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Title: A Pilot Study of Neoadjuvant Cetuximab in Advanced Squamous Cell Carcinomas of Skin (SCCS)

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LIST OF ABBREVIATIONS

(examples of some commonly used abbreviations, include any used in protocol)

AE	Adverse Event
ANC	Absolute neutrophil count
BUN	Blood urea nitrogen
BRS	Biospecimen Repository Service
CBC	Complete blood count
CINJOG	Cancer Institute of New Jersey Oncology Group
CT	computer tomography
CR	Complete response
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
DSMP	Data Safety Monitoring Plan
ECG	Electrocardiogram
FDA	Food and Drug Administration
HHS	Department of Health and Human Services
IRB	Institutional Review Board
kg	kilograms
mL	milliliters
mcg/μg	Micrograms
MRI	Magnetic Resonance Imaging
NCI	National Cancer Institute
NIH	National Institutes of Health
OHRS	Office of Human Research Services
OHRP	Office of Human Research Protection
PBMC	Peripheral blood mononuclear cells
PD	Progressive disease
PET	Positron Emission Tomography
PHI	Protected health information
PI	Principal Investigator
PR	Partial response
RWJUH	Robert Wood Johnson University Hospital
SAE	Serious adverse event
SD	Stable disease
sCr	Serum creatinine
SGOT	Serum glutamic oxaloacetic transaminase
SGPT	Serum glutamic pyruvic transaminase
ULN	Upper limit of normal

1. Purpose/Specific Objectives

The purpose of this protocol is to serve as a pilot study for neoadjuvant cetuximab in potentially resectable, advanced squamous cell carcinoma. The primary hypothesis is that cetuximab used in

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the neoadjuvant setting for locally advanced squamous cell carcinomas is both safe and well tolerated and that its use may enhance the treatment of advanced cases of SCCS when delivered preoperatively. The overall treatment strategy expressed in the protocol is to treat locally advanced/unresectable squamous cell carcinomas with 8 weeks of neoadjuvant cetuximab, and monitor patients for disease response, adverse events, and overall safety. Potentially, patients may be able to go on to surgical resection if adequate disease response is achieved. The hope is that the data derived from this study will lead to a large randomized trial testing the efficacy of this approach in this disease, which has few available treatment options.

1.1 Primary Objective(s)

The co-primary endpoints are to
a) assess the response rate of cetuximab by RECIST criteria in patients with advanced SCCS and, b) to assess whether neoadjuvant cetuximab given in this patient population is both safe and feasible.

1.2 Secondary Objective(s)

1.2.1 To measure the progression free and overall survival of patients with advanced SCCS who receive neoadjuvant cetuximab.
1.2.3 To determine the conversion to resectability of patients treated with neoadjuvant cetuximab and capture changes in reconstructive options rendered possible by neoadjuvant treatment.
1.2.3 Molecular correlates. All patients must have a biopsy of the locoregional disease (primary site or neck lymph nodes), and of the skin prior to therapy. Patients will also have tissue harvested at surgery that will undergo molecular analysis, or a second post treatment biopsy if surgery is not feasible. Our goals in the molecular analysis are to explore the following possibilities:

-Analyze the relationship of known DNA mutations in tumor per the FoundationOneTM genomic profile, and correlate to clinical endpoints such as clinical benefit and conversion to resectability to discover potential markers of response and/or resistance.
-Measure the downstream activation of signaling pathways without a known driver, including the EGFR pathway.
-Determine if tumor shrinkage with cetuximab is associated with increased apoptosis as evidenced by activated caspase-3, in pre- and post- treatment tumor tissues.
-Determine whether cetuximab results in increased ADCC in post-, compared with pre-treatment tumor tissues.

2. Background and Significance

2.1 Supporting Data and Rationale

Nonmelanoma skin cancers are the most common malignancies among Caucasians. Squamous cell carcinoma (SCC) of the skin is an increasingly common diagnosis, and is the second most common type of skin cancer worldwide (Alam and Ratner 2001). Specifically, results from a population based study performed in the United States using governmental data on skin cancer procedures and related office visits estimated the number of new skin cancer diagnoses to be over

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3.5 million in 2006 (Rogers, Weinstock et al. 2010). Regardless of the true incidence, it is known that the number of cases has consistently risen over the past 20 years. This observation can be related to improved detection of skin cancer, increased UV and tanning bed exposure, and the aging of the U.S. population, since the incidence of SCCS increases dramatically with age (Bauman, Eaton et al. 2007). It follows, then, that with a 10% decrease in stratospheric ozone annually and the continued growth of the aging U.S. population, the number of metastatic squamous cancers arising from a skin primary is certain to continue increasing annually for the foreseeable future. These cancers also plague patients who are recipients of solid organ transplants, historically a difficult population of patients for the delivery of cytotoxic systemic therapies.

It should be noted that SCC and its precursor lesions can carry a significant morbidity associated with diagnosis, with an opportunity for recurrence, local or distant metastases, treatment related complications, and increased risk for development of secondary cancers (Wassberg, Thorn et al. 1999). Most often, these lesions are localized and amenable to surgery. Larger and more invasive lesions often require multimodality care, but relatively little has been done to investigate a generalized management plan for these situations (Gaffney, Soyer et al. 2013). As a result, there is a lack of high-level data on systemic treatment options for cutaneous SCC unamenable to resection. A 10-year cohort study involving 985 patients with SCC found a 3.7% risk of metastasis and 2.1% risk of disease-specific death (Schmults, Karia et al. 2013). Published case reports have demonstrated responses with platinum-based chemotherapy with occasional complete responses noted in this patient population (Lawson, Otto et al. 2008, Nakamura, Okuyama et al. 2013). There are no prospective phase III studies available, and only one prospective phase II study regarding the use of platinum-based chemotherapy in this population. Cisplatin, either as a single agent or combined with 5-FU, has occasionally produced useful responses, but again, data supporting efficacy is limited. In the only phase II study of biochemotherapy with interferon alfa, cis-retinoic acid and cisplatin, 35 patients were assessed for response, 11 of which had distant metastases (Shin, Glisson et al. 2002). One of the 11 patients experienced a complete response. Twelve patients with only regional lymph node metastases were treated and 3 had either a partial (2) or complete (1) response. This lends some credence to a cisplatin-based regimen. Other studies are retrospective and most are anecdotal (Weinberg, Ogle et al. 2007, Cranmer, Engelhardt et al. 2010). In summary, historically, advanced SCCS is incredibly challenging to treat given its presence in a patient population which often has multiple comorbidities. In addition, the absence of randomized clinical trials that would provide guidelines for therapy further complicates this clinical situation. **These facts underscore that this population of patients represents an unmet medical need that is likely to grow as the elderly U.S. patient population increases and as such, is a ripe area for clinical investigation.**

One potential novel treatment option includes targeting the epidermal growth factor receptor which is highly expressed in many epithelial tumors, including squamous cell carcinomas of the skin (DeConti 2012). The epidermal growth factor receptor (EGFR) has also been implicated in SCC development, specifically, it has been shown to be involved in UV-induced skin carcinogenesis (Gaffney, Soyer et al. 2013). Additional evidence in support of a relevant role of EGFR expression in these cancers includes a retrospective study, which demonstrated that primary cutaneous SCC of the head and neck that subsequently metastasized were more likely to overexpress EGFR than those

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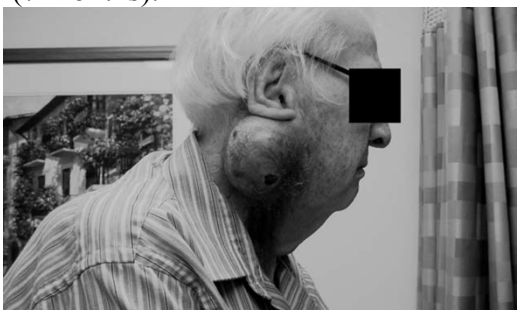
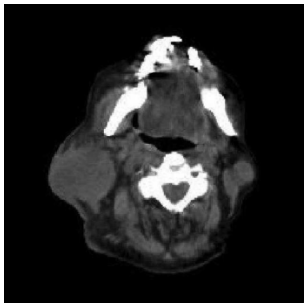
that did not (Bonner, Harari et al. 2006). Accordingly, the development of anti-EGFR drugs has been pursued for use in various malignancies.

One such new EGFR-directed therapy is cetuximab, a monoclonal antibody that competitively inhibits EGFR (Gaffney, Soyer et al. 2013). Its mechanism of action is likely dual, in that it competitively inhibits natural EGFR ligands, preventing EGFR phosphorylation and it elicits antibody-dependent cell cytotoxicity (ADCC) (Fan, Masui et al. 1993, Lopez-Albaitero and Ferris 2007). It has been approved in the treatment of SCC of the head and neck, in combination with radiation and/or platinum-based chemotherapy (Gaffney, Soyer et al. 2013). A randomized controlled trial by Bonner et al. in advanced oropharynx, hypopharynx, and larynx SCC of external beam radiation therapy + cetuximab versus EBRT alone revealed an improvement in 5 year overall survival for the cetuximab arm from 36.4% to 45.6% (Bonner, Harari et al. 2006). Cetuximab has also been used in EGFR-expressing, KRAS wild-type metastatic colorectal cancers in combination with chemotherapy regimens (Gaffney, Soyer et al. 2013). Additionally, studies demonstrating the efficacy of Cetuximab in recurrent squamous cell carcinomas have been promising (Bauman, Eaton et al. 2007). Data regarding use of cetuximab in advanced SCCS is scarce and consists of a few case series reports and one phase II trial (Nadiminti, Shao et al. 2013). The largest of these studies was published by Maubec et al, who reported the use of cetuximab as first line therapy for unresectable squamous cell carcinoma of the skin expressing EGFR in a phase II nonrandomized setting. The trial accrued 36 poor-prognosis patients and demonstrated an overall disease control rate of 69% (Maubec, Petrow et al. 2011). Additionally, a prospective study looking at cetuximab with or without systemic chemotherapy in patients with locally recurrent or unresectable disease demonstrated clinical improvement in pain, tumor ulcer, and bleeding compared to pretreatment symptoms. Treatment with cetuximab was generally well tolerated with the main side effect being skin rash (Nadiminti, Shao et al. 2013). Multiple published case and retrospective reports have documented tumor responses in patients with SCCS treated with cetuximab (Bauman, Eaton et al. 2007, Suen, Bressler et al. 2007, Miller, Sherman et al. 2010, Kim, Eleff et al. 2011, Kalapurakal, Malone et al. 2012), with one from our institution demonstrating an impressive complete response in an elderly patient with squamous disease (Kim, Eleff et al. 2011) (Figure 1).

Figure 1. Images of a clinical complete response to cetuximab in a 92 year old man. Images from left: Patient prior to cetuximab (photo and CT), six weeks after cetuximab. Cetuximab was administered weekly from July to October 2008. The clinical CR lasted until patient's last follow up in 2009 (7 months).





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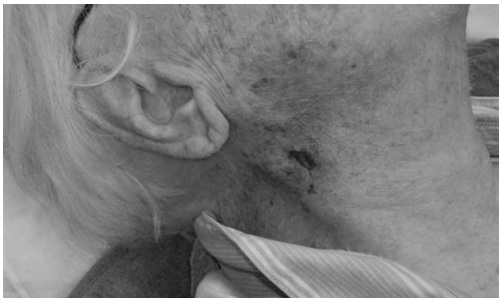

Despite the fact that cetuximab has clear activity in cutaneous SCC, the exact mechanism of action in this disease is not clear. Cetuximab is a chimeric monoclonal antibody of the immunoglobulin G1 class, which binds with high affinity to the extracellular domain of the human EGFR. As the affinity of cetuximab for EGFR is approximately 5 to 10 fold higher than that of the endogenous ligands, it blocks the binding of these ligands to the extracellular domain of the receptor as well as ligand dimerization, resulting in inhibition of the receptor function and signaling (Markovic and Chung 2012). Furthermore, cetuximab induces the internalization of EGFR, which can lead to downregulation of EGFR (Figure 2). Binding to EGFR blocks phosphorylation and activation of receptor-associated kinases, resulting in inhibition of cell growth leading to apoptosis (Kirkwood, Butterfield et al. 2012). However, despite overexpression of EGFR in 80-90% of head and neck cancers, clinical activity remains limited to 10-20%. In addition, unlike in non small cell lung cancer, activating mutations in EGFR are rare in squamous carcinomas arising in the head and neck, and in limited analyses done to date, also in squamous carcinomas arising in the skin (Chung, Ely et al. 2006).

It is possible that in squamous cancers of the skin, a tumor type prone to a heavy mutation burden given its exposure to and dependence upon UV radiation for initiation, driver mutations may play a lesser role in tumor development and maintenance, or are as of yet, undiscovered. In this disease, cetuximab may be exerting antitumor activity through other mechanisms. For instance, as a chimeric IgG1 type monoclonal antibody, cetuximab may initiate antitumor responses through targeting of cytotoxic immune effector cells towards EGFR expressing tumor cells (antibody dependent cell-mediated cytotoxicity) (Vermorken, Mesia et al. 2008, Martinelli, De Palma et al. 2009, Srivastava, Lee et al. 2013). This mechanism has recently been implicated in squamous malignancies of the head and neck.

In summary, cetuximab exhibits antitumor activity in advanced cases of squamous carcinoma of the skin, a population that represents a major unmet need with few proven treatment options. Our planned study will assess the ability of cetuximab to shrink locally advanced or aggressive tumors prior to surgery, measuring tumor response rate as a co-primary endpoint, and will investigate whether the delivery of this medication could possibly result in improved surgical reconstructive options. This trial will provide a unique window of opportunity to investigate the antitumor activity of cetuximab in patients with aggressive or recurrent squamous skin cancers who are candidates for neoadjuvant cetuximab. This trial will also allow us to assess the safety and feasibility of cetuximab in this patient population, which historically is of greater age and has more comorbid conditions than

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patients with other advanced squamous tumors, such as locally advanced squamous tumors of the head and neck.

An important strength of this study is the use of serial biopsies to allow us to investigate the mechanism of action of cetuximab and to discover potential predictors of response and/or resistance that can be validated in future trials. Our mechanistic studies will focus on 1) apoptosis and 2) ADCC as possible mechanisms of cell death. Pre-and post-treatment tissues will be assayed for evidence of increased caspase-3 as an indication of apoptosis and for evidence of ADCC. We will also measure changes in protein or mRNA production in response to cetuximab that may lead us to discover potential mechanisms of response or resistance. For instance, as we are also investigating in protocol CINJ# 031204, there is evidence that EGFR and IGF-1R interact on multiple levels, either through a direct association between the two receptors, by mediating the availability of each others ligands, or indirectly, via common interaction partners such as G protein coupled receptors (GPCR) or downstream signaling molecules, a cross-talk that may play a role in resistance to EGFR inhibitors. We will be able to explore protein expression of EGFR and IGFR pathway members in pre-and –post treatment tumor samples. Finally, we will utilize the FoundationOne genomic profile to assess the relationship of known DNA mutations with clinical endpoints such as clinical benefit and conversion to resectability. It is known that mutations in the TP53 tumor suppressor gene are very common in SCCs (Brash, Rudolph et al. 1991) and occur early in skin cancer development in keratinocytes (Jonason, Kunala et al. 1996, McGregor, Berkhout et al. 1997). Inactivation of CDKN2A and activating RAS mutations have also been described (Boukamp 2005). It is not clear, however, if these events are the main drivers of tumor initiation and maintenance, or if other potentially targetable genomic gains or losses occur which may be responsible. Our analysis will provide preliminary information that may shape personalization of treatment for these patients and optimize patient selection for therapy in the future. Of great use will also be the banked tumors that will be collected and stored as part of this study, an extremely useful resource for testing alternative hypotheses as additional information becomes available.

Figure 12 From *Chen LF, Cohen E, Grandis JR. New Strategies in Head and Neck Cancer: Understanding Resistance to Epidermal Growth Factor Receptor Inhibitors. Clin Cancer Res 2010;16:2489- 2495.*

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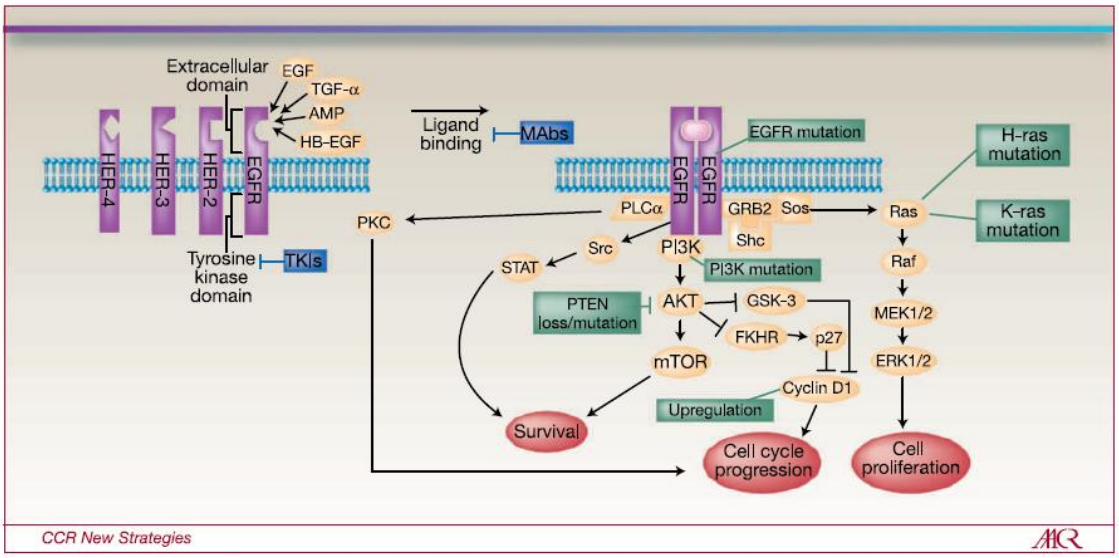

Fig. 1. EGFR signaling pathway and several mechanisms of resistance to EGFR-targeted therapies.

3. Participating Institutions

This protocol will be available at the Rutgers Cancer institute of New Jersey/RWJUH in New Brunswick and Hamilton Campuses. All biopsies and subsequent surgery will be performed at these facilities.

4. Experimental Design and Methods

4.1 Duration of Study

20 patients are planned to be enrolled. The patients will be under active treatment with cetuximab monotherapy for approximately 8 weeks. Afterwards, they will be assessed for disease response and determination of whether the lesion is potentially resectable will be made. We expect that patients will be accrued within 24 months and that followup time will average 18-24 months per patient.

5. Patient Selection Criteria

5.1 Inclusion Criteria

A patient is eligible for enrollment if all of the following inclusion criteria are met.

5.1.1 Patients must have untreated or relapsed SCCS that is considered to be aggressive and locally advanced by the following criteria: tumors 2 cm or more, tumors invading deep tissues such as muscle, cartilage or bone; tumors showing perineural invasion, and/or tumors metastatic to loco-regional lymph nodes. Patients may have had prior surgical interventions or been treated with investigational agents with residual or recurrent disease.

5.1.2 Patients must give informed consent.

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5.1.3. Patients must agree to pre- and post- treatment biopsies.
5.1.4 Patients must have an ECOG performance status ≤2 (Appendix B).
5.1.5 Estimated life expectancy of at least 12 weeks.
5.1.6 Negative pregnancy test

5.2 Exclusion Criteria
A patient will not be eligible for this study if any of the following exclusion criteria are met.

5.2.1 Second primary malignancy only if treatment would interfere with the patient's participation in this trial in the opinion of the treating physician. Clear exceptions are 1) patient had a second primary malignancy but has been treated and disease free for at least 3 years, 2) in situ carcinoma (e.g. in situ carcinoma of the cervix) and, 3) additional skin cancers that have been definitively treated by surgery and/or radiation. Patients with chronic lymphocytic leukemia will be allowed if their blood counts are within acceptable hematologic parameters and if they are not currently requiring cytotoxic or biologic anticancer treatment (supportive treatment such as IVIG is permitted).

5.2.2 Patients with distant organ metastases will not be included in this study.

5.2.3 Serious concomitant systemic disorders (including active infections) that would compromise the safety of the patient or compromise the patient's ability to complete the study, at the discretion of the investigator.

5.2.4 Age <18 years.

5.2.5 History of allergic reactions attributed to compounds of similar chemical or biologic composition to cetuximab or other agents used in the study.

5.2.6 Women who are pregnant, due to the teratogenic effects of radiation therapy and chemotherapy on the unborn fetus. Women of childbearing age must agree to undergo a pregnancy test prior to therapy and to use adequate contraception (hormonal or barrier method of birth control; abstinence) prior to study entry, for the duration of study participation and for 6 months after. Should a woman become pregnant or suspect she is pregnant while participating in this study, she should inform her treating physician immediately. Menopausal status is defined by one or more of the following:
Successful hysterectomy, bilateral tubal ligation or bilateral oophorecatomy OR
Amenorrhea ≥ 12 consecutive months without another cause or for women with irregular menstrual periods and taking hormone replacement therapy (HRT), a documented serum follicle stimulating hormone (FSH) level ≥35 mIU/mL

5.2.7 Presence of the following grade 3-4 electrolyte abnormalities (CTCAE, v. 4.0):

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- Serum calcium (ionized or adjusted for albumin) < 8 mg/dl (1.75 mmol/L) or > 12.5 mg/dl (> 3.1 mmol/L) despite intervention to normalize levels
- Magnesium < 1.4 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

5.2.8 Prior radiation therapy is not an exclusion however, patient must have documented progression at the radiation site.

5.3 Inclusion of Women and Minorities
Women and minorities are welcome to participate.

5.4 Participation of Children
Children younger than 18 years of age are not eligible for this trial. SCCS of the skin is exceedingly rare in this population, and it is not expected that subjects of this age group will be eligible.

5.5 Sources or Methods of Recruitment
Patients will be recruited mostly from the Rutgers Cancer Institute of New Jersey/RWJUH and from physicians participating in the Cancer Institute Oncology Group (CINJOG).

5.6 Study Enrollment Procedures
A copy of the institution's IRB-approved informed consent document and written justification for any changes made to the informed consent for this protocol must be on file at the Rutgers Cancer Institute of New Jersey's Office of Human Research Services (OHRS) before any participating institution may enter patients. The CINJOG institution consent form must be reviewed and approved by OHRS Regulatory Affairs and all documents must be received (i.e., IRB approved documentation, IRB approved consent form, etc.).

To register eligible patients on this study, each site will contact OHRS. Contact information will be provided at the time of site activation. The signed and dated eligibility checklist, completed signature page of the consent form and additional source documents if requested by OHRS will need to be provided. Once OHRS verifies eligibility, a unique patient study number will be issued. The patient will not be identified by name. This is the point that the patient is considered on study. Patients must not start protocol treatment prior to registration.

If a patient does not receive any protocol therapy, baseline data will be collected and submitted on the pre-study and follow-up electronic case report forms (eCRF). The reason for not starting protocol therapy will be documented in the "follow-up eCRF". Case report form completion instructions and training will be provided to each participating institution prior to study activation at the participating institution.

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6. Study Parameters

Evaluations	Pre-cetuximab	Weekly during neoadjuvant cetuximab	Post-cetuximab (Week 9)	At surgery or prior to RT[7]	30 days after surgery or XRT	Follow ups every 3 months after surgery or XRT for 2 years	After locoregional or distant failure
History, physical exam and tumor site assessment	X[1] (within 14 days of treatment)	X[6]	X[7]		X[1]	X[1]	X[1]
Photo of tumor and/or rash at head, neck, upper torso put into EMR	X (within 14 days of treatment)	X[6]	X[7]				
Incisional/core biopsy of primary tumor and loco-regional lymph nodes if involved	X[8] (within 30 days of treatment)			X[8] (any time during this interval)			X (within 30 days of relapse)
Biopsy of skin	X[8] (within 30 days of treatment)			X[8] (any time during this interval)			X (within 30 days of relapse)
CBC, differential, platelets	X (within 14 days of treatment)	X			X	X	
Serum Chemistries[2]	X (within 14 days of treatment)	X	X	X	X	X	
Liver Enzymes[3]	X (within 14 days of treatment)	X			X	X	
Pregnancy Test[4]	X (within 14 days of treatment)						

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Radiographic Assessments[5]	X[5] (within 30 days of treatment)		X[5]			X	X[5]

*A +/- 2 day window is allowed for all study assessments indicated on this trial except treatment for which a +/- 1 day window is allowed.

1. To include toxicity assessment, ECOG performance status, weight
2. Includes: Electrolytes, including serum magnesium, potassium, Calcium, BUN, Creatinine, Glucose,
3. Includes: Total and Direct. Bilirubin, AST/ALT, Alkaline Phosphatase, Albumin, Total Protein.
4. Women 18-55 who have not undergone menopause must have urine pregnancy test within 14 days of enrollment.
5. Tumor assessments as indicated by investigator, i.e. PET/CT, CT neck, chest/abdomen and pelvis or MRI of neck as needed to be obtained no more than 1 month prior to cetuximab; then per standard of care, in general, every three months after conclusion of surgery or XRT.
6. Every 7 days
7. Includes evaluation by surgery and radiation oncology for optimal local therapy. Surgery will assess optimal timing of rebiopsy during their evaluation of patient once neoadjuvant therapy is complete.
8. See section 11

7. Treatment Plan

7.1 General Considerations The experimental aspect of this protocol is in the use of neoadjuvant cetuximab monotherapy in these patients with locally advanced or recurrent SCCS. Once treatment response to cetuximab monotherapy is established, the determination of patient tolerance to the selected dose and disease response/potential resectability of the lesion will be determined.

7.2 Sequence of treatment

7.2.1 Prior to neoadjuvant cetuximab

Patients will be staged using imaging to delineate the extent of disease. Initial biopsy specimen (preferably a core biopsy as opposed to a FNA) will be procured from the primary cutaneous site. If the patient is found to have regional lymph node involvement, core biopsy of accessible node will also be obtained. Samples will be used for confirmation of diagnosis as well as DNA and RNA genotyping. These specimens will be flash frozen and brought that same day to the Biospecimen Repository Service (BRS).

7.2.2 Neoadjuvant Cetuximab

Patients who agree and are eligible for this protocol will initially receive 8 weeks of neoadjuvant cetuximab. The initial dose of cetuximab will be 400 mg/m^2 IV, followed by

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weekly doses of cetuximab 250 mg/m^2 IV to complete 8 total weeks of treatment. Even if a patient is found to have a cetuximab related folliculitis, they will complete the scheduled 8 weeks of neoadjuvant cetuximab.

7.2.3 Assessing for response during and after neoadjuvant cetuximab

Response to cetuximab will be assessed by RECIST criteria.

7.2.3.1 Response by RECIST criteria

After 8 weeks of Cetuximab has been completed, the patient will have a restaging CT scan with IV contrast for comparison to the first CT scan performed prior to neoadjuvant cetuximab. CT response will be evaluated using RECIST criteria for partial response versus progressive or stable disease (Eisenhauer et al. 2009). The RECIST criteria will be applied to the combination of primary site and associated neck lymphadenopathy.

RECIST Criteria

Complete Response (CR)	**Disappearance of all target lesions**
Partial Response (PR)	**At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.**
Progressive Disease (PD)	**At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of one or more new lesions.**
Stable disease (SD)	**Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.**

7.2.4 Repeat Bx after neoadjuvant cetuximab.

After 8 weeks of neoadjuvant cetuximab, tissue will either be harvested at surgery, or if the patient is not a surgical candidate, a biopsy specimen (preferably a core biopsy as opposed to a FNA) will be procured from the primary site or accessible lymph node. As

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this tissue will be used for DNA and RNA sequencing, tissue that is fresh and sufficient in quantity is required. These specimens will be flash frozen and brought that same day to the BRS.

7.3 Study Agent (Cetuximab)

Cetuximab is an anti-EGFR receptor humanized chimeric monoclonal antibody. It is supplied as 100 mg/50 mL, single-use vial or a 200 mg/100 mL, single-use vial. For more information on this agent, refer to the FDA approved Package Insert.

7.3.1 Dose Calculation

Doses will be calculated on day 1 of each cycle using the patient's actual weight in the determination of body surface area. A variance of 10% of the calculated total dose will be allowed.
BSA (m^2) =square root of ((*height inches*) *x* (*weight lbs*) /3131)

7.3.2 Treatment Administration

During neoadjuvant cetuximab, the initial dose is 400 mg/m^2 administered as a 120 minute intravenous infusion (maximum infusion rate 10 mg/min). The subsequent weekly doses are 250 mg/m^2 infused over 60 minutes (maximum infusion rate 10 mg/min). If a weight change of ≥ 10% occurs, the cetuximab dose should be adjusted.

Cetuximab should not be delivered as an intravenous push or bolus. Administer via infusion pump or syringe pump. Do not exceed an infusion rate of 10 mg/min. Administer through a low protein binding 0.22- micrometer in-line filter. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. The solution should be clear and colorless and may contain a small amount of easily visible, white, amorphous, cetuximab particulates. Do not shake or dilute.

7.3.3 Dose Modifications or Escalations

7.3.3.1 Cetuximab related Folliculitis

Patients will concomitantly be assessed for the presence of cetuximab related folliculitis given the published correlation of folliculitis with clinical benefit (Bonner 2006). After MD visits, the patient will be assessed for the development of folliculitis characteristic of EGFR inhibition. Though the rash associated with EGFR inhibition appears similar to acne vulgaris and is commonly referred to as acne, acne-like, or acneiform, these terms are technically inaccurate. EGFR-associated rash is dominated by pustules that contain an intrafollicular collection of neutrophils—the hallmarks of an infectious folliculitis. Per Perez-Soler, the typical EGFR associated rash has a clinical presentation

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characterized by pustular/popular appearance, usually involving the face, head, and upper torso, and often accompanied by pruritus, dry skin, and erythema (Perez-Soler, Zou et al. 2011).

In previous reports, the criteria used for significant EGFR associated rash has most commonly been grade 2+ on the CTCAE 4.0 criteria listed below.

CTCAE 4.0 Criteria

	1	2	3	4
Pruritus/itching	Mildor localized	Intense or widespread	Intense or widespread and interfering with ADL	_
Rash/Desquamation	Macular or papular eruption or erythema without associated symptoms	Macular or papular eruption or erythema with pruritus or other associated symptoms; localized desquamation or other lesions covering < 50% of body surface area (BSA)	Severe, generalized erythroderma or macular, papular or vesicular eruption; desquamation covering > 50% BSA	Generalized, exfoliative, ulcerative, or bullous dermatitis
Rash/Acneiform	Intervention not indicated	Intervention not indicated	Associated with pain, disfigurement, ulceration, or desquamation	_
Nail Changes	Discoloration; Ridging (koilonychias); pitting	Partial or complete loss of nail(s); pain in nail bed(s)	Interfering with ADL	_

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7.3.3.2 Infusion Reactions

Serious infusion reactions occurred with the administration of Cetuximab in approximately 3% of patients in clinical trials, with fatal outcome reported in less than 1 in 1000. Reduce the infusion rate by 50% for NCI CTCAE Grade 1 or 2 and non-serious NCI CTCAE Grades 3–4 infusion reactions. Once the infusion rate has been decreased due to an infusion reaction, it will remain decreased for all subsequent infusions. If the subject has a second infusion reaction at the slower infusion rate, the infusion should be stopped, and the subject should receive no further cetuximab treatment. Immediately and permanently discontinue cetuximab for serious infusion reactions that are life threatening and/or require hospitalization. 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.

Serious infusion reactions, requiring immediate, permanent discontinuation of cetuximab included rapid onset of airway obstruction (bronchospasm, stridor, hoarseness), hypotension, shock, loss of consciousness, myocardial infarction, and/or cardiac arrest. Severe (NCI CTCAE Grades 3 and 4) infusion reactions occurred in 2–5% of 1373 patients in clinical trials, with fatal outcome in 1 patient. Approximately 90% of severe infusion reactions occurred with the first infusion despite premedication with antihistamines.

Monitor patients for 1 hour following Cetuximab infusions in a setting with resuscitation equipment and other agents necessary to treat anaphylaxis (eg, epinephrine, corticosteroids, intravenous antihistamines, bronchodilators, and oxygen). Monitor longer to confirm resolution of the event in patients requiring treatment for infusion reactions. Immediately and permanently discontinue Cetuximab in patients with serious infusion reactions.

Infusion reactions may be managed per the following table:

Adverse Event Grade	Treatment Guidelines
Grade 1: Transient flushing or rash; drug fever < 38° C (< 100° F)	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.

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Grade 2: Rash; flushing; urticaria; dyspnea; drug fever ≥ 38 C (≥ 100° F)	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: Symptomatic bronchospasm with or without urticaria; parenteral medication(s) indicated; allergy related edema/angioedema; hypotension	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: Anaphylaxis	**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.

7.3.3.3 Rash: Dermatologic toxicities, including acneiform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis, cheilitis), and hypertrichosis occurred in patients receiving Cetuximab therapy. Acneiform rash occurred in 76–88% of 1373 patients receiving Cetuximab in clinical trials. Severe acneiform rash occurred in 1–17% of patients.

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Acneform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days. Monitor patients receiving Cetuximab for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during Cetuximab therapy.

Rash occurring with Cetuximab administration may be graded according to the following table from CTCAE 4.0.

	1	2	3	4
Pruritus/itching	Mild or localized; topical intervention indicated	Intense or widespread; intermittent; skin changes from scratching (e.g., edema, papulation, excoriations, lichenification, oozing/crusts); oral intervention indicated; limiting instrumental ADL	Intense or widespread; constant; limiting self care ADL or sleep; oral corticosteroid or immunosuppressive therapy indicated	_
Purpura	Combined area of lesions covering <10% BSA	Combined area of lesions covering 10 - 30% BSA; bleeding with trauma	Combined area of lesions covering >30% spontaneous bleeding BSA;	_
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	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	Papules and/or pustules covering any % BSA, which may or may not be associated with symptoms of pruritus or tenderness and are associated

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		instrumental ADL	indicated	with extensive superinfection with IV antibiotics indicated; life-threatening consequences
Rash/maculo-papular	Macules/papules covering <10% BSA with or without symptoms (e.g., pruritus, burning, tightness)	Macules/papules covering 10 - 30% BSA with or without symptoms (e.g., pruritus, burning, tightness); limiting instrumental ADL	Macules/papules covering >30% BSA with or without associated symptoms; limiting self care ADL	
Nail Discoloration	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	_	_	_
Nail Loss	Asymptomatic separation of the nail bed from the nail plate or nail loss	Symptomatic separation of the nail bed from the nail plate or nail loss; limiting instrumental ADL	_	_
Nail Ridging	Asymptomatic; clinical or diagnostic observations only; intervention not indicated	_	_	_

Cetuximab dose should be modified per the following table in case of severe (grade 3/4) rash:

Occurrence of Severe (Grade3/4) acneiform	Cetuximab modification

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rash	
1st Occurrence	Delay infusion 1 to 2 weeks. If there is improvement, continue cetuximab at at 250 mg/m^2. If there is no improvement, discontinue cetuximab.
2nd Occurrence	Delay infusion 1 to 2 weeks. If there is improvement, continue cetuximab at at 200 mg/m^2. If there is no improvement, discontinue cetuximab.
3rd Occurrence	Delay infusion 1 to 2 weeks. If there is improvement, continue cetuximab at at 150 mg/m^2. If there is no improvement, discontinue cetuximab.
4th Occurrence	Discontinue cetuximab

For the occurrence of grade 1 or 2 rash, see supportive care guidelines in section 7.4.5.1.

7.3.4 Dose modifications for other toxicity: due to lack of evidence that cetuximab contributes to these toxicities, cetuximab dose will not be altered for renal failure, fatigue, nausea/vomiting.

7.3.4.1 Hematologic Toxicity
Cetuximab will not be dose reduced or held for hematologic adverse events, such as neutropenia, neutropenic fever, or thrombocytopenia.

7.3.4.2 Non-Hematologic Toxicity

7.3.4.3 Pulmonary Toxicity
Interstitial lung disease (ILD), including 1 fatality, occurred in 4 of 1570 (<0.5%) patients receiving Cetuximab in clinical trials. Interrupt Cetuximab for acute onset or worsening of pulmonary symptoms. Permanently discontinue Cetuximab for confirmed ILD.

7.3.4.4 Dermatologic Toxicity
Dermatologic toxicities, including acneform rash, skin drying and fissuring, paronychial inflammation, infectious sequelae (for example *S. aureus* sepsis, abscess formation, cellulitis, blepharitis, conjunctivitis, keratitis, cheilitis), and hypertrichosis occurred in patients receiving Cetuximab therapy. Acneform rash occurred in 76–88% of 1373 patients receiving Cetuximab in clinical trials. Severe acneform rash occurred in 1–17% of patients. Acneiform rash usually developed within the first two weeks of therapy and resolved in a majority of the patients after cessation of treatment, although in nearly half, the event continued beyond 28 days. Monitor patients receiving Cetuximab for dermatologic toxicities and infectious sequelae. Instruct patients to limit sun exposure during Cetuximab therapy.

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7.3.4.5 Hypomagnesemia and Electrolyte Abnormalities
In patients evaluated during clinical trials, hypomagnesemia occurred in 55% of patients (199/365) receiving Cetuximab and was severe (NCI CTCAE Grades 3 and 4) in 6–17%. The onset of hypomagnesemia and accompanying electrolyte abnormalities occurred days to months after initiation of Cetuximab. Periodically monitor patients for hypomagnesemia, hypocalcemia, and hypokalemia, during and for at least 8 weeks following the completion of Cetuximab. Replete electrolytes as necessary.

7.4.3 Concomitant Medications
There are no concomitant medications that are contraindicated with cetuximab.

7.3.6 Supportive Care Guidelines

7.3.6.1 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:

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. Topical hydrocortisone cream will be provided for pruritis not relieved with antihistamine use.

Retinoids: No data to support use. Use is not advised. They will not be used prophylactically.

Benzoyl peroxide: Should NOT be usedas it 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.

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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.

7.3.6 Adherence/Compliance

Patients will receive weekly cetuximab per their medical oncologist. They should adhere to their oncologist's recommendations (based on the protocol) regarding administration of cetuximab. Failure to do so may result in removal from the study.

8. Toxicity Monitoring and Adverse Event Reporting

All patients who receive one dose of protocol therapy will be evaluable for assessment of toxicity. Prior to each cycle the treating physician will fully assess the patient's condition with respect to possible treatment related toxicities. All adverse events, whether observed by the physician or reported by the patient, occurring during the active portion of therapy, or up to 30 days after the last dose of treatment will be graded by a numerical score according to the NCI's Common Terminology Criteria for Adverse Events (CTCAE), Version 4.0 (http://ctep.cancer.gov/reporting/ctc.html) and recorded in the patient's medical record. For the purposes of reporting laboratory abnormalities, only Grade 3-4 adverse events will be recorded on the adverse event CRF pages. Grade 1-2 laboratory abnormalities will not be recorded on the adverse event CRF pages. Information entered on the adverse event CRF pages will include:

- Specific type and duration of reaction (i.e., start and stop dates, resolution).
- Severity/grade.
- Relationship to study drug (causality, attribution).
- Management of the event, if treated with medication and other actions taken to alleviate the clinical event.
- Whether or not it was considered a SAE.

A preexisting condition is one that is present at the start of the study. A preexisting condition will be recorded as an adverse event if the frequency, intensity, or the character of the condition worsens during the study period.

8.1 Adverse Event Reporting Requirements

An adverse experience is defined as any unintended or abnormal clinical observation that is not of benefit to the patient. Either the condition was not present prior to exposure to the study therapy, or it has worsened in intensity or frequency following exposure to the study therapy.

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All "unexpected" (defined below) and/or "serious" (defined below) adverse events occurring during the active portion of therapy, or up to 30 days after the last dose of treatment, will be reported to the OHRS at (732) 235-7577 or (732) 235-8675. Events will be promptly reported, in writing, to the local IRB in accordance with IRB policy. If a death occurs the IRB will be notified within 24-hours of initial receipt of information. All other SAEs must be reported to the IRB within three to ten days of initial receipt of information. Written follow-up reports are required when additional information is needed to fully characterize the event. Copies of each report sent to the IRB will be kept in the study regulatory file.

In addition to reporting to the local IRB, reporting to external bodies such as industry and/or the FDA may be necessary. The Oncology group affiliates site will report all SAEs to the OHRS will be responsible for forwarding SAE reports to the IRB and FDA.

Reporting SAEs using commercially available drugs:
In addition, any unexpected (*not listed in the package insert*) serious adverse events that are **associated** (definitely, probably or possibly related) with the use of cetuximab must be reported to the FDA within 10 business days using a FDA Form MedWatch 3500 form http://www.fda.gov/medwatch/safety/3500.pdf (fax # 1-800-FDA-0178).

8.2 Definition of Serious Adverse Events (SAEs)
A serious adverse event (experience) is one occurring at any dose level that results in any of the following outcomes:

- Death
- Life-threatening- immediate risk of death from the reaction.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Results in a congenital anomaly/birth defect.
- Requires intervention to prevent one of the outcomes listed in this definition.

The definition of serious adverse event (experience) also includes *important medical events*. Medical and scientific judgment will be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These events will usually be considered serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization.

8.3 Definition of Related
There is a reasonable possibility that the drug caused the adverse experience. That is, the event is judged by the investigator to be possibly, probably or definitely related to the treatment.

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8.4 Definition of Unexpected

Any adverse drug experience and/or specificity, that is not included in the current investigator's brochure and/or package insert.

9. Treatment Evaluation/Criteria for Response

For the purposes of this study, the response to neoadjuvant cetuximab is judged by 1) development of cetuximab related folliculitis as below and 2) response at the primary site or involved locoregional lymph nodes by CT using RECIST criteria.

Response and progression will be evaluated in this study using the international criteria proposed by the Response Evaluation Criteria in Solid Tumors (RECIST 1.1) Committee (Eisenhauer et al. 2009)Changes in only the largest diameter (unidimensional measurement) of the tumor lesions are used in the RECIST criteria. Note: Lesions are either measurable or non- measurable using the criteria provided below. The term "evaluable" in reference to measurability will not be used because it does not provide additional meaning or accuracy.

In addition, patients will be evaluated weekly during neoadjuvant cetuximab to assess for grade of rash using CTCAE 4.0 criteria.

9.1 Evaluation of folliculitis

Folliculitis will be graded weekly following the initiation of neoadjuvant cetuximab per the criteria in section 7.3.3.1

9.2 Evaluation of CT response at primary site

Measurable lesions are defined as those that can be accurately measured in at least one dimension as >10 mm with spiral CT scan. All tumor measurements must be recorded in millimeters (or decimal fractions of centimeters). As all CT scans in this protocol will be performed using spiral CT, no lesions smaller than 10 mm will be used to assess for response.

Response will be graded per RECIST criteria:

Recist Criteria

Complete Response (CR)	**Disappearance of all target lesions**
Partial Response (PR)	**At least a 30% decrease in the sum of the longest diameter (LD) of target lesions, taking as reference the baseline sum LD.**
Progressive Disease (PD)	**At least a 20% increase in the sum of the LD of target lesions, taking as reference the smallest sum LD recorded since the treatment started or the appearance of**

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	one or more new lesions.
Stable disease (SD)	**Neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD, taking as reference the smallest sum LD since the treatment started.**

10. Removal of Patients from Study/Off Study Criteria

In the absence of treatment delays due to adverse events, treatment may continue until one of the following criteria applies:

a) Intercurrent illness that prevents further administration of treatment,

b) Patient decides to withdraw from the study,

c) Noncompliance with treatment plan,

d) General or specific changes in the patient's condition render the patient unacceptable for further treatment in the judgment of the investigator,

e) Protocol violation - any patient found to have entered this study in violation of the protocol might be discontinued from the study at the discretion of the Principal Investigator.

11. Laboratory Evaluations and Procedures/Correlative and Pharmacokinetic Studies

11.1 An overview of the possible molecular investigations, and in order or priority include

1. FoundationOne genomic profile from paraffin embedded tumor samples taken before cetuximab, before/at definitive local treatment and after progression
2. Analysis of ADCC and caspase by IHC
3. RNA sequencing of tumor samples before and after cetuximab
4. RNA sequencing of skin samples before and after cetuximab
5. DNA sequencing of tumor and skin samples before and after cetuximab
6. IHC analysis of EGFR downstream pathways that are illuminated by the above

The laboratory investigations are very comprehensive, ranging from partial DNA sequencing (FoundationOne™) in order to check for a battery of known DNA mutations related to cancer, to RNA sequencing on fresh tissue, which will shed light on how protein production is altered when the tumor is treated with cetuximab. FoundationOne™ is targeted DNA sequencing that is performed on paraffin embedded tumor samples. As a pan-cancer test, FoundationOne™ is designed to interrogate the entire coding sequence of 236 cancer-related genes (3,769 exons) plus 47 introns from 19 genes often rearranged or altered in cancer. These genes are known to be somatically altered in human solid cancers based on recent scientific and clinical literature. ADCC and caspase will be examined

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by IHC as in the laboratory, using paraffin embedded tissue from pre- and post- treatment samples. In addition, RNA sequencing will be performed on tumor samples from before and after neoadjuvant cetuximab, to investigate changes in protein production caused by cetuximab ie changes in protein production downstream in the EGFR pathway or completely alternate pathways that may be triggered by cetuximab. Western blot will also be utilized to look at changes in protein production in the EGFR pathway and other relevant signaling pathways. In addition, HPV status can be easily determined from RNA sequencing. Once the cDNA library is created by the Cancer Institute Functional Genomics (Curtis Krier and, Emmanuel Zachariah), analysis will be performed by bioinformatics. We will have experience with the procedures necessary to perform these analyses that are ongoing in protocol CINJ #091305. In addition, these complementary protocols will allow us to conduct parallel investigations in squamous tumors of the skin versus those of the head and neck, and to see if similar mechanisms are operative or if in fact these tumors are distinct biologic entities.

11.2 Tissue to be collected

All patients must have a diagnosis of squamous cell carcinoma (SCC) of skin prior to entering into this protocol. This diagnosis is typically achieved by a biopsy from either the primary site or FNA from a neck lymph node. However, the scant amount of tissue obtainable from an FNA would not be adequate for the molecular biology aspect of this protocol, which include

1. Providing tissue to the pathology department so that they are able to confirm diagnosis of SCC in the tissue retrieved, which then will be sent to FoundationOne™ for DNA sequencing and analysis of genetic mutations.
2. Providing frozen tumor to the Cancer Institute Functional Genomics Facility for RNA sequencing
3. Providing frozen tumor and skin tissue to be used in Western Blot analysis.
4. Providing FFPE tumor and skin tissue for use in IHC analysis.

Thus, all patients on the protocol, prior to neoadjuvant cetuximab, will have an incisional/core biopsy from the primary site and a skin punch biopsy even though they already have a diagnosis of SCC. Incisional biopsy is favored over other types (core biopsy) for this biopsy because incisional biopsy has the best chance of supplying an adequate tumor sample.

After neoadjuvant cetuximab, additional tissue will be obtained at surgery or if the patient is not a candidate for surgery, biopsy will be obtained prior to treatment with XRT or with further systemic therapy. This tissue will only be used for RNA sequencing (and not sent to FoundationOne™ for DNA analysis), and thus a core biopsy may be employed here instead of incisional biopsy. A skin punch skin biopsy will also be performed after neoadjuvant cetuximab, preferably from a similar location as the first skin biopsy i.e. obtain two skin biopsies of neck and neck or right upper chest and right upper chest. If there is a locoregional/distant recurrence or persistence, a third incisional biopsy of locoregional/distant disease if possible and again paraffin-embedded sample will be sent to FoundationOne™ for analysis and fresh tissue may be obtained for RNA sequencing.

11.3 Collection and Handling Procedures

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Collection and handling procedures will be performed at RWJUH, New Brunswick campus.

1. Prior to day of procedure, OHRS will be informed of the pending biopsies.
   Incisional or excisional biopsy will be obtained from the primary site and BRS notified.
2. Tissues will be sent to RWJUH pathology and research specimens will be transported by BRS
3. At RWJUH pathology
   a. Part of the tumor sample will be made into a paraffin embedded block, part of which they will use to confirm SCC, and the remainder of the paraffin embedded block will be sent to FoundationOneTM.
   b. Part of the tumor sample will be put in dry ice and sent asap to the Cancer Institute Genomic Facility (Kurtis Crier).
   c. The skin sample will be logged in, put in dry ice and sent asap to Cancer Institute Genomic Facility. The skin sample does not require any pathologic diagnosis, and its purpose is solely to investigate etiology of the cetuximab folliculitis.

11.3.1 Handling of Fresh tissue at the Cancer Institute Functional Genomics Facility Clinical samples will be sent to:
Curtis Krier, Manager Functional Genomics Facility
125 Paterson Street, CAB 7050
RWJMS
New Brunswick, NJ 08901
Phone 732 235 6426

12. Pharmaceutical Information

12.1 Investigational Agents
There are no investigational agents involved in this study.

12.2 Commercial Agents Product description:
Cetuximab is a commercially available agent..
Preparation: Cetuximab® (cetuximab) is supplied at a concentration of 2 mg/mL as a 100 mg/50 mL, single-use vial or as a 200 mg/100 mL, single-use vial as a sterile, preservative- free, injectable liquid. It should be prepared as for standard preparation as per the package insert. 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° C to 8° C. Discard any unused portion of the vial.
Route of administration:

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Premedicate with an H1 antagonist (eg, 50 mg of diphenhydramine) intravenously 30–60 minutes prior to the first dose; premedication should be administered for subsequent Cetuximab doses based upon clinical judgment and presence/severity of prior infusion reactions.
Administer 400 mg/m2 initial dose as a 120-minute intravenous infusion followed by 250 mg/m2 weekly infused over 60 minutes. Reduce the infusion rate by 50% for NCI CTCAE Grade 1 or 2 infusion reactions and non-serious NCI CTCAE Grades 3–4 infusion reactions. Permanently discontinue for serious infusion reactions. Withhold infusion for severe, persistent acneform rash. Reduce dose for recurrent, severe rash.
Expected toxicities: The most common adverse reactions (incidence ≥25%) are: cutaneous adverse reactions (including rash, pruritus, and nail changes), headache, diarrhea, and infection. Refer to the package insert for a complete list of toxicities.
Drug Interactions: No known drug interactions with cetuximab.

13. Data Collection and Records to be Kept

13.1 Case Report Forms

A subset of the National Cancer Institute (NCI) CRFs, in electronic format, will be utilized. Completion of the electronic CRFs (eCRFs) will be done in accordance with the instructions in a study specific data capture plan. All eCRFs will be completed by clinical research coordinators of the OHRS. The eCRFs will be maintained in a confidential format in a secure database.

13.2 Data Submission Timeline and Forms

Completion of eCRFs will occur in accordance with NCI guidelines. Baseline (pre-study) eCRFs (e.g., enrollment, medical history, concomitant medications, disease assessment, etc.) will be completed no later than 14 days after the start of treatment. Treatment eCRFs (e.g., drug administration, adverse events, chemistries, etc.) will be completed no later than 14 days following each cycle of treatment. Off-treatment information (e.g., follow-up, best response, etc.) will be completed no later than 14 days after the end of protocol treatment.

13.3 Research Charts

A research chart (i.e., shadow chart) is maintained at OHRS for each patient enrolled. Copies of significant study source documents will be maintained in the research chart. Examples of source document copies that will be maintained in the research chart include: signed informed consent form, documents that verify eligibility and treatment and documents that verify Grade 3-4 adverse events and response. This information will be updated on a prospective basis and will be confidentially maintained at the OHRS.

13.4 Reports

Publications and annual reports for submission to the IRB will be written by the Rutgers Cancer Institute of New Jersey PI using the data captured on the e-CRFs.

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14. Data and Safety Monitoring

Monitoring of this study will occur in accordance with the Cancer Institute's NCI approved Data and Safety Monitoring Plan (DSMP). An "initiation audit" will be conducted in accordance with the DSMP following enrollment of the first two (2) or three (3) patients. Subsequent audits will occur on an annual basis prior to annual IRB continuing review, if the findings from the initiation audit were satisfactory. More frequent audits of patient data and study conduct will occur if necessary. Prior audit findings and/or situations that may arise during the course of the study will determine the need for more frequent auditing. All audit findings will be reported to the Cancer Institute's Human Research Oversight Committee and the PI.

15. Statistical Considerations

15.1 Primary Hypothesis
We hypothesize that the response rate to cetuximab is greater than 10%.

15.2 Sample Size Justification
Sample size was justified based on the primary hypothesis. We expect the response rate is 30%. With 20 patients, the one-sided Binomial exact test at a significance level 0.05 (actual Type I error = 4.32%) will achieve 76.2% power when true response rate is 30%.

15.3 Methods for Randomization and Stratification
This is a safety/feasibility study. There will be no randomization.

15.4 Outcome Measures
The primary outcome is the response rate of cetuximab by RECIST criteria in patients with advanced SCCS.

The secondary outcomes include time to progression, time to death of patients with advanced SCCS who receive neoadjuvant cetuximab. Molecular correlates and tumor size will be also obtained.

15.5 Statistical Analysis
A one-sided Binomial exact test will be used to test the primary hypothesis. The estimation of progression-free survival and overall survival will be performed by the Kaplan-Meier product limit method. Descriptive statistics for all outcome measures will be provided. To evaluate the association between variables, either chi-square test (categorical vs. categorical) or two sample t-test (categorical vs. continuous) or correlation (continuous vs. continuous) will be used depending upon the types of variables in comparisson.

16. Human Subjects
16.1 Subject Population

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The study population for this protocol is advanced squamous cell carcinoma of skin as defined in the eligibility criteria.

16.2 Potential Risks

Potential risks to the patient secondary to cetuximab include the potential for hypersensitivity reaction, rash, hypomagnesemia, and pulmonary complications. These will be monitored as detailed in Sections 7.3.3. In terms of the individual's cancer, there is a risk of treatment not being effective. Furthermore, if the drug is not effective, there is the possibility of disease progression.

16.3 Consent Procedures

Informed consent must be obtained prior to commencing any research procedures. The PI shall seek such consent only under such circumstances that provide the prospective patient opportunity to consider whether or not to participate and that minimizes the possibility of coercion or undue influence. The information given to the patient, or the representative, shall be in a language understandable to the subject or representative. The informed consent document may not include any exculpatory language through which the subject or representative is made to waive any of the subject's legal rights or releases, or appears to release the investigator, the sponsor or the institution from liability for negligence.

16.4 Potential Benefits

The benefits of participating in this study may be improvement in a patient's cancer either as a measure of disease activity or quality of life improvements.

16.5 Risk-Benefit Ratio

All risks and benefits of this treatment will be discussed with the patient prior to enrollment on this study. Along these lines, the basic principles of what we are hoping to accomplish with cetuximab followed by surgery will be explained. The potential risks detailed in Section 16.2 will be made clear as well, along with what measures are in place to minimize these risks.

Alternative treatment will also be discussed. These options include beginning standard chemotherapy if applicable, therapy, monitoring off therapy, or enrolling in another clinical trial. Additionally, the importance of the knowledge gained through this study will be discussed with the patient.

All told, with the combination of employing proper patient selection and study termination criteria, close clinical and lab follow-up (both of the cancer as well as other relevant body systems), and with the medical knowledge of cetuximab (as an FDA-approved medication, for oncologic medical purposes in head and neck and colon cancer) we believe that the potential benefits outweigh the risks of the trial..

16.6 Gender and Minorities

This protocol is open to both men and women and all races.

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17. Economic/Financial Considerations

There are no standards of care for patients with SCCS due to the lack of randomized studies in this population. However, phase II data for the use of cetuximab exist in this patient population and as such, this therapy is often widely available. Thus the treatment modalities of this protocol (cetuximab, surgery, radiation) will be paid per usual, by insurance or government agencies (charity care, medicare, Medicaid). Precertification of these modalities will occur prior to treatment on protocol. Funding will be sought for the pretreatment biopsies that are a mandatory part of this study. The additional investigational aspects of the study including, IHC, PCR, and RNA sequencing will be performed as funds allow, possibly financed through the Precision Medicine Group, or other grants.

19. Publication of Research Findings

The policies and procedures of Rutgers Cancer Institute legal department (see: Investigator's Handbook) will govern publication of the trial. It is expected that the results of this trial will be submitted for publication in a timely manner following the conclusion. The PI, and all co-authors prior to submission or use, must review any abstract or manuscript.

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