesium < 0.5 mmol/L (1.2 mg/dl) may receive corrective magnesium supplementation but should continue to receive either prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g., magnesium oxide) at the investigator's discretion.

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

3.1.11 Patients must provide study specific informed consent prior to study entry, including consent for optional tissue submission

3.2 Conditions for Patient Ineligibility

3.2.1 Prior invasive malignancy unless disease free for a minimum of 3 years; noninvasive cancers (For example, carcinoma *in situ* of the breast, oral cavity, or cervix are all permissible) are permitted even if diagnosed and treated < 3 years ago. Prior basal cell carcinoma and squamous cell carcinoma of the skin is allowed. Patients with a history of T1-2, N1, M0 resected differentiated thyroid carcinoma are considered eligible.

3.2.2 Prior systemic chemotherapy or anti-EGF therapy for the study cancer or for a different prior cancer;

3.2.3 Prior radiotherapy to the region of the study cancer that would result in overlap of radiation therapy fields;

3.2.4 Severe, active co-morbidity, defined as follows:

3.2.4.1 Unstable angina and/or congestive heart failure requiring hospitalization within 6 months prior to registration;

3.2.4.2 Transmural myocardial infarction within 6 months prior to registration;

3.2.4.3 Acute bacterial or fungal infection requiring intravenous antibiotics at the time of registration;

3.2.4.4 Chronic Obstructive Pulmonary Disease exacerbation or other respiratory illness requiring hospitalization or precluding study therapy at the time of registration;

3.2.4.5 Idiopathic pulmonary fibrosis or other severe interstitial lung disease that requires oxygen therapy or is thought to require oxygen therapy within 1 year prior to registration;

3.2.4.6 Hepatic insufficiency resulting in clinical jaundice and/or coagulation defects; note, however, that laboratory tests for coagulation parameters are not required for entry into this protocol.

3.2.4.7 Acquired Immune Deficiency Syndrome (AIDS) based upon current CDC definition; **note:** HIV testing is not required for entry into this protocol. The need to exclude patients with AIDS from this protocol is necessary because the treatments involved in this protocol may be significantly immunosuppressive. Protocol-specific requirements may also exclude immuno-compromised patients.

3.2.4.8 Grade 3-4 electrolyte abnormalities (CTCAE, v. 4.03):

Serum calcium (ionized or adjusted for albumin) < 7 mg/dl (1.75 mmol/L) or > 12.5 mg/dl (> 3.1 mmol/L) despite intervention to normalize levels;

Glucose < 40 mg/dl (< 2.2 mmol/L) or > 250 mg/dl (> 14mmol/L);

Magnesium < 0.9 mg/dl (< 0.4 mmol/L) or > 3 mg/dl (> 1.23 mmol/L) despite intervention to normalize levels;

Potassium < 3.5 mmol/L or > 6 mmol/L despite intervention to normalize levels;

Sodium < 130 mmol/L or > 155 mmol/L despite intervention to normalize levels.

3.2.5 Pregnancy or women of childbearing potential and men who are sexually active and not willing/able to use medically acceptable forms of contraception; this exclusion is necessary because the treatment involved in this study may be significantly teratogenic.

3.2.6 Prior allergic reaction to cetuximab.

4.0 PRETREATMENT EVALUATIONS/MANAGEMENT

4.1 Required Evaluations/Management

Baseline QOL and functional assessments prior to the start of treatment: the Functional Assessment of Cancer Therapy-Head & Neck (EORTC HN35); the Dermatology Life Quality Index (DLQI);

4.2 Highly Recommended Evaluations/Management

4.2.1 Evaluation for prophylactic gastrostomy tube placement (especially if the patient is > 10% below ideal body weight) within 4 weeks prior to the start of treatment;

4.2.2 Banking of tumor tissue and blood in the UCCI Head and Neck Tumor Bank is highly encouraged but not required for protocol enrollment.

5.0 Registration Procedures

Patients are registered and enrolled in OnCore at the University of Cincinnati by the clinical coordinators. For University of Michigan patients, a unique number will be assigned by the University of Michigan team who will notify the University of Cincinnati Clinical Trials Office at 513-584-7698 so that the patient may be entered into OnCore.

6.0 RADIATION THERAPY

Protocol treatment must begin within 3 weeks after registration.

6.1 Dose Specifications

The prescribed radiotherapy dose will be 60-66 Gy in 2 Gy once-daily fraction size (total of 30-33 fractions). Radiotherapy should begin on a Monday, Tuesday or Wednesday. The daily dose of 2 Gy will be prescribed such that 95% of the PTV volume receives at least 95% of prescribed dose. The spinal cord dose may not exceed 45 Gy to any volume larger than 0.03 cc.

6.2 Technical Factors

Treatment Planning/*Delivery:* Megavoltage energy photon beam irradiation is required, but may also include electron therapy as necessary to include superficial disease areas. 3D conformal or IMRT treatment planning may be may be used, and treatment verification films must be taken a least once weekly.

6.3 Localization, Simulation, and Immobilization

6.3.1 Patients must have an immobilization device (e.g., aquaplast mask) made prior to treatment planning CT scan.

6.3.2 All patients will undergo CT simulation for treatment planning. The treatment planning CT scan may be completed with or without IV contrast. The treatment planning CT scan must be performed with the immobilization device and in the treatment position. Slice thickness should be 0.3 cm or less.

6.4 Target and Normal Tissue Volume Restrictions

6.4.1 *Definition of Target Volumes*

6.4.1.1 CTV60: This volume will receive 2 Gy per day. CTV60 will include the primary tumor bed (based on preoperative imaging, preoperative physical exam/endoscopy, operative findings, pathologic findings) plus the post-operative neck. This volume may include the skin. It is recognized that after surgery, there can be considerable distortion of normal anatomy. If possible, preoperative GTV(s) should be fused onto the postoperative radiation therapy planning CT scan, and appropriate margins added for microscopic spread (1.5-2 cm).

CTV60 also will include the ipsilateral pathologically positive hemineck (if both sides of the neck are proven pathologically positive, CTV60 will include both sides). This generally means encompassing nodal levels 2a, 3, and 4 for all cases. Nodal levels 1, 2b, 5a, and 5b are included in CTV60 in selected circumstances. For questions, contact the Principal Investigator, Dr. Mierzwa.

6.4.1.2 CTV56: This will include all other regions felt to be at risk for harboring microscopic cancer that do not meet the criteria for CTV60. For example, this would apply to the contralateral hemineck being irradiated electively for a midline primary cancer. This volume will receive approximately 1.85- 2 Gy per day.

6.4.1.3 CTV66 **Optional:** This may be defined at the discretion of the treating radiation oncologist. This would include a region or regions felt to be at especially high risk for recurrence (e.g., an area of very close margin of resection or nodal extracapsular extension). This area will be receiving a daily fraction size of 2- 2.2 Gy and thus, the volume of CTV66 should be kept **as small as possible.**

6.4.1.4 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 to treat skin to full dose.

6.4.1.4.1 *PTV Expansion* The minimum CTV-to- PTV expansion is 3 mm (a larger expansion may be necessary for a target volume subject to significant intra-fraction variability, such as the non-immobilized oral tongue). In general, the CTV-to-PTV expansion should not exceed 10 mm.

6.4.2 *Definition of Normal Tissues/Organs at Risk (OARs)- adapted from RTOG 1016*

6.4.2.1 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.

6.4.2.2 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.

6.4.2.3 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 definition of lips is self explanatory. The oral cavity will be defined as a composite structure consisting of the anterior 1⁄2 to $^{2/3}$ of the oral tongue/floor of mouth, buccal mucosa, and palate.

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

6.4.2.5 OARpharynx: This will be defined as the “uninvolved” posterior pharyngeal wall plus adjacent constrictor muscles. This extends from the superior constrictor region (the inferior pterygoid plates level) to the cricopharyngeal inlet (posterior cricoid cartilage level). This should not overlap the PTVs.

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

6.4.2.7 Glottic/Supraglottic Larynx (GSL): Obviously, for patients who have had a total laryngectomy, this structure is not applicable. 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.

6.4.2.8 Mandible: This includes the entire boney structure of the mandible from TMJ through the symphysis. It is recognized that for oral cavity cancers, this may overlap with CTVs and PTVs.

6.4.2.9 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.

6.5 Treatment Planning and Delivery

Dose Prescription to PTVs

As described in Section 6.1, prescribed radiotherapy dose will be 60 Gy in 2 Gy once-daily fraction size. For inverse planning IMRT, the goal is for 95% of the PTV60 to receive 95% of 2 Gy with a minimum dose (cold spot) of no less than 56 Gy. It is recognized that portions of the PTV60 close to/within the skin may receive significantly less than 56 Gy. Bolus should be considered for these cutaneous areas deemed to be at risk for microscopic disease. Electron cones may also be employed to provide adequate dose to PTVs which emcompass cutaneous tissues.

For IMRT prioritization, PTV60 will be the highest priority target structure. PTV66 and PTV56, if applicable, will be ranked in the IMRT planning as lower priority than PTV60 although higher priority than normal structures other than spinal cord and brain stem.

6.5.4 Dose Constraints to Normal Structures

Spinal Cord: The PRVcord (as defined in Section 6.4.2.1) should not exceed 45 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). The spinal cord PRV should not exceed 50 Gy to any volume in excess of 0.01 cc. In treatment planning, the spinal cord PRV should be given the highest priority.

Brainstem: The PRVbrainstem (as defined in Section 6.4.2.2) should not exceed 50 Gy to any volume in excess of 0.03 cc (approximately 3 mm x 3 mm x 3 mm). In treatment planning, the PRVbrainstem should be given less priority than the PRVcord but more priority than the other critical structures listed below.

Lips: Reduce the dose as much as possible unless lips involved with primary tumor. The mean dose should be < 20 Gy. The maximum dose will be < 30 Gy.

Oral Cavity: Reduce the dose as much as possible. The mean dose should be < 30 Gy.

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. Additional planning goals may include: 1) At least 50% of one parotid will receive < 30 Gy; and/or 2) At least 20 cc of parotid tissue (from the combination of both glands) will receive < 20 Gy.

OARpharynx: Reduce the dose as much as possible. Some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the OARpharynx exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the OARpharynx exceeds 60 Gy.

Cervical Esophagus: Reduce the dose as much as possible. For oral or oropharyngeal cancer, some recommended (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 45 Gy; 2) Mean dose < 35 Gy; 3) No more than 15% of the esophagus exceeds 54 Gy. For larynx cancer, higher doses are expected and permitted. Some recommended doses (but not mandatory) treatment goals include: 1) No more than 33% of the esophagus exceeds 50 Gy; 2) Mean dose < 45 Gy; 3) No more than 15% of the esophagus exceeds 60 Gy.

Glottic and Supraglottic larynx (GSL): Reduce the dose as much as possible.

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. For tumors that were not clinically or pathologically involving the mandible, the CTV should be contoured off the mandible.

Unspecified Tissue Outside the Targets: For the typical case in which there is no CTV66, no more than 5% of unspecified tissue can receive greater than 58 Gy and no more than 1% or 1cc of unspecified tissue can receive 64 Gy or more. When a boost is used to increase the dose to high risk regions to as much as 66 Gy, these numbers can be increased. In this case, no more than 5% of the unspecified dose should exceed the level

of the boost dose, and no more than 1% or 1 cc should exceed the boost dose value plus 10%.

6.6 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 five treatment days at a time and ten 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.

6.7 Radiation Therapy Adverse Events The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03 will be utilized for grading all adverse events. 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, 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 skin/soft tissue fibrosis. Much less common radiation adverse events include: mandibular osteoradionecrosis, and cervical myelopathy (< 1% with restriction of spinal cord dose to max dose of 45 Gy).

7.0 DRUG THERAPY

Protocol treatment must begin within 2 weeks after registration.

7.1 Cetuximab Initial Dose (Prior to RT): Patients will receive an initial dose of cetuximab, 400 mg/m2, intravenously (i.v.) over 120 minutes. No chemotherapy or radiation will be given this day, and the 400 mg/m2 initial dose of cetuximab will precede the first 250 mg/m2 dose of cetuximab and the first radiation treatment by at least 5 days (the day of the loading dose is not included in these 5 days). The infusion rate of cetuximab must never exceed 5 mL/min.

7.2 Cetuximab subsequent dosing

Cetuximab weeks 2 through 7 or 8 (concurrent with RT depending on standard of care RT): Patients will receive cetuximab, 250 mg/m2, intravenously (i.v.) over 60 minutes on a weekly schedule. The infusion rate of cetuximab must never exceed 5 mL/min. Cetuximab will be given once a week prior to RT for a total of 6-7 doses concurrent with radiation therapy.

In cases of delay in the completion of radiation therapy, then the concurrent doses of cetuximab may continue beyond week 8 without dose interruption until radiation therapy is completed. The total of number of cetuximab doses should not exceed 11.

7.2.1 Safety

CAUTION: Infusion reactions may occur during or following cetuximab administration. Most infusion reactions occur with the first infusion of cetuximab,

but some patients' first infusion reactions have been reported following subsequent doses (a severe reaction occurred in one patient following the 8th dose). The infusion reaction may occur during the infusion or be delayed until any time after the infusion. Premedications are recommended and per discretion of the treating physician.

The medical staff must closely observe patients for treatment-related adverse events, especially infusion reactions during the cetuximab infusion and during a post-infusion observation hour. For the initial cetuximab infusion, vital signs (blood pressure, heart rate, respiratory rate, and temperature) should be monitored prior to the administration of cetuximab, a half hour into the infusion, at the completion of the infusion, and 60 minutes post the infusion in an area with resuscitation equipment and other agents (epinephrine, prednisone equivalents, etc.) available. A nurse must be present in the immediate treatment area throughout the infusion and observation period. A physician must be in close proximity to the patient treatment area.

For subsequent infusions, vital signs should be taken pre- and post-infusion.

7.2.2 Formulation Cetuximab is an anti-EGFR receptor humanized chimeric monoclonal antibody. Cetuximab is expressed in SP2/0 myeloma cell line, grown in large scale cell culture bioreactors, and purified to a high level purity using several purification steps including protein A chromatography, ion exchange chromatography, low pH treatment, and nanofiltration. Cetuximab is not known to be a vesicant.

7.2.3 Safety Precautions Appropriate mask, protective clothing, eye protection, gloves and Class II vertical-laminar- airflow safety cabinets are recommended during preparation and handling.

7.2.4 Preparation and Administration Cetuximab must not be administered as an *i.v.* push or bolus. Cetuximab must be administered with the use of a low protein binding 0.22-micrometer in-line filter. Cetuximab is supplied as a 50-mL, single-use vial containing 100 mg of cetuximab at a concentration of 2 mg/mL in phosphate buffered saline. The solution should be clear and colorless and may contain a small amount of easily visible white amorphous cetuximab particulates. Cetuximab can be administered via infusion pump or syringe pump.

. **Infusion Pump:**

Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike or other appropriate transfer device may be used).

Fill cetuximab into a sterile evacuated container or bag such as glass containers, polyolefin bags (e.g., Baxter Intravia), ethylene vinyl acetate bags (e.g., Baxter Clintec), DEHP plasticized PVC bags (e.g., Abbott Lifecare), or PVC bags.

Repeat procedure until the calculated volume has been put in to the container. Use a new needle for each vial.

Administration must be through a low protein binding 0.22-micrometer in-line filter (placed as proximal to the patient as practical).

Affix the infusion line and prime it with normal saline before starting the infusion.

Maximum infusion rate should not exceed 5 mL/min.

Use 0.9% saline solution to flush line at the end of infusion.

. **Syringe Pump:**

Draw up the volume of a vial using a sterile syringe attached to an appropriate needle (a vented spike may be used).

Place the syringe into the syringe driver of a syringe pump and set the rate.

Administration must be through a low protein binding 0.22-micrometer in-line filter rated for syringe pump use (placed as proximal to the patient as practical).

Connect up the infusion line and start the infusion after priming the line with cetuximab.

Repeat procedure until the calculated volume has been infused.

Use a new needle and filter for each vial.

Maximum infusion rate should not exceed 5 mL/min.

Use 0.9% saline solution to flush line at the end of infusion.

. Cetuximab should be piggybacked to the patient's infusion line. Following the cetuximab infusion, a one-hour observation period is recommended.

. **7.2.5** *Storage Requirements*/*Stability* Store vials under refrigeration at 2 C to 8 C (36 F to 46 F). **DO NOT FREEZE.** Increased particulate formation may occur at temperatures at or below 0 C. This product contains no preservatives. Preparations of cetuximab in infusion containers are chemically and physically stable for up to 12 hours at 2 C to 8 C (36 F to 46 F) and up to 8 hours at controlled room temperature (20 C to 25 C; 68 F to 77 F). Discard any remaining solution in the infusion container after 8 hours at controlled room temperature or after 12 hours at 2 to 8 C. Discard any unused portion of the vial.

7.3. Dose Modifications (adapted from RTOG 1016)

Cetuximab Dose Levels

	Starting Dose	Dose Level –1	Dose Level –2
Cetuximab	400 mg/m^2 (week 1 only)		
Cetuximab	250 mg/m^2 (weekly)	200 mg/m^2 (weekly)	150 mg/m^2 (weekly)

Note: If a weight change of ≥ 10% occurs, the cetuximab dose should be adjusted.

7.3.2 Cetuximab Dose Modifications for Hematologic Adverse Events

Cetuximab will not be dose reduced or held for hematologic adverse events, such as neutropenia, neutropenic fever, or thrombocytopenia< 50 mL/min

7.3.3 Cetuximab Dose Modifications for Non-Hematologic Adverse Events (adapted from RTOG 0920)

Toxicity Grade (CTCAE, v. 4)	**Cetuximab Dose** [a]
Renal-Calculated Creatinine Clearance	
≥ 50 mL/min	Maintain dose levels
< 50 mL/min	Maintain dose levels
Fatigue (Asthenia) ≥ Grade 3	Maintain dose levels
Nausea/Vomiting ≤ Grade 2 with maximal medical management	Maintain dose levels
≥ Grade 3 with maximal medical management	Hold drug until ≤ grade 2, then resume at same dose level
Other Non-hematologic Adverse Events [b, c]	
Grade 3- 4, except for weight loss (if possibly related to cetuximab, or likely to be exacerbated by continuation of cetuximab, e.g. diarrhea)	Hold drug until < grade 3, then resume at 1 dose level reduction
Any grade 1-2	Maintain dose levels

[a]Dose levels are relative to the previous dose. Dose reductions of cetuximab below the –2 dose level will not be allowed. If a dose reduction below the -2 dose is mandated by the toxicity grade, cetuximab will be permanently discontinued. In any case of cetuximab treatment delay, there will be no re-loading infusion, and all subsequent treatment will be at the assigned dose level.

[b]With the exception of infusion reaction ;

[c]For depressed K or Mg, administer replacement therapy. Chemotherapy should continue at the discretion of the treating physician. (see table below for management of hypomagnesemia).

Hypomagnesemia- Electrolyte repletion, principally magnesium, was necessary in some patients treated with cetuximab and in severe cases, intravenous replacement was required. The time to resolution of electrolyte abnormalities is not well known, hence

monitoring during and after cetuximab treatment is recommended:

CTCAE, v. 4 Grade	Serum Magnesium		Guidelines for management	Action
	mg/dL	mmol/L		
1	< LLN – 1.2	< LLN – 0.5	Consider replacement with IV magnesium sulphate 2-5 g in normal saline or D5W. Infusion schedule based on institutional guidelines.	Maintain dose and schedule
2	< 1.2 – 0.9	< 0.5 – 0.4	As above for grade 1 and consider prophylactic weekly infusion of magnesium and/or oral magnesium supplementation (e.g. magnesium oxide) if grade 2 of higher hypomagnesemia persists.	Maintain dose and schedule
3	< 0.9 – 0.7	< 0.4 – 0.3	As above for grades 1 and 2	Hold cetuximab until recovery to ≤ grade 2, then resume at same dose level or reduce by 1 dose level
4	< 0.7	< 0.3	As above for grades 1 and 2	Hold cetuximab until recovery to ≤ grade 2, then resume at same dose level or reduce by 1 dose level

7.3.4 Management of Cetuximab Infusion Reactions (adapted from RTOG 1016)

CTCAE, v. 4 Adverse Event Grade	Treatment Guidelines[a]
Grade 1: Mild transient reaction; infusion interruption not indicated; intervention not indicated	For mild infusion reactions manifesting only as delayed drug fever, consider administering prophylactic antihistamine medications for subsequent doses. Maintain the cetuximab dose, but slow the infusion rate by 50%. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.
Grade 2: Therapy or infusion interruption indicated but responds promptly to symptomatic treatment (e.g., antihistamines, NSAIDS, narcotics, *IV* fluids); prophylactic medications indicated for $\leq$ 24 hrs	For moderate infusion reactions manifesting only as delayed drug fever, slow the infusion rate for cetuximab by 50% and consider administering antihistamine medications and/or steroidal medications. Maintain the cetuximab dose. Acetaminophen or a non-steroidal anti-inflammatory drug (NSAID) may be administered prior to subsequent cetuximab infusions, if not otherwise contraindicated in subjects.
Grade 3: Prolonged (e.g., not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement; hospitalization indicated for clinical sequelae	Severe infusion reactions **require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab.** Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.
Grade 4: Life-threatening consequences; urgent intervention indicated	**NO FURTHER STUDY DRUG THERAPY.** Life threatening infusion reactions **require immediate interruption of cetuximab infusion and permanent discontinuation from further treatment with cetuximab.** Appropriate medical therapy including epinephrine, corticosteroids, diphenhydramine, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Subjects should be carefully observed until the complete resolution of all signs and symptoms.

If a patient has an infusion reaction, the infusion rate must be decreased. If a second infusion reaction occurs at the reduced infusion rate, the cetuximab must be stopped.

7.3.5 Cetuximab Special Instructions If cetuximab is omitted for more than four consecutive infusions for adverse events due to cetuximab, or for an intercurrent illness (e.g., infection) requiring interruption of therapy, the subject should be discontinued from further cetuximab therapy. Cetuximab doses held due to toxicity should not be made up. If a cetuximab dose is missed for reasons unrelated to drug toxicity, then the missed dose may be made up at the discretion of the Medical Oncologist, at the next appropriate time point. If adverse events prevent the administration of cetuximab, the subject may continue to receive radiation therapy.

7.3.5.1 Management of Cetuximab Infusion Reactions Severe or life threatening (grade 3 or 4) infusion reactions require the immediate interruption of cetuximab therapy and permanent discontinuation from further treatment. Appropriate medical therapy including epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen should be available for use in the treatment of such reactions. Patients should be carefully observed until the complete resolution of all signs and symptoms. In clinical trials, mild to moderate infusion reactions were managed by slowing the infusion rate of cetuximab and by continued use of antihistamine pre-medications (e.g., diphenhydramine) in subsequent doses. If the patient experiences a mild or moderate (grade 1 or 2) infusion reaction, the infusion rate should be permanently reduced by 50%. For grade 1 or 2 reactions manifesting only as delayed drug fever, see below. Cetuximab should be immediately and permanently discontinued in patients who experience severe (grade 3 or 4) infusion reactions.

7.3.5.2 Treatment of Isolated Drug Fever In the event of isolated drug fever, the investigator must use clinical judgment to determine if the fever is related to the study drug or to an infectious etiology. If a patient experiences isolated drug fever, for the next dose, pre-treat with acetaminophen or non-steroidal anti-inflammatory agent, repeat antipyretic dose 6 and 12 hours after cetuximab infusion. The infusion rate will remain unchanged for future doses. If a patient experiences recurrent isolated drug fever following pre-medication and post- dosing with an appropriate antipyretic, the infusion rate for subsequent dosing should be 50% of previous rate. If fever recurs following infusion rate change, the treating Medical Oncologist should assess the patient's level of discomfort with the event and use clinical judgment to determine if the patient should receive further cetuximab.

7.3.5.3 Cetuximab-related Rash

Manifestations Rash associated with EGFR-inhibitors is a relatively new dermatologic condition. It appears to be "acneiform" but it is NOT considered a form of acne; rather, it is a form of folliculitis. Skin changes may be manifested in a number of ways: erythema; follicle based papules, which may ulcerate; pain; itching; cosmetic disturbance; and/or nail disorders. The rash may become infected and transform into cellulitis.

Grading of Cetuximab-induced Rash According to physician judgment, if a patient experiences grade 3 rash, cetuximab treatment adjustments should be made. In patients with mild and moderate skin adverse events, cetuximab should continue without adjustment. **NOTE:** Rash intensity (i.e., the size and number of papules or the level of discomfort and extent of erythema) may be an important consideration. However, the absolute number of lesions, **without associated physical discomfort,** does not necessarily constitute a basis for a dose reduction or delay.

Skin and nail changes should be graded as follows, with dose modification for ≥ grade 3 changes.

	1	2	3	4
Pruritus*	Mild of localized	Intense or widespread	Intense or widespread and interfering with ADL	-
Rash/acneiform*	Papules and/or pustules covering <10% BSA, which may or may not be associated with symptoms of pruritus or tenderness	Papules and/or pustules covering 10-30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; associated with psychosocial impact; limiting instrumental ADLI	Papules and/or pustules covering >30% BSA, which may or may not be associated with symptoms of pruritus or tenderness; limiting self care ADL; associated with local superinfection with oral antibiotics indicated	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated with extensive superinfection with IV antibiotics indicated; life threatening consequences
Paronychia*	Nail fold edema or erythema; disruption of the cuticle	Localized intervention indicated; oral intervention indicated (e.g., antibiotic, antifungal, antiviral); nail fold edema or erythema with pain; associated with discharge or nail plate separation; limiting instrumental ADL	Surgical intervention or IV antibiotics indicated; limiting self care ADL	-

	1	2	3	4
Rash: dermatitis associated with radiation – Select: – Chemo-radiation – Radiation	Faint erythema or dry desquamation	Moderate to brisk erythema; patchy moist desquamation, mostly confined to skin folds and creases; moderate edema	Moist desquamation other than skin folds and creases; bleeding induced by minor trauma or abrasion	Life-threatening consequences; skin necrosis or ulceration of full thickness dermis; spontaneous bleeding from involved site; skin graft indicated

adapted from RTOG 1016

Cetuximab Dose Modification Guidelines for Dermatologic Changes (≥ Grade 3)			
	Cetuximab	Outcome	Cetuximab Dose Modification
1st occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Continue at 250 mg/m^2
		No Improvement; remains grade 3	Discontinue cetuximab
2nd occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Reduce dose to 200 mg/m^2
		No Improvement; remains grade 3	Discontinue cetuximab
3rd occurrence	Delay infusion 1 to 2 weeks	Improvement to ≤ Grade 2	Reduce dose to 150 mg/m^2
		No Improvement; remains grade 3	Discontinue cetuximab
4th occurrence	Discontinue cetuximab		

7.3.5.3.1 Drug Related Rash Management

Patients developing dermatologic adverse events while receiving cetuximab should be monitored for the development of inflammatory or infectious sequelae, and appropriate treatment of these symptoms initiated. Below are suggestions for managing cetuximab-induced rash adapted from: Perez-Soler R, Delord J, Halpern A, et al. HER1/EGFR inhibitor-associated rash: Future directions for management and investigation outcomes from the HER1/EGFR Inhibitor Rash Management Forum. *The Oncologist.* 10:345–356, 2005.

Antibiotics: The benefit of routine antibiotics in uncomplicated (uninfected) rash is unclear. Some clinicians have used oral minocycline (Minocin), mupirocin (Bactroban), or topical clindamycin (Cleocin). Rash complicated by cellulitis should be treated with appropriate antibiotics based on clinical judgment or microbial sensitivity analysis.

Antihistamines: Benadryl or Atarax may be helpful to control itching.

Topical Steroids: The benefit of topical steroids is unclear.

Retinoids: No data to support use. Use is not advised.

Benzoyl peroxide: Should NOT be used--may aggravate rash.

Makeup: Rash can be covered with makeup; this should not make it worse (use a dermatologist-approved cover-up, e.g., Dermablend, or any other type of foundation). Remove makeup with a skin-friendly liquid cleanser, e.g., Neutrogena, Dove, or Ivory Skin Cleansing Liqui-Gel.

Moisturizers: Use emollients to prevent and alleviate the skin dryness, e.g., Neutrogena Norwegian Formula Hand Cream or Vaseline Intensive Care Advanced Healing Lotion.

Sunlight: It is recommended that patients wear sunscreen and hats and limit sun exposure while receiving cetuximab as sunlight can exacerbate any skin reactions that may occur.

Over-the-counter medications: Over-the-counter acne vulgaris medications (e.g., benzoyl peroxide) are not advised. This rash is not like acne vulgaris and these treatments could make it worse.

7.4 Adverse Events

The descriptions and grading scales found in the revised NCI Common Terminology Criteria for Adverse Events (CTCAE), version 4.03. will be utilized for AE reporting. All serious adverse events will be reported to the IRB per institutional protocol.

8.0 TISSUE/SPECIMEN SUBMISSION

8.1 Tissue/Specimen Submission

Tumor tissue and blood will be collected from all patients when possible. Tumor tissue will be collected at the time of resection and will include specimens from the primary tumor and nodal disease as available. All University of Cincinnati specimens will be maintained in the UCCI Tumor Bank per institutional protocol or will be requested from pathology. All University of Michigan specimens will be maintained at University of Michigan. Tissue and blood submission is encouraged but not required for protocol enrollment.

8.2 Buccal swab collection

For University of Michigan patients ONLY, buccal swabs will be collected from the area within the anticipated radiation field pre-cetuximab (between days -7 to 0), after the first dose of cetuximab (between days 3 and 7), and during radiotherapy (between days 22 and 30). Specimens will be collected as follows: After subject rinses his/her mouth with water, buccal cells (mucosal cells), will be scraped using sterile Cell Lifter (Manufacturer: CORNING LIFE SCIENCES PLASTIC 3008).

In order to obtain enough cells for analysis of proteins, cell lifer will be twirled 3-4 times gently. Total time will be about 20-30 seconds. The cells will be collected from the cell lifter into 50 ml sterile collection tube containing ice cold 5 ml of sterile PBS with protease and phosphatase inhibitor. These collection tubes will be transported to research laboratory located in Med Sci I (Room # 4311) on ice as soon as possible. The swabs will be transfer to freezer until testing.

Objective of Study:

1. Deep sequencing of DNA from normal and tumor specimen to identify driver oncogenes in given patient.
2. Analyze pharmacodynamic changes in the normal tissue collected before and during (total 3 time points/patient) radiotherapy for driver molecules identified by DNA sequencing using high density immunoblotting.

Correlate findings from objective 1 and 2 with clinical outcome in terms of toxicity and response

9.0 PATIENT ASSESSMENTS

9.1 Study Parameters:

Gross total resection/surgical pathology (for post-operative patients) or biopsy (for definitive patients) must be completed within 7 weeks prior to registration.

A general history & physical by a Radiation Oncologist and/or Medical Oncologist must be done within 2 weeks prior to registration, and an examination by an ENT or Head & Neck Surgeon must be done within 8 weeks prior to registration per routine standard of care.

9.2 Evaluation During Radiotherapy

A general history & physical by a Radiation Oncologist and/or Medical Oncologist must be done weekly per routine standard of care.

Patients must have CBCw/diff, CMP, and Mg every other week during radiation therapy per routine standard of care for cetuximab administration.

Biopsy of any lesion(s) suspicious for tumor recurrence is urged.

9.3 Evaluation in Follow Up

A history and physical by one of the following: a Radiation Oncologist, Medical Oncologist, an ENT, or a Head and Neck Surgeon must be performed at 1 and 3 months post-XRT, then q3 months for 2 years, every 6 months for 3 years, then annually for a total of 5 years. This is required for study entry and is chosen as it coincides with standard of care practice in follow-up for head and neck cancers. This should include a complete head and neck and cutaneous exam and review of systems focusing on head and neck, cutaneous and pulmonary complaints.

QOL and functional assessments (the Functional Assessment of Cancer Therapy-Head &

Neck (EORTC HN35); the Dermatology Life Quality Index (DLQI)) will be performed at Month 3, Month 12 and Month 24.

Chest imaging will be performed as indicated clinically.

Biopsy of any lesion(s) suspicious for tumor recurrence is at the discretion of the treating physician.

9.4 Outcomes Criteria

No evidence of disease (NED): All patients must have not measurable tumor following surgery. Local-Regional Relapse: Recurrent cancer in the tumor bed and/or neck not clearly attributable to a second primary neoplasm; both imaging and biopsy confirmation are recommended but not required. LRR will be further subdivided into three subcategories:

In-Field Local-Regional Relapse- Review of the imaging of the local-regional relapse and the patient's previous RT treatment data reveals that the "epicenter" of the local-regional relapse is within CTV60 and received an estimated dose of at least 50 Gy.

Marginal Local-Regional Relapse- Review of the imaging of the local-regional relapse and the patient's previous RT treatment data reveals that the "epicenter" of the local-regional relapse was "near" CTV60. This is defined as an estimated dose to this region that is between 20 and 50 Gy.

Out-of-Field Local-Regional Relapse- Review of the imaging of the local-regional relapse and the patient's previous RT treatment data reveals that the "epicenter" of the local-regional relapse was not near CTV60 or CTV56 and received an estimated dose < 20 Gy.

Distant Relapse: For clinical evidence of distant metastases (lung, bone, brain, etc.); biopsy is required. A solitary lung mass/nodule should be considered a second primary upper aerodigestive neoplasm unless proven otherwise.

Second Primary Neoplasm: All second primary neoplasms will be biopsy proven with documentation of specific histology. Modified rigorous criteria for a second primary (below) have been adapted from the definition by Warren and Gates (1932).

A distinct lesion separated from the primary tumor site by > 2 cm of normal epithelium; a new cancer with different histology; Any cancer, regardless of head and neck mucosal subsite, occurring 5 or more years after initial treatment; In the lung, new primary tumors, if squamous cell cancer, must have histologic findings of dysplasia or CIS.

Second Primary Upper Aerodigestive Neoplasm: The emergence of a new, invasive malignancy in the upper aerodigestive tract as a second primary should be documented. These neoplasms include lung cancer, esophageal cancer (including GE junction cancer), or 2nd primary head and neck cancer that is clearly remote from the index cancer.

9.5 Quality of Life and Functional Assessments

The assessments will be completed prior to the start of cetuximab (baseline) and at 3, 12, and 24 months from the end of RT.

9.5.1 *The Functional Assessment of Cancer Therapy-Head & Neck (FACT HN)* is a multidimensional, patient-self report quality of life (QOL) instrument specifically designed and validated for use with head and neck patients.

9.5.2 *The Dermatology Life Quality Index (DLQI)* consists of 10 items and covers 6 domains including symptoms and feelings (e.g., felt itchy, sore, painful, embarrassed), daily activities, leisure, work and school, personal relationships, and treatment.

9.6 Criteria for Discontinuation of Protocol Treatment

Reasons for discontinuation of protocol treatment will include unacceptable toxicity, patient withdrawal of consent, progression of disease or development of a second primary malignancy. In the event that a patient discontinues protocol treatment, follow-up and data collection will continue as specified in the protocol.

9.7 Off study criteria

Reasons for patient discontinuation of study include completion of study follow-up, death or lost to withdrawal of patient consent (including patients lost to follow-up). A patient may withdraw consent partially or fully at any time during the study. Partial withdrawal of consent will be defined as patient refusal to continue protocol therapy while continuing to consent to follow-up on study. Full withdrawal of consent will be defined as refusal of any further participation in the study.

10.0 Statistical Considerations

This is a Phase II trial to characterize the 2 year loco-regional control of patients with locally advanced cutaneous squamous cell carcinomas of the head and neck treated with post-operative radiotherapy and cetuximab. Our secondary goal is to characterize the oncologic and quality of life outcomes associated with this treatment. Cetuximab has previously been given safely in conjunction with head and neck radiotherapy for mucosal squamous cell carcinoma in multiple phase III trials, and so Phase I data is not necessary here. Patients receiving at least 80% of the radiotherapy dose prescribed will be considered to have completed protocol therapy. Patients who complete therapy but become non-evaluable for toxicity before the post-treatment observation period ends will be counted as evaluable in the final analysis, and weighted in statistical analyses by the proportion of the 18-week toxicity observation period for which they were evaluable.

Patient accrual is projected to be 20-25 cases per year based on current estimates of the number of patients with locally advanced CSCCHN diagnosed/treated annually at the University of Cincinnati and the University of Michigan. Otolaryngology billing records from University of Michigan suggest that 65-75 patients annually undergo resection of locally advanced cutaneous squamous cell carcinoma and all would be potential trial candidates. It is expected that this trial will be open to accrual for 24-36 months.

This is a Simon 2-stage design with 40 patients in stage 1 and an additional 70 in stage 2.

The null hypothesis is 0.65 LRC at 2 years and the alternative is 0.78 LRC at 2 yrs. An interim analysis will be performed after 40 patients are accrued and the first 20 patients have had 2 years of potential follow-up. Kaplan-Meier estimates will be used to determine futility. The trial may go on to accrue a total of 110 patients.

The sample size of 110 patients begins with the hypothesis that the use of concurrent cetuximab and radiotherapy post-operatively improves 2 year loco-regional control (LRC) compared to radiotherapy alone. Using Simon's optimal two stage design with locoregional control as the primary efficacy point, 2 year loco-regional control for patients with locally advanced CSCCHN has historically been 55-70 % with resection and post-operative radiotherapy alone at 2 years, with 5 year overall survival of approximately 40-55% and median survival of 20-25 months. In the multi-center, randomized trial of mucosal SCCHN by Bonner et al., the additional of cetuximab to radiotherapy increased 2 yr LRC from 41 to 50% and correspondingly increased 5 yr OS from 36 to 45%. Based on these results, our target loco-regional control would be 78% based on the University of Cincinnati experience achieving 65% loco-regional control with post-operative RT alone. We would reject the null hypothesis if greater than if Kaplan Meier curves estimated greater than 72% loco-regional control.

Initial statistical design was formed with the help of Jareen Meizen-Derr, PhD, MPH in the Division of Biostatistics and Epidemiology at CCHMC. Data collection would be completed by the UCCI Clinical Trials Office and data analysis would be completed by a biostatistician within the Department of Radiation Oncology. Changchun Xie, PhD in the Dept of Epidemiology and Biostatistics will be the statistician analyzing data for this trial going forward at the University of Cincinnati. The trial will also be opened at the University of Michigan.

Loco-regional control and overall survival will be estimated by the Kaplan-Meier method.

Definitions of Endpoints

2 year LRC will be defined as the absence of tumor appearance in the primary site or neck within 2 years, as assessed and documented through clinical exam and imaging completed q3 months by treating physicians during the follow-up period. Loco-regional recurrence should be confimed by biopsy when possible, and the precise location documented (primary site versus neck).

2 yr DFS will be defined as absence of loco-regional recurrence or the development of metastatic disease within 2 years, as assessed by q3 month clinical exam and annual chest imaging. Distant metastases should be biopsied when possible, and a solitary spicualted lung nodule is considered a second primary neoplasm unless proven otherwise. 2 and 5 year OS will be defined as the absence of death from any cause during those time periods.

The QOL analysis is the change of QOL score on the FACT-HN and DLQI from baseline to the 3, 12 and 24-month intervals. The mean summary score and standard deviation of these scales will be calculated and the mean change summarized for each time point.

11. Data collection and Data and Safety Monitoring

Each site will be responsible for oversight of the trial as well as data and safety monitoring. See below for each site specifications.

11.1 Data collection

At the University of Cincinnati, patient data will be collected at time of study visits or through the electronic medical record and data will be stored securely within OnCore. The University of Michigan will utilize Velos.

Per our data use agreement, de-identified study data may be shared between University of Cincinnati and University of Michigan.

11.2 Data and Safety Monitoring

UCCI: All cancer related therapeutic clinical trials conducted at the University of Cincinnati Cancer Institute (UCCI) require monitoring by a safety committee as part of their Data Safety and Monitoring Plan. The internal UCCI Data Safety Monitoring Board (DSMB) will monitor all investigator initiated studies. The DSMB is an independent group of experts who will advise the study investigators and report relevant findings to IRB or other appropriate authorities.

Study parameters may vary depending on the type and risk of the study under evaluation. Each study will be evaluated at least twice a year. The DSMB will focus on the analytic plan to include: hypothesis, primary objective, endpoints and will monitor study conduct including accrual, protocol required tests, IND, toxicities and efficacy. The DSMB will use case report forms, and data points to complete their safety assessment and make recommendations for a continued monitoring plan. All meetings are recorded by the DSMB Coordinator.

DSMB initial study evaluation will occur after previous Protocol Review and Monitoring committee (PRMC) and Institutional Review Board (IRB) approval. If the DSMB recommends a study design amendment or the PI desires to amend the study, PRMC approval will be required.

All serious adverse events will be reported immediately to the DSMB Chair and other members of the DSMB by the study sponsor or designee. The DSMB Chair or DSMB Administrator will notify the Study Sponsor (or sponsor designee) directly of any findings of a serious and immediate nature or recommendations to discontinue all or part of the trial. An Immediate Action report will be created and submitted to the UCCI CTO Regulatory Coordinator for appropriate dissemination to regulatory authorities.

UM: This trial will be locally monitored in accordance with the NCI approved University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Plan.

The study team will meet quarterly or more frequently depending on the activity of the protocol. The discussion will include matters related to the safety of study participants (SAE/UaP reporting), validity and integrity of the data, enrollment rate relative to expectations, characteristics of participants, retention of participants, adherence to the protocol (potential or real protocol deviations) and data completeness. At these regular

meetings, the protocol specific Data and Safety Monitoring Report form will be completed and signed by the Principal Investigator or by one of the co-investigators.

Data and Safety Monitoring Reports will be submitted to the University of Michigan Comprehensive Cancer Center Data and Safety Monitoring Committee on a quarterly basis for independent review.

Data and Safety Monitoring Reports will be submitted to the coordinating center, UCCI, for overall review of study conduct.

12. Study Calendar

Screening labs should be completed within two weeks of starting treatment. Chest CT or PET/CT required within 8 weeks prior to registration.

Day	Screening	Wk1	Wk2	Wk3	Wk4	Wk5	Wk6	Wk7	Wk8	Follow-up
Cetuximab[a]		X	X	X	X	X	X	X	X	
Radiation[b]			X	X	X	X	X	X	X	
Informed consent	X									
Demographics	X									
Medical history	X									
Concurrent meds	X	X	X	X	X	X	X	X	X	X
Physical exam[c]	X	X	X	X	X	X	X	X	X	X
Vital signs	X							X		X
Height	X									
Weight	X							X		X
Performance status	X	X	X	X	X	X	X	X	X	X
CBC w/diff, plts	X		X		X		X		X	
CMP/Mg	X		X		X		X		X	
Pregnancy Test[d]	X									
Radiologic evaluation[d]	X									X[e]
Adverse event evaluation	X							X		X
PD blood draws/Tissue collection	X[f]									
QOL	X									X[g]

a. On days when Cetuximab is given with RT, Cetuximab should be given prior to RT. Cetuximab should be given 1 week prior to beginning radiation and then every week during radiation for a total of 7-8 doses. There is a +/- 2 day window for cetuximab treatments. In cases of RT delay, cetuximab may continue beyond week 8 until radiation completed not to exceed 11 doses.
b. M-F per standard of care
c. To be performed by medical oncologist (or NP), radiation oncologist or ENT surgeon
d. Serum pregnancy test (women of childbearing potential).
e. CT chest or PET/CT at screening and then Chest Xray, or Chest CT or PET/CT as clinically indciated
f. optional
g. Follow-up months 3, 12 and 24

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